Randomization versus “real world” studies

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Introduction

The introduction of digital database analysis in this millennium has generated a growing number of observational works that have proliferated in medicine.

This has led us to consider the beneficial and weak points of these designs to establish a critical and not superficial analysis of the vast literature that virtually demands of us.

From the analysis of observational studies, among which are the so-called “in the real world”, some points to consider are obtained: the generation of hypotheses, the geographical and temporal evaluation of health care, the value of the interventions and the improvement in quality with an audit of the results and a feedback to rethink the health circuits.

Delimiting the evidence does not consist of sectorizing and excluding designs, but rather, in understanding their usefulness and favouring the appropriate use of the information.

Randomized studies: the unbiased and controlled evidence base

One of the imperatives of randomized studies is their strength based on having an unbiased assessment of the information.

This is of vital importance since the balance generated by the randomization between the groups allows known and unknown confounders to be neutralized in the arms and thus determine a certain effect of the treatment (beneficial or harmful).

The inclusion of the “blind” reinforces the value of this design since it minimizes the bias of the treatment effects, especially with subjective end points such as symptoms or changes in mood.

Therefore, these two essential conditions of randomized studies: limiting bias and balancing confounders allow us to identify a reliable source of evidence that supports the transformation of clinical practice.

The clinical guidelines put the best evidence as class IA/III, when this design incorporates a substantial conclusion in favour or in detriment of a specific therapy.

However, the limitations of this design focus specifically on the adequate inclusion of the population.

Many of the controlled studies restrict inclusion to young populations, with fewer comorbidities or marked gender differences.

This underrepresentation of “daily clinical” populations does not make it convenient to extrapolate results or strategies since the presence of biological, comorbid conditions or the evolution of the disease are restricted in the eligibility of the sample.

This transferred to the "real world" creates inconveniences when incorporating the evidence.

We do not have to think that randomized trials are “all or nothing” in medicine since this low powered design, methodological or logistical flaws do not generate a firm evidence for the patient care.

Observational Studies: common sense and "uncontrolled" bias

Observational studies can generate hypotheses when they relate an association between exposure and events. These hypotheses can be corroborated in prospectiverandomized trials that demonstrated this association, conferring a firm evidence framework.

This represents the strengths (hypothesis generation, external validity) and weaknesses (common sense, biases, and confounding adjustment) that the observational design presents.

Although, as we previously commented, the inclusion of pts in randomized studies is more restrictive and not as broad as in observational ones, the ideal should find an anchor point between the best design (randomized) and the strengths of the observational ones (broad criterion of population inclusion).

The common sense on which many of the observational studies are based on risk markers rather than in the modification of the factor that produces it or on soft hemodynamic or physiological endpoints or imaging that does not translate to clinical benefit.

An example of this, in patients with an image of a thrombus in prosthetic valves, common sense would determine that anticoagulants would be benefitial from a clinical point of view, however, controlled studies do not confirm this.

Some inotropic drugs in unstable patients with heart failure improve cardiac output and decrease pulmonary pressure, common sense would convey a positive clinical result given the hemodynamic improvement that is generated, however controlled studies have not demonstrated their usefulness.

In conclusion, the mechanistic or pathophysiological common sense associated with clinical observation frequently does not translate to relevant clinical benefits either through an incomplete understanding of the pathophysiology or for a synthesis of the disease setting.

Another limitation is the incomplete adjustment of confounders (unmeasured confounders) and biases in this design.

An example of this is hormonal therapy in perimenopausal women where observational studies concluded a reduction in cardiovascular events. In the randomized WHI study, cardiovascular events increased in the intervention arm (hormone therapy). This discrepancy was mainly due to the fact that the observational studies included a younger and healthier population that determined a lower incidence of events (inclusion bias).

Combination of strengths: randomization in the "real world"

Incorporating the strengths of both designs converges towards a best and most reliable evidence.

This is explained in the following way: a broader inclusive criterion (external validity) of controlled studies in a not so bureaucratic regulatory and operational framework that makes this design can be used more frequently.

The clinical guidelines in general incorporate reliable controlled studies in their class IA in about 15% of the cases.

The new forms of big data and artificial intelligence that incorporate "infinite" knowledge networks are not without biases and poor quality of the data they address.

The incorporation of observational data in electronic health databases can identify hypotheses that are transferred to randomization and allow adequate interoperability, monitoring and less restrictive inclusion.

Although the following table summarizes strengths and weaknesses of both designs, it is necessary to seek to arrange electronic health databases (with high-quality records) and network registries of multinational databases or through local networks (which allows a longer and more effective monitoring as well as being able to detect unanticipated end points, such as adverse drug reactions).

	Observational studies	Randomized studies
Strengths	Hypothesis generation.	Confounding balance.
	Wider Inclusion criteria (external validity).	Unbiased assessment of efficacy and safety of treatment.
	Longer exposure to treatment.	
	Low cost.	
Weaknesses	Potential bias in treatment effect.	More restrictive inclusion criteria.
	Uncontrolled confounders.	Short-term exposure to treatmente.
	Oriented by common sense (incomplete knowledge of the pathology).	High cost.

Recommended Bibliography

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