X. From Clinical Judgment to Cohort Design

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After the clinical trial, the second research design with the best quality of information is the cohort. Although the possibility of randomization of the maneuver is not available, there is the opportunity of having the subjects followed over time. Any research that tries to explain the causality fenomenon is at risk of incurring biases; however, the cohort studies distinctive features try to avoid them. Its main characteristics are: 1 being observational, situation where the investigator only measures the presence of the maneuver, which is a characteristic that divides the subjects into exposed and non-exposed; 2 being longitudinal, which offers the opportunity to follow the subject over time, documenting the time-sequence of appearance of the causality phenomenon components; 3 measurements have directionality, which generates the existence of prolective, retrolective and retro-prolective cohorts (the first are the ones with the highest quality, since they perform a real-time measurement of the variables of interest; 4 being comparative.

Key words
cohort studies
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longitudinal studies
prospective studies
retrospective studies

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The cohort study is characterized for the follow-up of a group of subjects with similar characteristics over time. After the clinical trial, this is the second research design with the highest quality in the collection of information. Although there is no assignment of the maneuver that characterizes the clinical trial, there is the opportunity of having the subjects followed over time and, consequently, with the consistency of having the maneuver measured before the onset of the outcome (observational maneuver, since it is not assigned by the investigator —also known as "measuring the exposure"—).

It is important to mention that any research study that attempts to explain the phenomenon of causality is at risk of generating biases, either when defining the baseline state (by inadequate assembly and susceptibility bias), during the maneuver (performance bias) or when measuring the outcome (detection bias and transfer bias), as shown in Figures 1a, 1b and 1c, previously described in "Clinical Research III" and "Clinical Research IX" from this same series. However, the characteristics of the cohort studies try to avoid them.

Main Characteristics (Table I)

Exposure to the Maneuver

This is an observational study and, hence, the researcher is able only to measure the exposure to the maneuver, unlike the clinical trial, where the investigator assigns it. It should be mentioned that, although the clinical trial is the ideal design for assessing a therapeutic maneuver, its assessment by means of observational studies such as cohort studies is currently accepted (the effect of a drug prescribed by someone other than the investigator can be assessed, for example, phase IV trials). It even happens to be the ideal model when trying to assess a maneuver that cannot be assigned by the investigator due to ethical issues.

It is important to mention that the maneuver divides the cohort into the groups to be compared; at their baseline state, the subjects comprise the cohort as a single group sharing similar characteristics and, with the principal maneuver, they are distributed into *exposed* and *unexposed*. The effect of the main variable on the baseline state to generate the outcome shall be estimated, always adjusting for confounders that may be present at the baseline state (inadequate assembly and susceptibility bias) or during the action of the principal maneuver (performance bias). In a clinical trial, random assignment of the maneuver

