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HOW TO READ AND GENERATE SCIENTIFIC PUBLICATIONS. HYPOTHESIS AND OBJECTIVES OF A CLINICAL RESEARCH PROJECT

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ABSTRACT

In the clinical research process, the formulation of a well-founded hypothesis and objectives concordant with the research question are key to the proper conduct of the project. The following article reviews the fundamental principles for the adequate formulation of hypotheses and objectives of clinical research projects, providing practical recommendations and examples.

Keywords: hypothesis; investigation objectives; clinical research.

INTRODUCTION

Biomedical research is a discipline that goes back to the origins of the scientific method and is in constant development. In every project that seeks to contribute to biomedical knowledge, there must be a careful design that allows to give strength to the findings found. To properly conduct this process, it is necessary to formulate, not only a structured, interesting, novel and ethical question, but this must also be followed by a well-founded hypothesis and clear and concordant objectives for the question, which ultimately will allow to reach its answer.

Below, we present some fundamentals, reflections and practical recommendations for the formulation of hypotheses and objectives in clinical research studies.

HYPOTHESIS

The term comes from Greek: hypo = under; thesis = a placing, proposition; giving the idea of a starting point or base. A hypothesis is a statement made by the researcher after understanding thoroughly the theory on the subject that interests him (theoretical framework). It is the link between theory and new knowledge (1). The above shows that the hypothesis must be **consistent with the question** (structured on the basis of the PICOT format) (2), well grounded in the theoretical framework and feasible to demonstrate. In this way, it is a key element that guides and directs the rest of the research process. It must be written in **clear terms** (with logical consistency), it must be **specific**, referring to **concrete and verifiable facts**, always formulated as an assertion and **without making value judgments** (3). **A good hypothesis determines the type of study to be followed** (methodology).

Hypotheses indicate what we are trying to prove and are defined as tentative explanations of the phenomenon investigated. They can derive from the existing theory, from the systematic observation and from the extrapolation of observations in other scenarios, with biological plausibility. They should be formulated as propositions, in the present tense. In fact, they are provisional answers to research questions. It should be noted that in our daily lives we constantly elaborate hypotheses about many things and we then investigate their veracity.

A good hypothesis implies that a structured and clear research question was previously formulated. The hypothesis must contain the same PICOT elements of the question and add to this statement the frequency or numerical difference that is expected to be found. This numerical proposal is the one that will allow us to subsequently make a sample size calculation. Furthermore, this numerical proposal may come, as previously mentioned, from what is described in the literature or from empirical observation and must be clinically relevant, in order to justify the study.

Should all studies have a hypothesis? No, "exploratory" studies, for which prior information in literature is scarce, do not necessarily have to have an explicit hypothesis. An example of this are pilot studies. Qualitative

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studies also do not require a formal hypothesis. These studies are called "hypothesis generators". **All other research projects must have an explicit hypothesis.**

There are several types of hypotheses that we will analyze during this module. All of them must follow basic general principles that must be taken into account.

From the point of view of the design of the study, the hypotheses can be classified as descriptive and analytical.

The **descriptive hypothesis** is a univariable proposition that responds to a descriptive problem.

Example. Theoretical framework (adapted version of (4)): acute rotavirus gastroenteritis is a frequent cause of morbidity in children <5 years of age worldwide. Currently, 2 rotavirus vaccines are available on the market that would cover the most frequent genotypes worldwide, although the circulation of genotypes varies from one country to another. These vaccines have shown efficacy >85% and effectiveness of up to 80% in developed countries, where the circulation of genotypes included in vaccines predominates. In Chile, circulating rotavirus genotypes are not known at present, which would be desirable before deciding the possible incorporation of this vaccine to the PNI (National Immunization Plan).

Question: What are the rotavirus genotypes that are associated with acute gastroenteritis in children <5 years of age treated at Chilean public hospitals?

