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REVIEW

Introduction to Clinical Research in Dermatology: The Link Between Clinical Practice and Research

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Abstract. Clinical research involves studying patients with a view to improving their care. It enhances the health system, benefits both patients and physicians, and represents the «natural» form of investigation for physicians. It can be conducted at both large and small sites. On initiating a line of research, a specific question should be formulated in terms of PICO (patient, intervention, comparison, and outcome). Each of these components should be precisely defined. The question will subsequently be assessed using the FINER mnemonic (that is, whether it is feasible, interesting, novel, ethical, and relevant). If shortcomings are detected, the research question can be refined or rejected directly. When we have an appropriate question, the next step will be to write our protocol with the assistance of someone trained in clinical research methodology.

Key words: investigation, research projects, research design, epidemiology, dermatology.

INTRODUCCIÓN A LA INVESTIGACIÓN CLÍNICA EN DERMATOLOGÍA. UN NEXO ENTRE CLÍNICA E INVESTIGACIÓN

Resumen. La investigación clínica es aquella que tiene como objetivo el estudio de pacientes para mejorar su atención. Favorece al sistema de salud, a los pacientes y a los clínicos y es la forma «natural» de investigación para estos últimos. Puede hacerse en centros grandes y pequeños. Para comenzar una investigación debe plantearse una pregunta y concretarla convirtiéndola en una pregunta PICO (paciente, intervención, comparación, *outcome* [resultado]). Cada uno de estos puntos debe ser definido con precisión. La pregunta se evaluará posteriormente mediante la regla FINER (factible, interesante, novedoso, ético y relevante). Si no es adecuada puede modificarse para mejorarla o descartarla. Si es una buena pregunta el siguiente paso será escribir nuestro protocolo, habitualmente con la ayuda de alguien formado en metodología de la investigación.

Palabras clave: investigación, proyectos de investigación, métodos de investigación, epidemiología, Dermatología.

Clinical Research in Dermatology: Our Unique Position

For many physicians, clinical research is a distant entity. Should this be the case? Can any dermatologist carry out clinical research? Let's imagine a typical day at the clinic. Our first patient has chronic urticaria. Are diagnostic studies useful? How can we achieve long-term control of the symptoms? Can we establish a prognosis? The next patient consults for atopic dermatitis and asks us if it is feasible to keep a dog at home. What is our reply? The third patient has a morphea-like plaque. Is it better to do nothing, or prescribe corticosteroids, calcipotriol, or phototherapy? As physicians, we ask ourselves many questions on a daily basis; we should try to answer them by consulting the best sources available.[1] Sometimes, we cannot find a suitable answer, either because there is none or because there may be a better one. Thus, we are faced with a question involving clinical research: Can such a question be answered on the basis of a patient visit? We believe that it can. What is most important is to generate sound ideas that are linked to clinical practice, and this is in the

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hands of clinicians. Converting these ideas into a research project requires a grounding in research methodology and the opportunity to learn through collaboration.

What Is Clinical Research? A Comparison Between Clinical Research and Basic Research

Research is often associated with the study of disease mechanisms, and includes knowledge of areas such as biology, biochemistry, and pathophysiology. This type of research, known as basic or "laboratory" research, requires the know-how and resources that are particular to other sciences. It assumes that knowledge of a disease mechanism will allow us to predict its behavior and decide how to treat that disease. For this type of research to provide results, we must have sufficient understanding of how the object of our study works so that we can predict what will happen if we introduce changes. However, it usually takes a long time for a basic scientific discovery to be applied in clinical practice, because the efficacy and safety of an innovation must be tested empirically and, perhaps, because the gap between basic and clinical research is wide. Although substantial progress has been made with this model, it may not be the most efficient. The journey often begins in the opposite direction: clinical findings generate a new area for basic research. Such was the case of the clinical discovery of the usefulness of retinoids to treat acne, or of phototherapy in psoriasis.[2]

Figure. Our usual practice is the "natural laboratory," where clinical research takes place.

