IX. From Clinical Judgment to Clinical Trial

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Two strategies are described, intended to understand causality and documenting it with the best evidence: the clinical judgment and clinical trial. In the first one, the baseline state, the maneuver and the outcome are identified, each one with characteristics showing the complexity of the causality phenomenon, whose control allows for systematic errors to be prevented: in the baseline state, inadequate assembly and susceptibility bias; during the application of the maneuver, the performance bias; in the outcome measurement, detection and transfer biases. In the clinical trial, the tactics that try to isolate the effect of the principal maneuver from that of other components of the causality phenomenon —previously described in the clinical judgment section— are mentioned. For that purpose, the opportunity for the maneuver to be manipulated, and the temporary nature of the causal relationship are used. Its characteristics include allocation and blinding of the maneuver, feasibility of its early interruption, the analysis according to the adherence to the maneuver, the groups to be compared, the transient nature of the comparative maneuver and the informed consent. When the physician applies this knowledge in a conscious and structured manner with his/her patient, he/she improves his/her efficiency and brings medical practice closer to clinical research.

Key words
clinical trial
bias

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In "Clinical Research III" of this series, clinical reasoning (clinical judgment) was addressed as a logical model to explain the phenomenon of causality, which was previously described by Dr. Alvan Feinstein in his books *Clinical Biostatistics* and *Clinical Epidemiology. The Architecture of Clinical Research*. According to Dr. Feinstein, every sensible physician should know this reasoning. We dare saying that not only every sensible doctor knows it, but applies it during his/her clinical practice as well. However, sometimes doctors fail to do it consciously and, consequently, in a structured way. Similarly, in number I of this series, research designs were mentioned as a strategy to obtain evidence of such causality. Among them, clinical trials provide the highest quality evidence.

The present article shows these two strategies for explaining and documenting the phenomenon of causality and tries to show them in parallel, in such a way that based on one, the reason for the other is easily understood:

- Clinical judgment, or clinical reasoning/architecture of clinical research, as a phenomenological description of clinical research.
- Clinical trial, as the design that offers the highest quality of information during the clinical research process, by attempting to control or at least to document the involvement of every component within the causality phenomenon.

Clinical Judgment

In order to explain the causality phenomenon, the baseline state, the maneuver, and the result (and its characteristics) are described, as well as five sources of systematic error that can arise if they are overlooked: two in the baseline state, one during the execution or measurement of the maneuver and two in the outcome.

Sources of Error in the Baseline State (Figure 1)

a) Inadequate assembly. Usually occurs when components of the diagnostic demarcation are omitted. It is defined by the population place of origin, the diagnostic criteria and the selection criteria.

b) Prognostic susceptibility bias. Generally observed when the prognostic stratification is omitted. In it, all the factors present at the baseline state that may impact on the outcome must be considered, regardless of the effect of the maneuver.

Sources of Error in the Maneuver (Figure 2)

a) Performance bias. Usually occurs when the different components are not considered in order