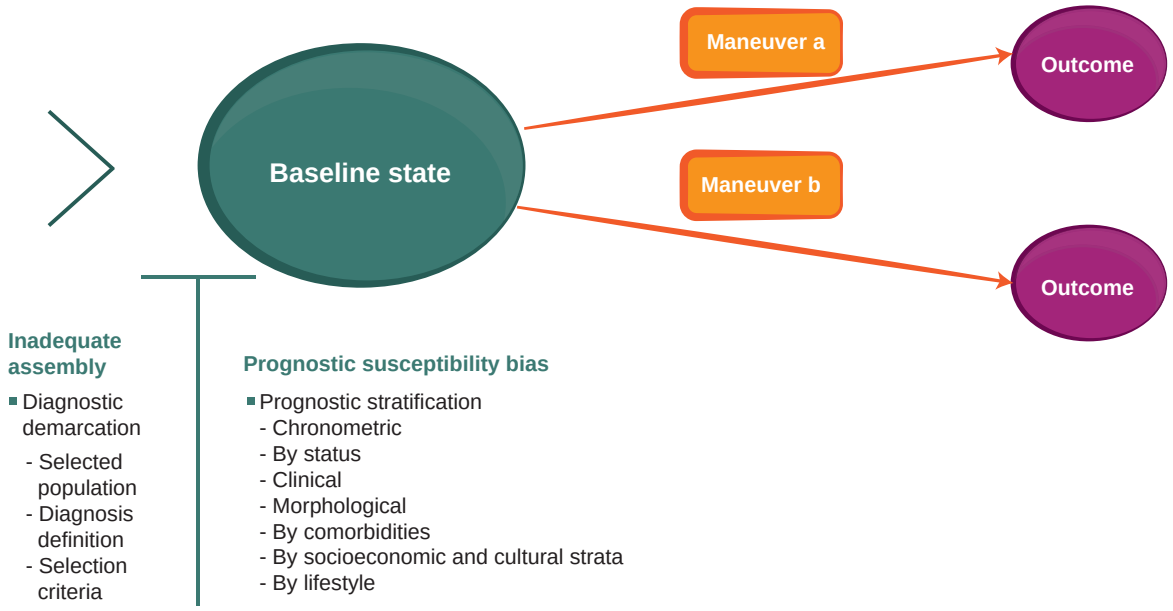


Figure 1a Characteristics that have to be considered in order to prevent an inadequate assembly and susceptibility bias

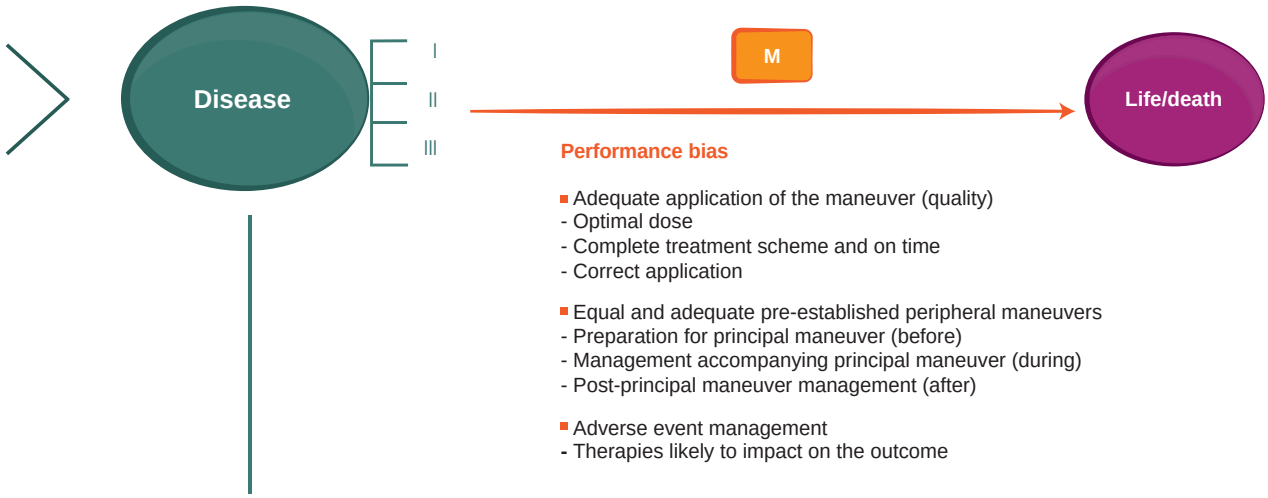


Figure 1b Characteristics that have to be considered in order to prevent performance bias

tries to control the confounding variables, a possibility that does not exist in the cohort design; hence, possible confounding variables should be thoroughly measured.

Subject Follow-up

The second and most important feature of this design is its *longitudinal* nature, i.e., there is a follow-up of the subject under study, with the variable(s) of interest being measured over time, so that change (e.g., glucose values) or the appearance of the variable of interest (e.g., infarction, death, adverse event) can be documented.