Clinical research involves studying sick people (patients or former patients) in order to enhance their care. Goldstein and Brown[3] described the situation very clearly by talking of being able to shake hands with the patient in the course of the research. Most clinical research questions involve etiology, diagnosis, treatment, and prognosis, although some studies analyze the health system itself and others—secondary research—take the form of systematic reviews. The main tool of clinical research is clinical epidemiology. Careful observation of real life enables us to formulate guidelines that can subsequently be applied in similar situations, although, as the systems being studied are complex, we often do not completely understand the mechanisms that underlie these guidelines. Epidemiology does have the advantages, however, that its methodology seems more familiar than that of other types of research, and that advances can by applied to daily practice very quickly. When a physician decides to begin a research project, clinical research is the most "natural" form, and probably also the most efficient (Figure).

Clinical research is as important as basic research. It was traditionally assumed that knowledge of disease mechanisms enabled a physician to deduce, by some logical process, the best way to treat a patient. However, the field of medicine goes beyond applied biology, and the leap from biology to the patient may be too large. There are many instances of how we are seldom able to suitably predict the seemingly logical consequences of our interventions. At the time, it was proposed that the tumor necrosis factor α inhibitor thalidomide could improve toxic epidermal necrolysis. However, contrary to what was expected, in practice the drug increased mortality.[4] Another example can be seen in the development of drugs that act on T cells as mediators of psoriasis. In clinical practice, other options seem to be more effective.[5] Medicine advanced enormously in the 19th century, when clinical practice began to submit to empirical approaches.[6] Basic research can generate ideas for clinical research and vice versa; however, in an ideal world, the effects of medical activity should be assessed using clinical research.

Why Should We Be Involved in Clinical Research?

Research can only fulfill its function of enhancing patient care if it is closely linked with clinical practice. Clinical problems generate questions for both patients and health professionals, and research should provide the answers to these questions.

Clinical research is useful for the health service in that it can improve the efficiency and effectiveness of the system, it provides satisfaction for professionals who are interested in it, and it generates prestige. If research is considered as an investment, then clinical research will provide sounder results. In comparison with basic research, clinical research represents a conservative approach: good clinical research always generates results that can be applied in practice, even though its potential for important discoveries is smaller.

For the professional, greater awareness of the limits between what we know and do not know is instructive, increases our efficiency, should involve some type of professional reward, and, above all, is attractive and satisfying.

Furthermore, clinical research must be independent. Today, it originates mainly from the pharmaceutical industry, which generally performs studies that are rigorous, yet focused on areas that are expected to generate a profit. Consequently, most clinical trials analyze a few common diseases, and do not generally turn their attention to more unusual diseases or those that are typical of developing countries. Research into diagnosis, prognosis, and nonpharmacologic treatment is also lacking. Clinical research allows dermatologists to take charge of their specialty and direct it toward problems that are important for patients and physicians.[7]

Can Clinical Research Be Carried Out at Any Type of Center?

Clinical research is not restricted to large centers; it can be carried out in small centers, and some important studies have been carried out in private clinics.[8] Intermediate-level centers are where most dermatologic conditions are treated, and thus the institutions where most clinical research in dermatology should be conducted.

However, when the phenomena we study are uncommon (eg, morphea), we must turn not only to specialized centers but also to collaborative studies.

How Can a Dermatologist Become Involved in Research?

Almost all clinical researchers begin by reporting cases and case series. These are valuable in terms of teaching and refresh our memory on the manifestations of diseases. They are only considered research when they provide new knowledge, which can be of several types.

Case reports occasionally reveal the most atypical forms of a disease, although this is of little relevance to daily clinical practice. The main objective of case reports and case series—and they rarely fulfill this objective—is to generate new hypotheses, which can subsequently be confirmed with other types of study. For example, reports of case series of *Pneumocystis* pneumonia and atypical Kaposi sarcoma led to the discovery of AIDS, and the report of a case series of angioma that improved with propranolol[9] led to the hypothesis that this agent could be a useful therapy.

Taking the step into clinical research requires us to acquire some basic notions of epidemiology. As physicians, knowledge of epidemiology will prove useful when interpreting the literature and applying it to our patients.[10] And in clinical research it is essential.[11] In many cases, the best approach involves learning some basic notions and collaborating with experts. Only by using suitable methodology will we be able to provide studies that answer clinical questions ethically, clearly, and easily for patients and researchers. We hope that the present article will at least help to avoid fruitless studies.

