Back to the clinic. Methods I. Research designs. Higher quality of information, more certainty to the answer

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Abstract

Research designs refer to the way information is obtained and are limited by ethical, economic and temporal viability. Research designs are standardized strategies to reduce biases, which in the architectural model of research are identified in the baseline state, the maneuver and the outcome; hence, there are no specific designs for each question. The design with the lowest probability of bias is the clinical trial, followed by cohort and case-control studies and, finally, by cross-sectional surveys. Among the main characteristics that give merit to research designs are the following: population inquiry, which refers to the situation of the population in relation to the clinical course/natural history of the disease; the maneuver, or action that is expected to modify the baseline state, which can be observational or experimental; follow-up, or documented monitoring that is given to each subject, which can be longitudinal or cross-sectional; and directionality, which can be prospective or retrospective and refers to the timing of data collection for research purposes. It will always be better having a valuable question, even when answered with a design with higher risk of bias, than a question that is irrelevant or has no applicability.

KEY WORDS: Designs. Inquiry. Assembly. Maneuver. Biases.

Introduction

There is no specific design for each question. Designs refer to the way information is collected and are determined by ethical, economic and temporal feasibility.

Once the objective and rationale of any research project or article is reviewed, the first section that is addressed is that of methods, which refers to the research design, a characteristic that allows identifying how the information was or will be collected.^{1,2} Hierarchically, from the highest to the lowest quality of information, there is the clinical trial, followed by the cohort study, the case-control study and, finally, the cross-sectional survey.³ Based on these types of research, there are several designs that combine

features, such as case-control studies nested within a cohort study⁴ or longitudinal studies, created after cross-sectional surveys,⁵ among many possible combinations, there is even the possibility of a cross-sectional survey nested in a cohort.

The different ways of collecting information seek to avoid biases in the different components of the architectural model of research⁶, either at baseline state, in the maneuver or in the outcome (Figure 1):

- At baseline state, the diagnostic demarcation should be considered, in order to avoid an “inadequate assembly”, as well as prognostic demarcation, in order to attenuate the “prognostic susceptibility bias”.
- During the maneuver, the quality of the main maneuver, the presence of peripheral maneuvers and the management of adverse events have to

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Figure 1. Architectural model of research.

be considered, in order to decrease the “Performance bias”.

- An identical outcome measure must be guaranteed in all individuals without distinction, much less dependent on the type of maneuver, as well as equality in times and procedure at each measurement, in order to avoid “detection bias”.
- It is necessary to document the losses to follow-up, in order to enable for the evaluation of similarity characteristics between lost subjects and those who continue until the end of the study to be assessed, and this way weighing the presence of “transfer bias”.

Research design characteristics (Table 1)

It should be pointed out that population inquiry is the feature that most determines errors in research designs. population inquiry refers to the moment within the phenomenon of causality where the population candidate to participate is considered. This is how it can be carried out concordant with the baseline state, as it occurs in experimental cohort (clinical trial) or Observational cohort design, or discordant with the baseline state, as it occurs in case-control or cross-sectional survey designs, where the candidate population is sought once the outcome has occurred. While the population inquiry is directed to the universe where all candidates to be assessed come from, the population assembly is made up of those subjects that, having met the health or disease criteria of interest (diagnostic criteria), meet the selection criteria;⁶

Among the other components that are characteristic of research design, we will highlight three:

- *Exposure to the maneuver.* Is the action expected to modify the baseline condition of the patient producing a change that is known as the outcome. When the maneuver is assigned as part of the research of interest, it is known as experimental, which characterizes the clinical trial.^{7,8} When the maneuver had reasons beyond the investigation for its application and, if this is the case, this previous application is subsequently identified, but now for research purposes, it is considered an observational maneuver (e.g.: smoking as a self-selected cause and age as cause by action of nature, and even the use of a drug by recommendation or self-medication). Because of this characteristic, cohort, case-control and cross-sectional survey designs are known as observational studies.^{9,10}
- *Follow-up.* It refers to the monitoring given to each subject with regard to the clinical course or natural history of the disease. A study is recognized as longitudinal when there is real-time documented evidence of each one of the components within the phenomenon of causality, whether recorded or not for research purposes; initially, the baseline state is or should have been recorded, then, as time elapses, the maneuver and, finally, the outcome are. The reasons beyond the research that might have given origin to the record include medical care, periodic medical examination, etc.¹¹ In contrast, the cross-sectional