Hypothesis: Rotavirus genotypes associated with gastroenteritis in children <5 years of age will be predominantly (> 80% of the variants identified) those included in currently available vaccines, without significant differences in the distribution of genotypes among the different regions of Chile analyzed.

Comment: In this hypothesis, the population to be studied is clearly defined (Child rotavirus <5 years in age with gastroenteritis, treated at public hospitals), the place and time (Chile, currently), the main variable to be analyzed (rotavirus genotypes) and the expected result (>80% genotypes similar to vaccine and similar distribution among regions). In this case, to construct this hypothesis, elements of the theoretical framework were used and a percentage of genotype frequency that was clinically / epidemiologically relevant was proposed, in order to

to be able to justify the study from the ethical point of view and the efforts / resources that it requires.

The **analytical hypothesis** is the statement that proposes a certain relationship between 2 or more variables. This in turn can be causal (the directionality of the relationship is explicit), relational (association is established between the variables without necessarily having a dependency relationship between them) or of difference between groups (determines differences between the compared groups).

From a statistical point of view, the **null hypothesis** (H0), states that there are no significant differences between the groups to be compared; and the **alternative hypothesis** (H1) states that there are differences. In the latter case, only the presence of differences can be made explicit, or go a step further and propose directionality in these relationships ("greater than", "less than" or "cause of").

Example: Theoretical framework (adapted version of (4)): Urinary tract infections are a relevant problem in pediatrics, particularly in the presence of vesicoureteral reflux (VUR), because the latter could favor renal kidney damage and the generation of eventual scars. Until now, the management of patients with VUR has included the use of permanent antibiotic prophylaxis. In recent years, antibiotic resistance, particularly of urinary tract pathogens, has increased, which has supported the rational use of antimicrobials, avoiding unnecessary exposure to these drugs.

Question: Is there a higher risk of urinary infection during the first 2 years of life in infants with VUR without antibiotic prophylaxis compared to infants receiving cefadroxil prophylaxis?

Hypothesis: There is no statistically significant difference in the risk of urinary infection during the first 2 years of life in infants with VUR with and without prophylaxis with cefadroxil.

Comment: In this hypothesis the population to be studied is clearly defined (infants <2 years with VUR), the intervention (prophylaxis with cefadroxil), the comparator (group without prophylaxis), the main variable to be analyzed (development of urinary tract infection) and the expected result (there is no difference in the risk of urinary infection). In this case, we chose to propose the null hypothesis (H0).

OBJECTIVES

Objectives are statements that express what the researcher will effectively do to answer his research question (1). They are **actions** that **lead** the research process, therefore, they should be expressed in the form of verbs (in infinitive); they must be formulated in a **simple, clear, precise and feasible** way to achieve (3).

As with the hypothesis, there are objectives for descriptive studies and others for analytical studies. The difference between both is basically the verb that heads the statement, because it must express different actions. In the case of analytical studies, generally within their specific objectives, descriptive actions are included.

In hierarchical terms, general and specific objectives are distinguished.

The **general objective** is that which determines the scope of the study and expresses the action that will answer the research question globally. It should start with the verb that best represents the overall solution of the question and the rest of the statement should use the same elements of the question (PICOT) (2).

Specific objectives serve as a guide to conduct the study in stages. They are intended to be solutions to each of the sub-problems that will give a response to the research question as a whole. In this sense, it is important to break down the question into the elements or stages that will allow orderly progress in the study process. The specific objectives should be addressed to the basic elements of the problem (disaggregated); they must be measurable, observable, clear and precise; they must be operational and follow a logical order (then the method can be defined according to specific objective); except for exceptions, they should not be more than 4.