First Step: How to Begin. The Research Question

The procedure to be followed is the same irrespective of the magnitude of our research. First, we must propose a question that needs to be answered. If we are not clear, then our plans will be vague and it is unlikely that we will manage to complete the study.

Where Do Research Questions Originate?

Clinical research originates in our daily work. It is a good habit to ask oneself clinical questions during visits, note them down, and try to answer them.[10] The other necessary ingredients for generating good questions are as follows: a sound knowledge of the literature on a specific area, a certain degree of skepticism, and the ability to discuss clinical issues (often part of training). Questions can arise from a critical analysis of our working method, challenges to established ideas (especially more traditional ideas with no clear experimental basis), observation of discrepancies between what we read and what we see in practice, regional variations in practice, controversial issues, curious observations, and the application of new technology.[12,13] We suggest to our readers that they take some time to think of examples from each of these sources of ideas.

The seeds of inspiration are also to be found at the end of any discussion section, where the clinical relevance of findings should be justified and ideas for new studies are often proposed.

Other sources reveal gaps in our knowledge. Cochrane reviews and the reports of health technology assessment

agencies summarize the state of the art in a particular area and suggest research requirements and mistakes to avoid. Lastly, there are initiatives to prioritize important research for patients and physicians, including the James Lind Alliance[14] or the Database of Uncertainties about the effects of treatments.[15] Both allow physicians to formulate questions and are excellent sources of research questions.

Being Specific: Formulating Questions in Terms of Patient, Intervention, Comparison, and Outcome (PICO)

Once we have our question, the next step is to be specific. Questions are usually vague at the outset: How does cyclosporine affect atopic patients? What is the best way of confirming onychomycosis? Evidence-based medicine has developed a methodology to make it easier to answer clinical questions. Although not purpose-designed for research, it is perfectly applicable in this context.

The first stage involves converting the vague question into a 4-part clinical question (PICO question).[10] The creator of the acronym, David Sackett, recommended adding a T (time) to the end (PICOT) after using the term in Chile during a talk that we can only imagine to be as unforgettable as the acronym itself. A question formulated in terms of PICO requires us to define the following: patient, intervention or exposure, comparison group, and outcome (Table 1). The system was created for questions about treatment; therefore, it may not fit as well with other areas of research.[10] Thus, the term "patient" can be replaced by another object of study (eg, biopsy specimen, physician, presenting complaint). There are also descriptive questions for which no explicit comparison exists.

Formulating a question in this way makes it easier to answer. We recommend the reader to apply the PICO approach to the questions presented in the first paragraph of this article and to seek the answer. If our question remains unanswered, or can be improved, then we have a clinical research question.

The leap from clinical practice to research requires us to make some changes, such as ensuring that each of the terms in the question is as accurate and quantifiable as possible. This is seen clearly when we define a case. For example, is our definition of rosacea suitable for daily practice? If we want to carry out a study, will we include cases with telangiectasis? And, what about cases of rhinophyma? The definitions used in epidemiology studies should be refined somewhat so that it is easy to understand what type of case we are reporting. This is particularly true when there are no standard diagnostic tests, or when we find it difficult to distinguish between disease and normal health.[16] We should also be precise in our definitions of interventions, controls, and outcome, and, where possible, attempt to use previously validated methods.

Is My Research Question Sound? (FINER)

So, now we have an adequately presented unanswered question. The immediate temptation is to begin data collection; however, this temptation must be avoided at all costs! Before launching quickly into a study, we must review the potential of our question and develop it. It is only worth going beyond this point if the results expected are useful. The FINER rule will help us decide whether this is the case: a sound question is feasible, interesting, novel, ethical, and relevant (Table 2).[13]

Table 1. PICO[10]: Examples of Study Questions

Patient (or study participant)	*Intervention*	*Comparison Group*	Outcome
Patient with rosacea	Sunscreen	No sunscreen	Reduction in the number of pustules
Intradermal nevi	Shave excision	Conventional excision	Possible greater risk of recurrence
Local schools	Instructions given to children with molluscum contagiosum		
Psoriatic patients treated with phototherapy	Narrow-band UV-B	Psoralen-UV-A	Patient preference
Young people	Eating chocolate	Not eating chocolate	Greater prevalence of acne

Note that the term "patient" can be replaced by another object of study and that there are also descriptive questions for which no explicit comparison exists. The rule was created for questions about treatment; therefore, it may not work as well with other areas of research.[10]

In order to determine whether a question is novel, we must examine the state of the art. The leading studies frequently begin with a systematic review, which is in itself a research project. We must also consider the relevance of the question—the best questions are those whose answer will lead to a change in our working method. We can improve our question by writing it down, reflecting upon it, and discussing it with colleagues. Even if our question does not pass the FINER test, the rule will show us which points need to be improved to formulate a sound question.