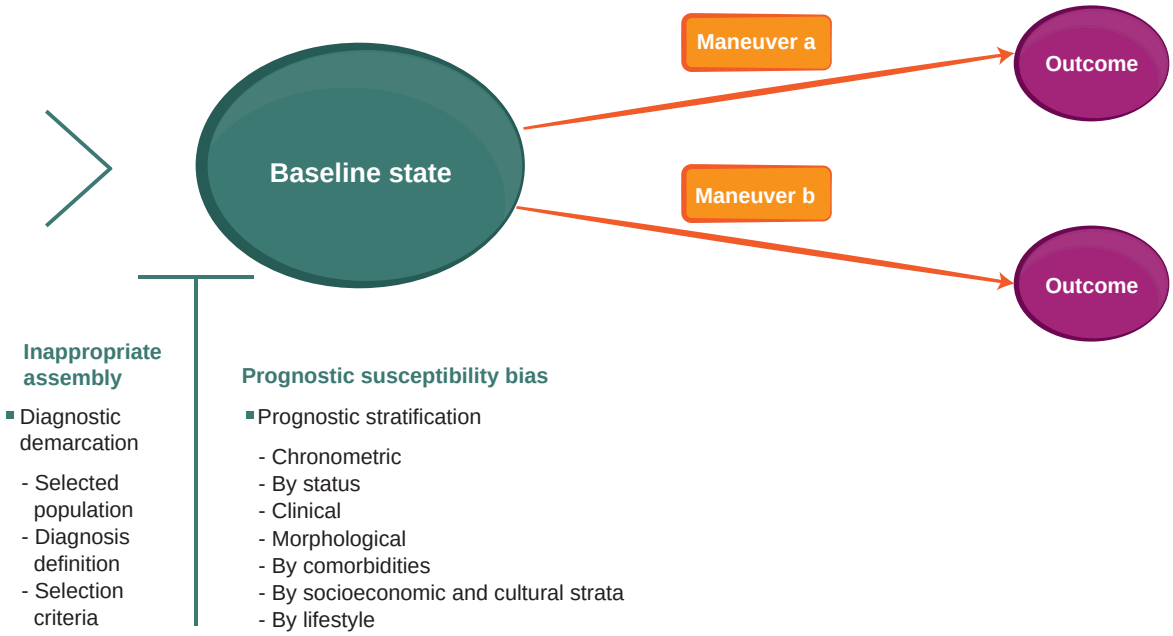

Figure 1 Characteristics to be considered in the basal state to prevent an inadequate assembly and susceptibility bias

for the maneuver to have optimum power and, therefore, the quality of the maneuver turns out being deficient; it also occurs when those actions accompanying it before, during or afterwards are not considered, and which are known as co-maneuvers or peripheral maneuvers. In addition, the comparability of the maneuver has to be specified (efficacy, effectiveness and efficiency), as well as the multiplicity of maneuvers and the temporary concurrence of the comparative maneuver.

Sources of Error in the Outcome (Figure 3)

a) Detection bias. Uneven identification of the outcome, either by diagnostic suspicion or uneven number of outcome assessments between groups.

b) Transfer bias. Patients lost to follow-up not due to random effects. The 20 % sample size increase does not solve the problem when losses are associated with the maneuver; it simply maintains data stability in order for the power of the test to be preserved during the statistical analysis.

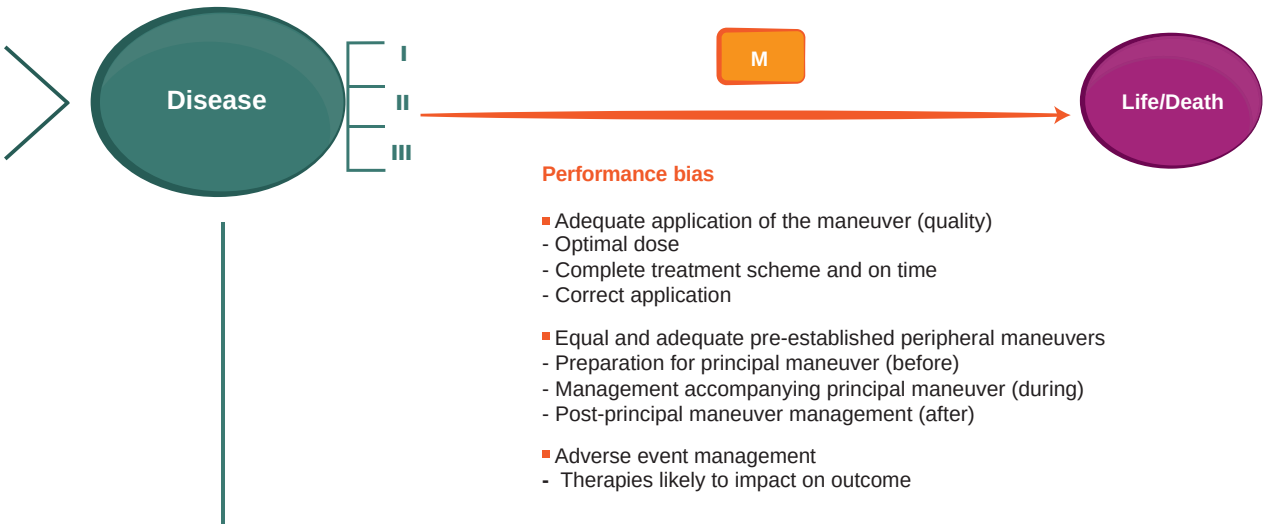

Figure 2 Characteristics to be considered in the maneuver to prevent performance bias