Example of objectives of an analytical study:
Question: What is the effectiveness and safety of X (new) treatment compared to Y (standard) treatment for the management of type 2 diabetes mellitus in Chilean adults> 50 years in age?
General objective: To determine the effectiveness and safety of treatment X compared to treatment Y for the management of type 2 diabetes mellitus in Chilean adults >50
Specific objectives:

- Compare the demographic, clinical and metabolic laboratory characteristics of the patients before starting treatments X and Y (descriptive objective).
- Determine the effectiveness of drug X compared to Y in terms of glycaemia reduction at 12 weeks of therapy (analytical objective).
- Compare the frequency of clinical and laboratory adverse reactions to drug X and Y at 6 and 12 weeks of therapy (analytical objective).

Below are some verbs used frequently in the formulation of objectives, (in alphabetical order in Spanish), with their respective definitions applied to clinical research and examples (adapted from 4):
1. Analyze: can be used in two circumstances:
a. When you want to compare the differences of a dependent variable (effect) between two or more groups.
b. When you want to find a relationship or association between an independent or predictor variable (which is postulated to produce the effect) and a dependent variable (effect or observed outcome). The studies that are framed under these contexts are considered "analytical".
Ex: Analyze the difference in effect between intravenous erythropoietin versus subcutaneous erythropoietin in the increase of hematocrit in patients with terminal kidney failure.

2. Associate: Establish the relationship between people or things.
Ex: Associate the average daily intake of salt with the prevalence of hypertension by age group in patients seen at Office A.

3. Sort: Sort or arrange by classes.
Ex: Classify patients treated for Chronic Traumatic Encephalopathy, at the Emergency Room of Hospital A, according to the Glasgow scale entry score.

4. Compare: Measure the attributes of two or more objects to discover and estimate their differences or similarities.
Ex: Compare the prevalence of obesity by gender in subjects treated in Office A.

5. Quantify: Express numerically a magnitude.
Ex: Quantify the basal and peak plasma levels of vancomycin in patients with terminal kidney failure.

6. Describe: Represent one or more persons or elements through the language and measurements taken in the study, referring or explaining their different parts, qualities or circumstances. In research it is generally the data description of a sample composed by either individuals or elements of the study.
Ex: Describe the epidemiological and clinical characteristics of patients with acute liver failure, admitted to Hospital A between 2005-2010.

7. Determine: Point, fix something for an effect (for a description or comparison), either a measure that represents them, an effect, among others.
Ex: To determine the degree of histological damage in duodenal biopsies in patients with untreated celiac disease, seen at Hospital A.

8. Establish: Demonstrate a principle, a theory, an idea, etc.
Ex: Establish the effect of smoking cessation, on functional capacity at one year of follow-up in patients with COPD.

9. Identify: Recognize if a person or thing is the same that is supposed or sought. Ex: Identify the risk behaviors related to pregnancy before the age of 15 in adolescents assisted at Community Center A.

10. Hierarchy: Sort something gradually (ideas, criteria, characters, data, among others).
Ex: Hierarchize the cardiovascular risk factors identified, according to their level of impact on the prevalence of acute myocardial infarction in patients treated at Hospital A.|

11. Measure: Define numerically an amount with its respective unit.
Ex: Measure the level of procalcitonin in blood of patients with septic shock using methods A and B, and determine the concordance of their results.

12. Relate: Establish an association or link between people, things, ideas or facts (not necessarily a causal relationship).
Ex: Relate the nutritional status with the IQ level in school children between 8-10 from school A.

It is not recommended to use the verbs **"evaluate" and "study" in clinical research projects.** This is because they do not clearly state the action that will actually be done to answer the question.

CONCLUSION

Hypothesis and objectives are fundamental elements in the formulation of a research project. Remember to start the process by structuring the PICOT factors. Based on this, formulate an appropriate question and then use the same elements to formulate the hypothesis and objectives, in order to maintain at all times the congruence between these 3 elements, which will allow to conduct the rest of the research process. A good hypothesis (independent of whether it is finally confirmed or rejected) will allow us to choose an appropriate design and make a sample size calculation. Good objectives will allow to conduct the study successfully.

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