During the follow-up of the cohort, there is the possibility of including subjects in a similar moment within the clinical course of their condition —generally at the beginning, which is known as an *inception cohort*— and homogeneously following them during a previously established period, either until the end of the follow-up period or until the outcome. In these cases, the study is known as a *closed cohort* study, characterized by having similar follow-up periods (Figure 2a). In contrast, there is the *open* or *dynamic cohort*, when the inclusion and exit of study subjects at different points during the clinical course of the disease is accepted, with follow-up periods being heterogeneous in this case (Figure 2b).

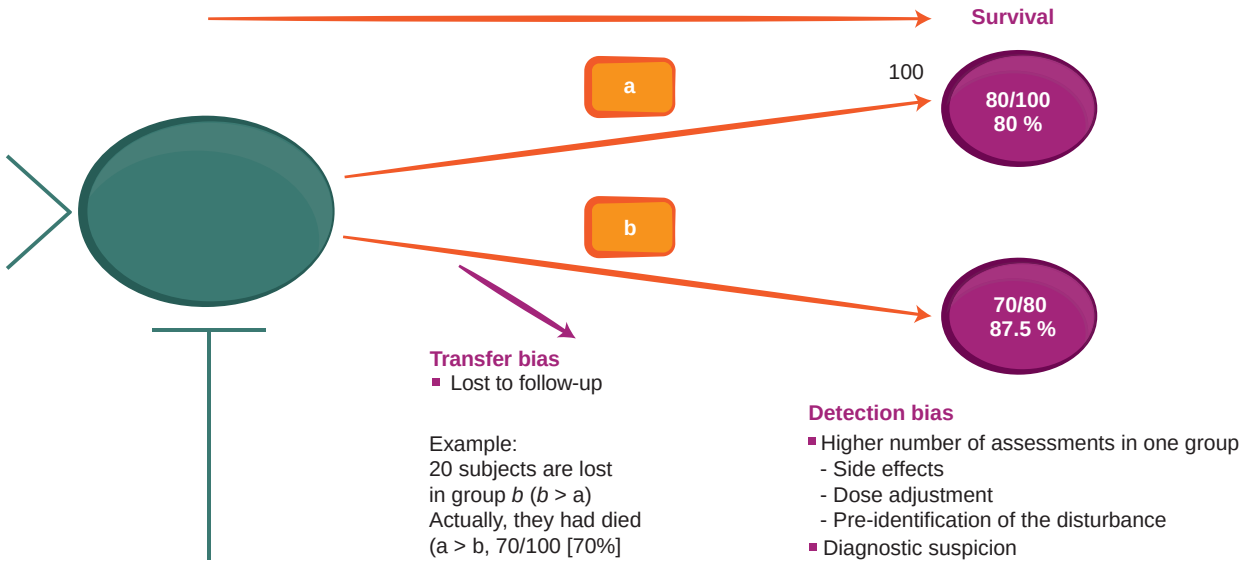


Figure 1c Characteristics that have to be to considered in order to prevent detection and transfer bias

Due to the follow-up of the study subjects, there is a possibility for execution bias to occur if the maneuver is not homogeneous and constant within each group and upon heterogeneous peripheral maneuvers between groups. Moreover, being a design that involves following subjects over time, the possibility of losing them is elevated, which provokes a transfer bias. Finally, it should be mentioned that particularly in dynamic cohorts, inadequate assembly or susceptibility bias can be induced when including subjects with less or more likelihood of suffering the outcome; for example, when only survivors are included in periods subsequent to the baseline (*survivor cohort*).

Directionality in Measurements

The third characteristic of cohort design is the directionality in the measurement of information, which results in what we know as prolective cohort study (prospective), historical cohort or retrolective cohort (retrospective) and the ambispective or retro-prolective cohort (retro-prospective) (Figure3).