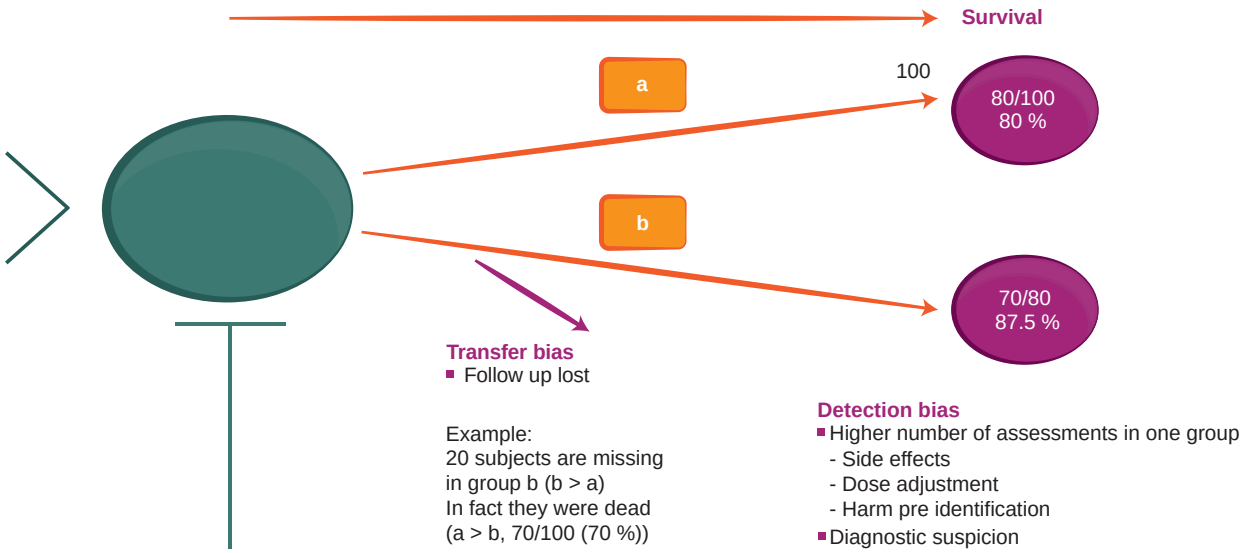

Figure 3 Characteristics that have to be considered in the outcome to prevent diagnostic detection and transfer bias

Clinical Trial

Clinical trials allow for information to be obtained with such quality that it attempts to isolate the result provoqued by the principal maneuver on the baseline state and controls for components that may participate in the outcome or provoque a biased assessment of it. Clinical trials, unlike observational studies, allow for the maneuver to be manipulated, which confers distinctive characteristics to it.

Among the characteristics accompanying the maneuver, either in an immediately previous period, during or in a subsequent period, the following are exclusive of clinical trials (Figure 4):