If we consider our question to be well defined, it is time to evaluate the best design and to develop a protocol. In most cases, it is wise to obtain the collaboration of someone with a grounding in methodology. Just as no one would operate on a tumor without having learned to do so beforehand, it is unreasonable to attempt to reinvent or improvise research methods.

Table 2. The FINER Rule

Feasible	Will it be feasible to answer our question? We should have the necessary resources and knowledge, see sufficient study patients (or, rather, sufficient results), and the question should not be too vague or wide-ranging.
Interesting	Is the question interesting to the researcher? The amount of time invested in the question requires that it satisfy our needs.
Novel	Will it generate new findings? Will it enhance existing information by avoiding the possible errors of previous studies?
Ethical	Can we answer our question while respecting the principles of ethics and fulfilling our obligations to patients?
Relevant	Will it change our working method in clinical practice or in research?

Adapted from Hulley.[13] A research question is sound if it can be answered by fulfilling the 5 requirements that make up the acronym. If our question does not fulfill these conditions, then it could be modified in such a way that it does fulfill them. We should try to assess the questions that underwent the PICO approach.

Second Step: Organizing the Study. The Protocol

The organization of a study requires a written protocol. Depending on the complexity of the study, a protocol can be as short as a couple of pages "for internal use only" (eg, a case series), or as long as several volumes in the case of multicenter clinical trials.

We should avoid participating in research studies that do not have a written protocol. There are 3 basic reasons for such a categorical statement. First, the Declaration of Helsinki for the protection of human subjects stipulates that "the design and performance of each research study involving human subjects must be clearly described in a research protocol."[17] This statement is the basis of all legislation, and scientific journals demand that published articles adhere to these legal requirements.

Second, we must make every effort not to waste time or medical resources. Developing a written protocol requires us to analyze many aspects of our study before taking action. At this stage, our objective should be to weed out potential problems in the development of the study in order to avoid them or minimize their importance. When a study is still at the project stage, it is easy to introduce changes that can improve it. As the project advances, this becomes increasingly difficult. How often have we seen studies in which, after months of collecting data, a basic aspect has been overlooked, thus preventing conclusions from being drawn? Or studies with no clear objectives that seem to go on forever? Good planning may seem more laborious at the outset, although in the long term it makes for a more ethical, useful, easy, and gratifying study.

Lastly, a written protocol is necessary if we are to obtain authorization from the ethics committee and request funding. When reporting the results of the study, the protocol provides an excellent script to follow.

The structure of a protocol can show us the aspects of the study to be defined, as well as the techniques to be mastered (Table 3).[18] Even if we draw up a short protocol for a very simple study, it is worth reviewing each and every point, as this will provide us with ideas and prevent errors.

The choice of study design is paramount, and, in most cases, will depend on the type of question to be answered (Table 4). Investigators new to research should act wisely and begin by becoming involved in short studies. This is easier in the case of common diseases and in retrospective cohort, case-control, or cross-sectional studies, and if research questions that can be answered using these designs are chosen. Cohort studies and clinical trials are much more complex to perform, and are more suited to areas where there are more resources and experience.