The prospective or prolective cohort is characterized by the measurement of baseline, follow-up where the maneuver is included and outcome characteristics in real-time and under previously established standards, which provides high quality to the collection of such information and, therefore, the assessment of the impact of the principal maneuver on the baseline state in order to generate an outcome is highly accurate.

In the measurement of the main maneuver and other variables involved in the phenomenon of causality (confounding variables), there are multiple possibilities likely to be generated, such as measurement using criteria as specific as desired or measuring the degree of exposure to it, either at baseline state or during the follow-up —simulating adherence in

Table I Characteristics of the cohort design

Design	Exp/Obs	Long/Trans	Prol/Retrol	Comp/Desc	Measure
Cohort	Observational	Longitudinal	Prol/Retrol/Rp	Comparative	Incidence

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 (Comp) and descriptive (Desc), respectively. Measurement of outcome occurrence (Measure), either through incidence, prevalence, or simply the case-control ratio

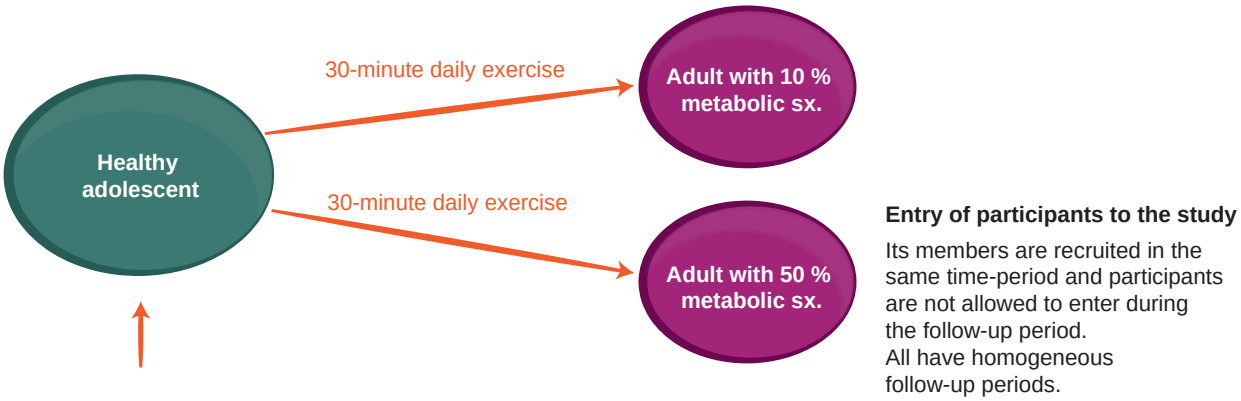


Figure 2a Closed cohort design

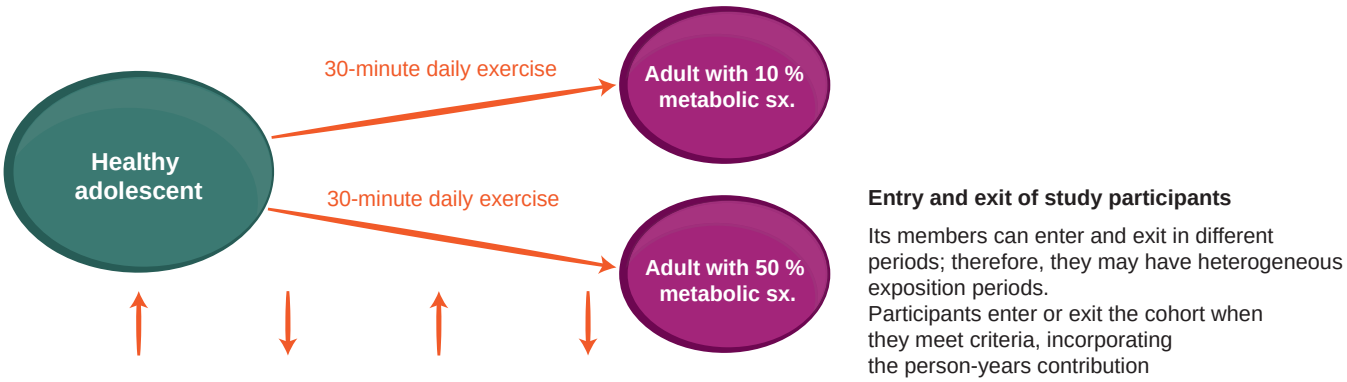
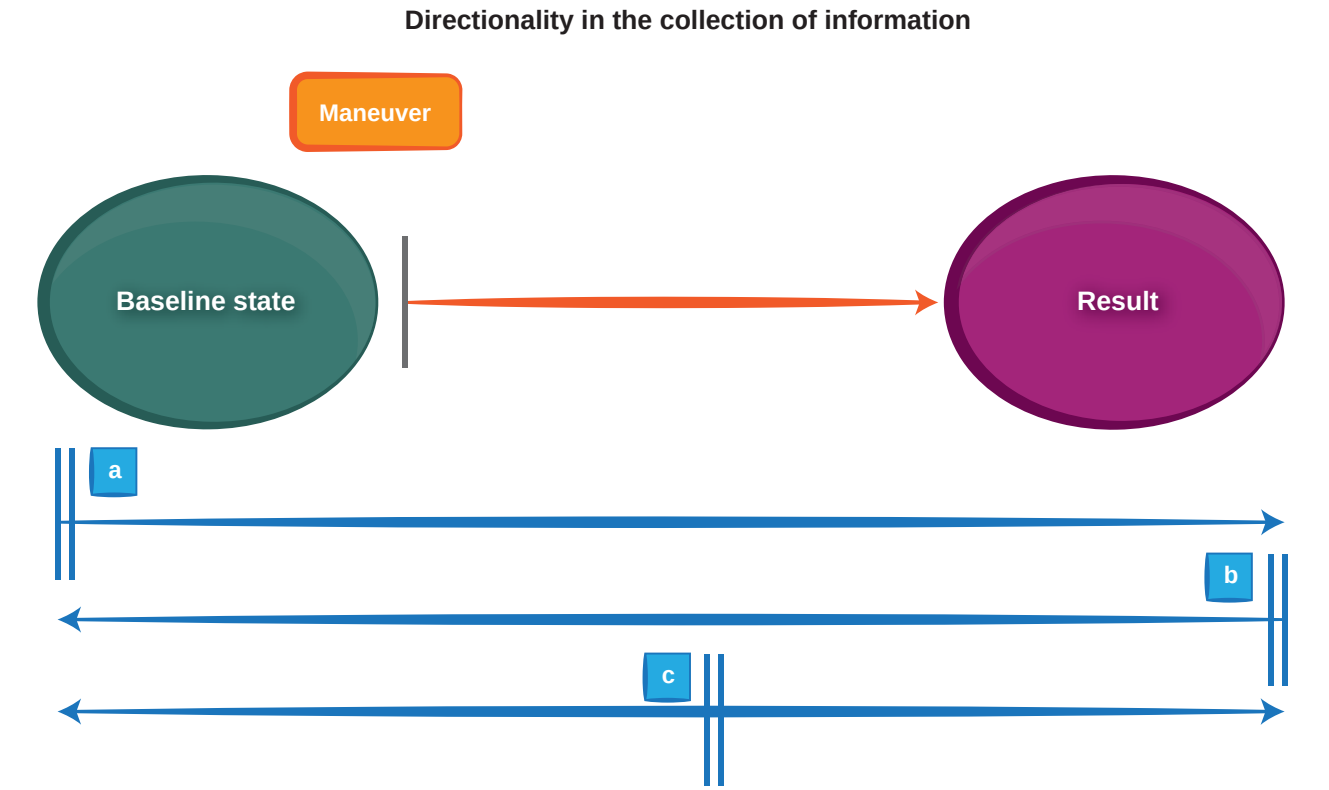


Figure 2b Open or dynamic cohort design

the case of the principal maneuver (which prevents performance bias)—. Prediction and measurement of possible maneuvers that may lead to confusion allow for adjustments to be made, either at the baseline state (thereby avoiding susceptibility bias) or during the execution of peripheral maneuvers (in order to avoid performance bias). Finally, objective, specific and homogeneous measurement of the absence of the outcome at the baseline state and the occurrence thereof during follow-up or at study termination prevents an inadequate assembly at the beginning (when the outcome was already present in an early form at the beginning of the study) and subsequently, the detection bias.