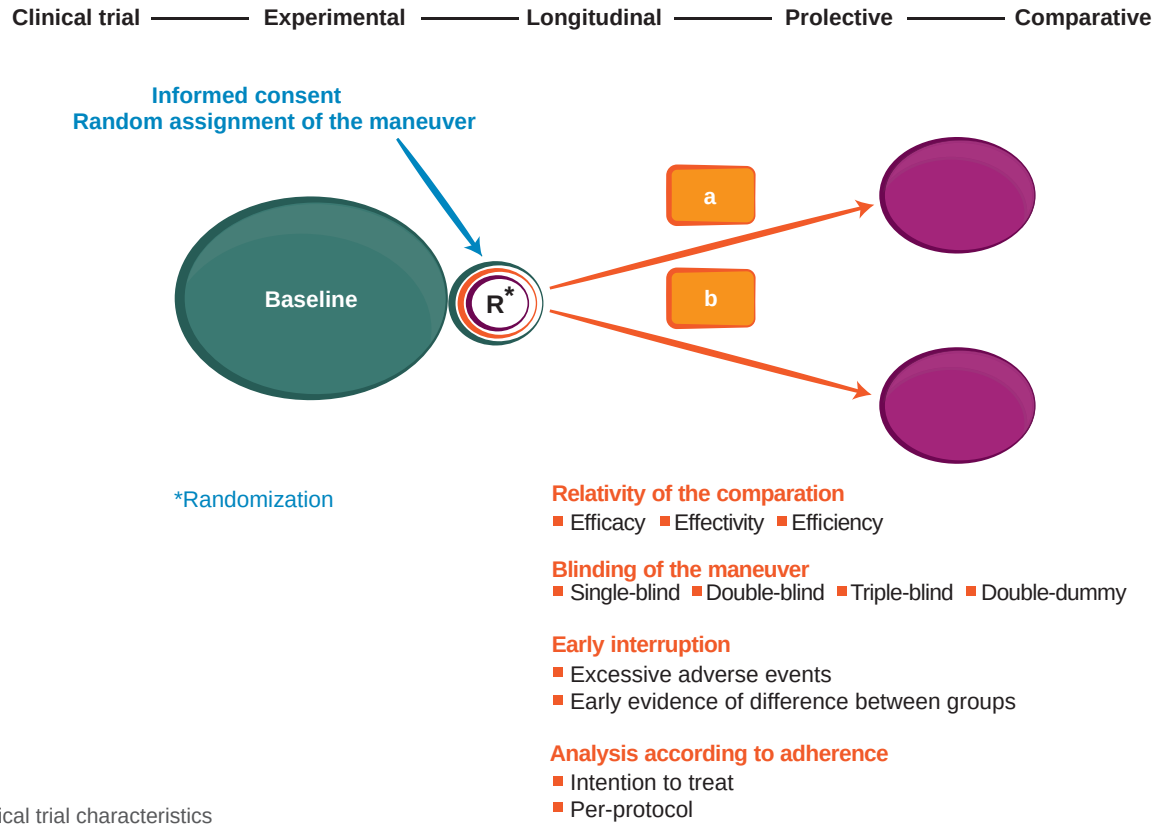

Figure 4 Clinical trial characteristics

- Maneuver assignment: is the distinctive characteristic between the clinical trial and other designs, since only the clinical trial offers the opportunity for the maneuver to be assigned. Random assignment of the maneuver attempts to generate groups with similar baseline conditions between the different maneuvers (to avoid prognostic susceptibility bias), thereby preventing discrepancies that might later be the cause of outcome differences. Even though this is a highly popular strategy, it does not prevent the presence of the "trans-stratification" phenomenon, nor does it specify the impact of the maneuver on different prognosis strata (see "Clinical Research III"). This phenomenon can be prevented if a randomization by strata is performed, provided the analysis of the results is carried out within each stratum and not just globally. Similarly, randomization has other functions such as compliance with the ethical principle of offering each individual the same opportunity of receiving the experimental maneuver, and the possibility that subjects with similar maneuver adherence probabilities are assigned to each treatment arm (to avoid performance bias) and similar probability of dropping out from the study (which reduces the transfer bias). Finally, it is worth mentioning that randomization facilitates the blinding of the maneuver. This is how the maneuver reduces the probability of biases that are distinctive of the baseline state, the maneuver and the outcome.
- Blinding of the maneuver: this strategy seeks primarily to prevent the involvement of subjectivity in the assessment of the outcome (in order to avoid detection bias). It is subdivided in three categories depending on who does not know the treatment maneuver within the research process:

a) *Single-blind:* this is considered when the patient ignores which treatment he/she is receiving, i.e., doesn't know to which maneuver he/she was assigned.
b) *Double-blind:* when the patient and the investigator do not know the treatment arm.
c) *Triple-blind:* when the patient, the investigator and the one who analyzes the data do not know the treatment arm.