Other important aspects the clinical investigator must take into consideration range from the ability to organize work for a group, including a clear definition of responsibilities and authorship of the resulting articles, to how to publish the findings in a written communication or paper.[19,20] The bibliography contains basic texts for those who wish to learn more about these aspects.[7,10,13,19,20]

In summary, the main idea put forward by the present article is that there must be research based on clinical practice. If a physician is considering carrying out research, then clinical research must be the first option. Therefore, we propose that all dermatologists, especially those in

Table 3. Practical Map of Epidemiologic Knowledge: Relationship Between the Parts of a Protocol and the Theoretical Knowledge Necessary to Produce It

Section of Protocol	*Relevant Theoretical Knowledge*
Title and collaborators	
Background and rationale	Clinical epidemiology: clinical questions, systematic reviews
Objectives and hypotheses	Contrasting of hypotheses
Methods:	
Description of the study General epidemiology: study designs	
Design	
Site	Measurement of frequency and association
Study population	
Intervention (where applicable)	
Outcome measures: exposure, confounders, outcome	Relationship between outcome measures: randomness, bias, confusion, association, cause
Study population	Sampling and inference. Generalization
Inclusion and exclusion criteria	Case definition. Bias
Reference population: sampling	
Procedures	
Enrollment and follow-up	
Measurements	Measurement errors
Laboratory methodology	Creation of questionnaires
Data collection and processing	Data management
Data analysis	Statistics: assessment of randomness and confusion
Sample size	Calculation of sample size
Ethics: informed consent, ethics assessment	Ethics
Logistics: time, resources, responsibilities	Funding
References	

Table 4. Choice of Study Type According to the Type of Research Question

Type of research question	*Type of Study*
Prevalence or burden of disease	Cross-sectional study
Etiology	Cohort or case-control study
Diagnosis	Cross-sectional study
Prognosis	Cross-sectional study
Treatment	Clinical trial

This is a simple guide, which could be subject to variations

training, must be able to generate research questions (PICO), perform an initial assessment of these questions (FINER), and refine the questions. They must also be aware that, if they wish to answer the questions, their next step must be to obtain methodological support.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Williams HC, Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B, editors. Evidence-based dermatology. 2nd ed. Oxford: Blackwell Publishing/BMJ Books; 2008.

2. Rees J. Complex disease and the new clinical sciences. Science. 2002;296:698-700.
3. Goldstein JL, Brown MS. The clinical investigator: bewitched, bothered, and bewildered–but still beloved. J Clin Invest. 1997;99:2803-12.
4. Wolkenstein P, Latarjet J, Roujeau JC, Duguet C, Boudeau S, Vaillant L, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. Lancet. 1998;352:1586-9.
5. Sabat R, Sterry W, Philipp S, Wolk K. Three decades of psoriasis research: where has it led us? Clin Dermatol. 2007;25:504-9.
6. Wulff H, Pedersen S, Rosenberg R. Philosophy of medicine: an introduction. Oxford: Blackwell Scientific Publications;1986.
7. Naldi L. Metodi di ricerca clinica in dermatologia. Brescia: ISED; 1998.
8. Penso-Assathiany D, Flahault A, Roujeau JC. Verrues, piscine et atopie: étude cas-témoin realisée en cabinet de dermatologie libérale. Ann Dermatol Venereol. 1999;126:696-8.
9. Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358: 2649-51.
10. Sackett DL. Clinical epidemiology: a basic science for clinical medicine. 2nd ed. Boston: Little, Brown; 1991.
11. Haynes RB. Clinical epidemiology: how to do clinical practice research. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
12. Crombie IK, Davies HTO. Developing the research question. Research in health care: design, conduct, and interpretation of health services research. New York: Wiley; 1996. p. 44-64.
13. Hulley SB. Designing clinical research. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
14. The James Lind Alliance. Available from: http://www.lindalliance.org.
15. National Health Service. Database of Uncertainties about the effects of treatments (DUETs). Available from: http://www.duets.nhs.uk.
16. Williams HC. Defining cases. In: Williams HC, Strachan DP, editors. The challenge of dermato-epidemiology. Boca Raton: CRC Press; 1997. p. 13-23.
17. World Medical Association. Declaration of Helsinki. Available from: http://www.wma.net/s/ethicsunit/helsinki.htm
18. Rodríguez del Águila MM, Pérez Vicente S, Sordo del Castillo L, Fernández Sierra MA. Cómo elaborar un protocolo de investigación en salud. Med Clin (Barc). 2007;129:299-302.
19. Huth EJ. Writing and publishing in medicine. 3rd ed. Baltimore: Williams & Wilkins; 1999.
20. Hall GM. How to write a paper. 4th ed. Malden, Mass: Blackwell Publishing; 2008.