In order to simulate the blinding of the maneuver, typical only of clinical trials, in the cohort study the measurement of variables at the baseline state is expected to have been performed by staff that is independent to those who assess the exposure to the maneuver and, in turn, that both these are independent from those assessing the outcome. The advantages offered by early planning of events within the causality phenomenon are only characteristic of prolective cohort studies and clinical trials. Thus, among observational studies, the prolective cohort is the model with the highest quality in the collection of ideal data for assessing causality.

The *historical* or *retrolective* cohort does not allow for the maneuver impact to be measured with the same accuracy as the prolective cohort, since no variable is measured in real-time in any of the components described in the architectural design —reasoning or clinical judgment—. In the historical cohort, the population selected to be assessed has already been exposed to the variable of interest and has already suffered or not the outcome, with the follow-up period having concluded. However, although no component can be measured in real-time, there must be specific criteria for each variable to be measured, but own and expectable in a routine clinical record. During the planning of the study, the researchers must have specified criteria for each variable to be measured and strategies to improve the quality of the information. One of these consists in fragmenting the clinical record into three sections: one that corresponds to the baseline state, other to the exposure



a = Prolective cohort: all variables, either from the baseline state, from exposure to the maneuver or from the outcome, are measured in real-time. b = Retrolective cohort: measurement is performed when the follow-up period is over and the outcome has happened; consequently, exposure to the maneuver, baseline conditions and outcome are not measured in real-time. c = Retro-prolective cohort, is a combination: basal conditions already occurred, exposure to the maneuver has occurred entirely or for a partial period, but the outcome has not yet occurred and, therefore, it is measured in real-time

Figure 3 Type of cohort according to directionality of variables

to the maneuver and other to the measurement of the outcome, so that each block of information can be reviewed independently (similar to that described in the prospective cohort). Although this strategy has the great disadvantage that some of the information may not be found in the clinical record or its quality may be questionable, the historical cohort shows what happens in real practice; therefore, when assessing a therapeutic maneuver, the result is closer to that what will happen once it is applied in the population, unlike to what happens with the clinical trial or the prolective cohort, without the effect of surveilance and thoroughness in measurements or follow-up of the subject.

Search for Association

The fourth characteristic of the cohort design is the search for association. Actually, at present few descriptive studies are performed; however, every study describes the characteristics of its population in the first paragraph of the results. The cohort is a comparative study, either because it compares the study subjects' exposure with different maneuvers or with the change or appearence of some characteristic over time.

Comments

It is important to emphasize at what moment the assembly of the population occurs in cohort design, since it is one of the characteristics that clearly differentiates this study from other observational designs. In the cohort, the population enters at the baseline state, regardless of the directionality of measurements. For instance, if we are dealing with a prospective cohort of patients with type 2 diabetes mellitus and we want to follow them for 10 years, every newly-diagnosed patient with the disease in a specific population who meets the selection criteria will be able to enter and will be followed for 10 years, with variables being measured in real-time. But if we have a ret-

rolective cohort (historical), every patient belonging to the population of interest that 10 years ago or more was diagnosed with type 2 diabetes mellitus, and that at that time fulfilled the selection criteria, will be able to enter and will be followed in his/her records from that time until the follow-up time is covered or until the onset of the outcome; clearly, in that case variables will not be measured in real-time.

Recommended readings

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