In addition to this, when the form of delivering a drug is different (e.g., drug *a* is administered twice-daily and drug *b* thrice-daily; or drug *a* is orally administered and drug *b* intramuscularly), or when the physical appearence of the drug is different (drug *a*, blue pill; drug *b*, yellow) a double simulation is used (double-dummy); for example, if the patient receives drug *a* only twice a day and drug *b* three times a day, three drug *b* placebos will have to be added to drug *a*, which have to be taken the same way three times daily and two drug *a* placebos will have to be added to drug *b*, which have to be taken twice daily.

- Early interruption: clinical trials may be interrupted for two inherent reasons to the treatment: early difference between groups in the primary outcome, provided there is no probability of such differences to be lost once the sample or the follow-up are completed; and due to the presence of adverse events, above the upper limit of the 95 % confidence interval, estimated according to the corresponding sample size or follow-up period.
- Analysis according to adherence to the maneuver: hardly a clinical trial with a follow-up period exceeding a few days ends with an adherence of all participants to the maneuver of at least 80 % (e.g., taking the drug at 80 % of the doses). In general, non-adherent patients are expected to be similar in number and characteristics —at baseline and in peripheral maneuvers— between treatment groups; similarly, subjects lacking adherence are expected to have similar characteristics to those reaching the end of the study with adequate adherence. Thus, assuming a random lack of adherence between groups, data are analyzed using two strategies:

a) *Intention to treat* (ITT) analysis, which is characterized for including in the outcome assessment both those subjects who complied with an adequate adherence (≥ 80 %) and those who did not (< 80 % adherence).
b) *Per-protocol analysis*, when the decision consists in including in the analysis only data from subjects with a ≥ 80 % adherence.

In the intent-to-treat analysis, a decrease in differences between treatment groups is usually observed, whereas in the per-protocol analysis, that what could be the real difference between the maneuvers is usually preserved, provided losses have been random; otherwise, one of the groups might end up being favoured (let's imagine that those subjects with more adverse events are not adherent and that these are differentials between the maneuvers, or that the subjects with better or worse response to the treatment are not adherent and that the response was also differential between the groups; if this occured, performance bias would be present).

Other non-exclusive characteristics to clinical trials, since they can also be considered in observational studies, include the following (Figure 4):