Table 1. Research designs main characteristics

Research Design	Population Inquiry	Maneuver	Follow-up of the individual	Directionality the information	Description of the characteristic
Clinical trial (experimental cohort)	Concurrent to baseline state (time 0)	Experimental	Longitudinal	Prolective	<i>Research design</i> , the way information is obtained, "quality of information". <i>Population inquiry</i> , moment within the clinical course/natural history of the disease in which the population is sought. <i>Maneuver</i> , action that is expected to modify the baseline condition: 1. Experimental, maneuver assigned for research purposes. 2. Observational, maneuver present by causes beyond the investigation (e.g.: by action of nature [age], self-selected [smoking], by other indications [medical care]). <i>Follow-up</i> refers to the monitoring given to each subject with regard to the clinical course or natural history of the disease. 1. Longitudinal, there is documented evidence of baseline state and maneuver prior to the outcome. 2. Cross-sectional, the patient is assessed in a stationary form; both baseline state and the maneuver, as well as the outcome are measured in a single time. <i>Directionality of the information</i> , moment of information collection for research purposes; 1. Prolective, in real-time, when the phenomenon is occurring. 2. Retrolective, the information is collected when the phenomenon has already occurred. The information could have been recorded before in real time, but for reasons beyond to the investigation.
Cohort (observational cohort)	Concurrent to baseline state (time 0)	Observational	Longitudinal longitudinal	Prolective Retrolective (historical)	
Case-control	Divergent to baseline state (time 3)	Observational	Cross-sectional/longitudinal	Retrolective	
Cross-sectional survey	Divergent to baseline state (time 3)	Observational	Cross-sectional/longitudinal	Retrolective	

study is when the patient is assessed in a stationary form, with the baseline state and the maneuver, as well the outcome being measured at a single time. At this point, it should be mentioned that even when everything is measured in a single moment and there is no documented evidence of the actual time the facts occurred, artificially reconstructing the real temporality of each section should be tried; for example: in a patient with a five-year history of diabetes in whom studying the damage to a target organ as a result of metabolic control is wanted, his/her baseline state can be rebuilt by asking about his/her situation five years back, taking into account both the criteria that at the time would have been applied, and his/her baseline characteristics and the metabolic control he/she has experienced since then and until the moment the study is carried out. This way, patients who in the reconstruction of their characteristics were not candidates for entering the study should not be included; similarly, it will be necessary trying to identify at what moment they may have suffered target

organ damage, if it is documented at present time. Fortunately, technological development has facilitated the existence of records that for different reasons monitor health status, which increases real-time follow-up of many people who subsequently will become research study subjects; thereby, longitudinal follow-up has become and will continue to become increasingly common. This fact will increase the quality of information, thus reducing memory-inherent measurement errors.¹² The only case where these errors do not exist, is in the description of the baseline state of patients with a disease of recent onset (or any state of recent onset), where no association is sought, but only to characterize these baseline conditions; however, once the information has been collected, it is common that comparisons are made between the baseline status and subsequent time points.¹³

- *Directionality of the study*. Timing of collection of information for research purposes. A study is considered prolective when data collection it is made in real time and for research purposes at

Figure 2. Longitudinal studies design (cohort or randomized clinical trial) and their main biases. RCT = randomized clinical trial, A = random assignment by the investigator.

the moment when the causality phenomenon is occurring. The baseline state is initially documented for research purposes; subsequently the maneuver and, eventually, the outcome are.¹⁴ A study is retrolective when information is collected for research purposes once the causality phenomenon has already occurred; it includes cases where the information was collected in real time—when the phenomenon of causality is occurring— but with purposes unrelated to research, as in medical care or medical examinations.¹⁵

Research designs^{16,17}

In the clinical trial, also known as experimental cohort, as in the prospective cohort, the collection of information corresponding to the different components of the phenomenon of causality is made in real time and for research purposes. In turn, in historical or retrospective cohorts, the real-time collection of information was carried out for purposes other than research; usually, data collection is made at a given moment with the purpose to provide medical care¹⁸ or during medical examination,¹⁹ among others.

As previously mentioned, in these designs there is a concordance between the population inquiry and the assembly of candidates. In the clinical trial, there is assignment of the maneuver for research purposes, while the cohort study only the exposure to the maneuver is measured. In both, follow-up is longitudinal²⁰ (Figure 2).

Mistakes are often made, and designs that do not correspond to retrospective or historical cohorts are assumed as such; e.g.: some studies are referred to as cohort studies when they are actually case series

because the inquiring the population was carried out based on the outcome and, in consequence, it is discordant with the population assembly (the assembly is always made in the baseline state) and only a portion of the original cohort is available, which makes up a population of survivors that corresponds to a survivor case series.^{21,22} If the candidate population is searched in the registry of patients attending for medical care at the moment of the research, all patients who died or who stopped attending for medical care for any reason within the previous period between what their baseline state was and the moment at which the investigation is carried out will have been left out.²³ Overestimation of the prognosis and therapeutic benefits are common problems deriving from this type of designs.

One way to avoid the above-mentioned error and generate a historical cohort is by keeping in mind the inquiring of the population and its concordance with the assembly. To this end, it is important to investigate the population in a previous date in order for the quantified years so far correspond to the average follow-up that is wanted for said cohort; i.e., if studying the incidence of target organ damage in diabetic subjects at 10 years of evolution is wanted, instead of looking for them in current patient records (2019), it will be necessary looking for them in the admission records of newly diagnosed patients 10 years back (2009). Once these patients are identified, the causality phenomenon is reconstructed, starting with the assembly, prognostic stratification, the maneuver and peripheral maneuvers, and so on successively until arriving to the outcome. This way, patients who died or were lost to follow-up may be identified, and the condition they were at on their last assessment will be known, which are events

Figure 3. Case-control study. Inquiring only offers the candidate population; subsequently, this population has to be assessed according to the logical thinking of causality, i.e., it starts from the baseline state towards the outcome. The selection criteria are applied at the baseline state, just as the architectural design is constructed, and those cases and controls not included (not selected) must be replaced in number until reaching the sample size.

that are unknown when a case series that only includes survivors is wrongly regarded as a cohort.²⁴

Case-control study²⁵

The case-control study, as its name indicates, carries out the inquiring of the candidate population based on the outcome, where a group of cases (subjects already with the outcome) and a group of controls (subjects without the outcome) are selected; therefore, it is a retrospective compilation of information for research purposes,^{26,27} even when there is the possibility that such information has been collected in real time, but for purposes unrelated to research (medical record, vaccination card and medical examination, among other sources).

Subsequently, the timing of the causality phenomenon occurrence is artificially reconstructed. That is, once the candidate population is identified, although artificially, the reconstruction of the causality phenomenon is made either through some existing record or patient or family member recollection, with the selection criteria being assessed at the moment at which the baseline state temporarily existed (which, as in previous example, could have been 10 years back) and, similarly, exposure to the maneuver at the subsequent corresponding moment and so on until the assessment of the outcome is reconstructed. This way, rebuilding the timing of the real phenomenon, although artificially, is attempted; the inquiring of the population is often mixed up with its assembly, and

the selection criteria are wrongly applied at the moment of inquiring of the population and, in consequence, the principles of causality are broken. We should not forget that while the inquiring of the population in the case-control study is in the outcome, the assembly is made at that which was the baseline state (Figure 3).

The fact that the inquiring is carried out at the time of the outcome results in the use of a population of survivors and often from a non-specific origin –survivors may come from different populations of origin–. Although there may be biases of different magnitude due the quality of the information in the reconstruction of events that occurred some time ago (it will always be better if it comes from a medical record than from recall), the existence of transfer bias can never be avoided, which will depend on mobility and mortality of the population where the study subjects corresponding to the group of survivors come from.²⁸⁻³⁰

Cross-sectional survey³¹

In the cross-sectional survey, the inquiring of the population (as in the case-control study) is made when there is the possibility of finding subjects with the outcome of interest, even when a population is being not looked for specifically by the presence or absence of the outcome. In this case, there will be subjects with the outcome according to its prevalence in said population. In the cross-sectional survey, subjects can be found at any stage of the causality phenomenon;

Figure 4. Cross-sectional survey. Screening only offers the candidate population; subsequently, this population has to be assessed following the logical thinking of causality, i.e., starting from the baseline state towards the outcome. The selection criteria are applied at the baseline state, just as the architectural model is constructed, and subjects not included (not selected) must be replaced in number until reaching the sample size.

i.e., there will be subjects whose clinical evolution or natural history of the disease is located in a time at which the outcome can exist and, consequently, subjects will be found with and without the outcome, while others will be found in the period of exposure to the maneuver and others perhaps at the beginning of the baseline condition of interest (Figure 4).

By artificially reconstructing the phenomenon of causality, the research goes back in time to obtain information on the baseline state, the maneuver and the outcome, just as described for the case-control study. As in the latter, included subjects can come from multiple populations and, again, they are only survivors; consequently, there is the risk of transfer bias. Sometimes, cross-sectional survey studies are referred to without the purpose of making comparisons thinking that biases are avoided; however, it would be necessary to establish the moment at which clinical evolution or natural history of the disease the individuals are found in and differentiate those at their baseline state from those at the stage of exposure to the maneuver or at the outcome. There is no way to avoid transfer bias.³²

Conclusions

Research designs describe the way to collect information; there is no specific design for each research question. The design preserves the structure of causal thinking, which in turn is approached through the architectural model of research.

The same question can be answered by any of the designs. Prospective designs with inquiring at baseline state –clinical trial and prospective cohort– are the ones with the highest information quality; however, economic, ethical and time limitations often force to consider retrospective designs. Within the latter, the historical cohort (whose inquiring takes place at baseline state) is the best, since it reduces the transfer biases that are characteristic of retrospective designs where the inquiring is discordant with the baseline state (case-control study and cross-sectional survey).

It will always be better having a valuable question, even when it is answered with a design of lower quality, than having an irrelevant question answered with a higher quality design. That which has no relevance or applicability, doesn't make sense in clinical research.

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