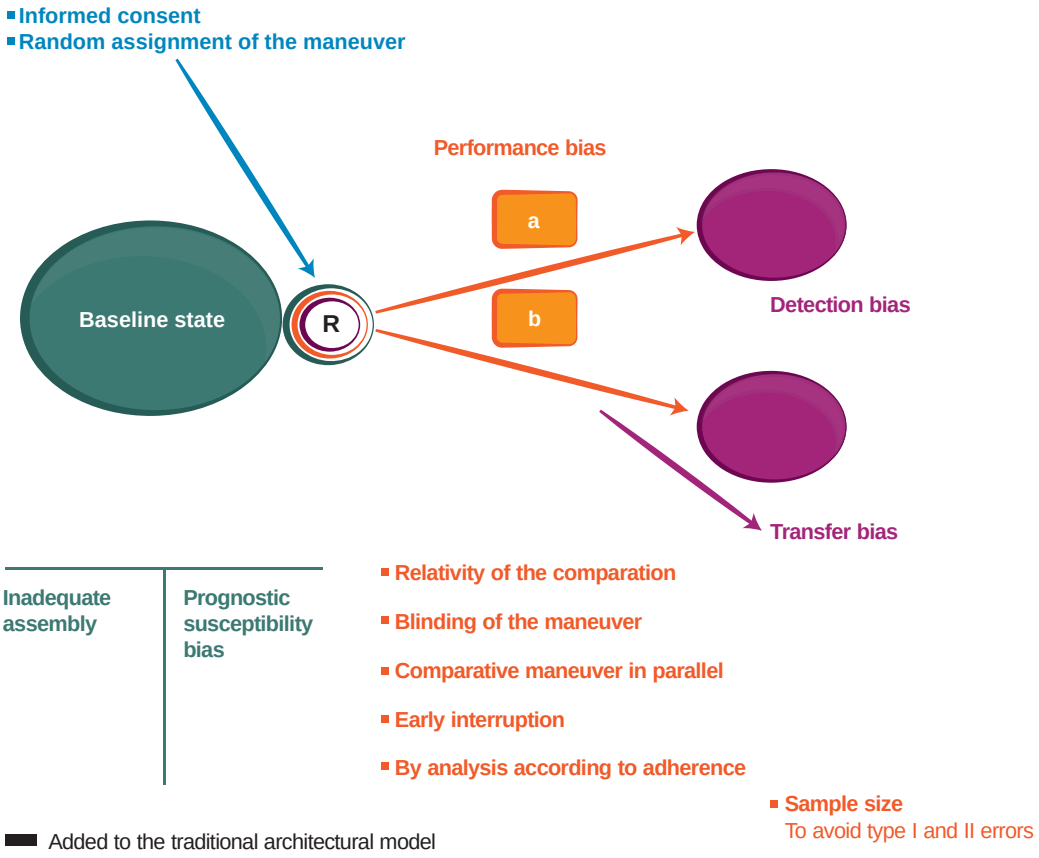

Figure 5 Clinical trial characteristics in parallel to clinical reasoning

- Groups to be compared. It is important assessing which is the comparator of the principal maneuver, since depending on this, clinical trials have been classified in efficacy, effectiveness and efficiency studies:

a) *Efficacy*: when the active maneuver is compared against placebo or against nothing. This comparison tries to demonstrate that the active maneuver works better than doing nothing or just giving a placebo

b) *Effectiveness*: represents the comparison of the active maneuver with a standard treatment; therefore, it tries to demonstrate the superiority of a maneuver against another. This study must be weighed carefully, since not finding any significant differences does not mean that the maneuvers are equal or equivalent. If that what is sought is to demonstrate equivalence, the sample size will have to be estimated for a maximum difference of about 3 %. If that what is looked for is non-inferiority, a maximum difference of 9 % will have to be considered.

c) *Efficiency:* it refers not to a comparison, but to the impact of the maneuver once it is applied in the community.

- Transient nature of the comparative maneuver. In most cases, clinical trials comparing two or more maneuvers have the virtue of doing so within a time schedule and, consequently, with simultaneous (in parallel) application of the maneuver. Other different comparison modality are the crossover studies, where the maneuvers to be compared are carried out on successive periods and alternately in each one of the subjects under study; the big advantage is that the subjects to be compared are the same and, therefore, the remaining variables outside the principal maneuver are identical; however, these studies have some problems, such as: 1) the carry-over effect, in which when introducing the second maneuver, the subject's basal conditions have changed by the action of the first, or 2) when the disease has changed by itself during the period of time of application between the first and the second maneuver. On the other hand, this type of design is typical in stable pathologies with minimum changes expected in the scheduled study period (where after removing the first maneuver the subject actually returns to the previous baseline state) and in cyclical pathologies (whose behavior is practically the same at each cycle).

When comparing different maneuvers at the same time or at very close periods, diagnostic conditions of the pathology under study are expected to be similar, and the possibility of accessing to peripheral maneuvers to be alike; in this way, the possibility that the differences between therapies are not due to differences in diagnosis (susceptibility bias) or in accessibility to peripheral maneuvers (performance bias), or in diagnostic criteria (inadequate assembly), or in outcome assessment criteria (detection bias) is avoided. Finally, we should mention that in a clinical trial, the baseline conditions and follow-up time of subjects included and randomized to one therapy or another is the same.

- Informed consent. Since in all cases the maneuver will be assigned, even if it entails a minimal risk, ethical principles of research in human beings must be protected. (Therefore, the principles that must be considered to safeguard the rights and wellbeing of patients participating in research projects will be highlighted.)

Conclusions

Identifying and mentally organizing the details of the causality phenomenon during the clinical course of a disease, and knowing the reasons of the distinctive characteristics of a clinical trial, allows for the bond of clinical practice with clinical research to be understood and, consequently, it facilitates a reasoned and structured bidirectional exploitation of both for the benefit of patients. It is important to note that, as mentioned by Dr. A. Feinstein, the people more used to the handling of causality is the clinician, since everytime he assigns a maneuver to a patient he/she is applying this knowledge and skills, and that doing it in a conscious and structured way, undoubtedly will improve his efficiency and will bring medical practice closer to clinical research (Figure 5).

Recommended readings

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