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Questioning clinical trials

Interpelando a los ensayos clínicos

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Commentary on: Ugalde A, Homedes N. Four words regarding clinical trials: Science/profit, risks/benefits. Salud Colectiva. 2011;7(2):135-148.

Antonio Ugalde and Núria Homedes present in their article "Four words regarding clinical trials: science/profit, risks/benefits" (1) a series of arguments about the vicissitudes of clinical trial development in Latin America. The four words constitute two binomials, each term in tension with its counterpart. The arguments of the authors are of unquestionable weight and are founded in unobjectionable information that makes them difficult to contradict. The authors focus on clinical trials conducted in Latin America, but the article – fortunately – provides abundant examples that also implicate the so-called central countries in fabrications, concealments and ethical transgressions of great magnitude in research studies carried out in their own territories and on their own citizens. The article could be of great assistance in designing local antidotes to this problem, as reflective and critical analyses of this kind are only developed in certain small circles, with some involvement from the area of bioethics, very little from the health services field and almost none from our universities.

Science or profit

Clinical trials represent one part of the scientific activity that aims at making new drugs available to humans. The first, and maybe the most obscure scientific activity, is that of the discovery and/or the design of molecules that have therapeutic purposes; the second activity is that of demonstrating – using scientific methods – that this therapeutic effect is real and that, in addition to being effective these molecules are safe for the desired purposes. This is the ferrying mechanism of clinical trials: they make the passage from molecule to drug viable. True scientific innovation stems from the discovery and/or design of molecules, while the testing of the qualities of these molecules in people – clinical trials – involve methodological procedures that use standardized and sophisticated statistical tools (2 p. 63- 71). In this sense, the development of clinical experimentation with drugs cannot be considered in and of itself pharmaceutical innovation, an idea which tends to be coarsely and self-interestedly disseminated by the transnational pharmaceutical industry. Another concept connecting science and clinical trials refers to the participation of different fields in scientific activities: the biological disciplines (which could be defined as medicine and physiopathology) and the pharmaceutical disciplines. The overriding question is whether knowledge of physio-pathological mechanisms induces the discovery of molecules capable of interfering in these mechanisms, or if is the other way around, with the chemistry of the molecules shedding new light on the physiopathology. This issue would be secondary if it were simply a reflection on the origin of what stimulates of knowledge, but the question is not innocent: in the framework of the development of the pharmaceutical industry, the chemistry of molecules "produces physio-pathologies" categorized as diseases (2).

What is it that leads the chemistry of molecules to subject physiopathological knowledge?

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And then yet another subjection: that of chemistry to the "methodology of clinical trials." The development of trials within the pharmaceutical industry, and with great financial stimuli, makes it so that

> ...clinical trials are not simply one more test in the perfection of a drug, but in fact the center of the matter, the point where the scientific, medical and financial aspects intertwine in order to determine what will earn the title of progress and allow a lot of money to be made. (2)

The pharmaceutical industry itself states that its activity is an industry, and obscenely refers to itself as an industry without chimneys (3), thus associating itself as if in passing with tourism, the business activity usually referred to in this way. This industry represents for the transnational pharmaceutical industries an essential base from which to expand profits, far from providing authentic pharmaceutical innovations to the world. The issue of innovation is thoroughly analyzed by M. Angell (4), who states that, in the five-year period of 1998-2002, the Food and Drug Administration (FDA) approved no more than twelve innovative drugs per year, which amounts to only 14% of the total licenses granted (4 p.76-77).

But where do the substantial profits for the pharma industry come from if there is so little innovation? The answer is found putting a new face on molecules of known drugs, that is to say, modifying them only slightly: these are the "me-too" drugs. And in this way the industry without chimneys puts its machinery in motion to justify that the new drugs are no less effective than the previous drugs, or more effective than placebos.

The displacement of clinical research development from university centers to for-profit clinical research organizations – the so-called Contract Research Organizations (CRO) – fostered by the industry itself to guarantee total control over the design and execution of the trials and above all of their results, is the background that explains the frauds and data falsifying that Ugalde and Homedes comment upon: "It is no longer the researchers but rather the sponsors who control the clinical trials" (4 p.123).

Clinical trials are a particular type of scientific activity, for the reasons mentioned above and because they convene a particular type of researcher, mainly pragmatic doctors. These are strange creatures within the canons of traditional scientific research because they do not participate in the identification and definition of the research question, in the formulation of the hypothesis, in the design of study protocol, in the analysis of the data collected; and they have no knowledge of the study's results. Ugalde and Homedes called them *maquiladores*, a sort of subject/object of an assembly line.

In the last five years in Argentina, criticism of the way clinical trials have been conducted from the a bioethics and human rights point of view has increased, particularly due to the events that took place in studies with vaccines in children (5) that were made public (6), and due to the subsequent sanctions imposed on the principal researchers and the sponsoring laboratory by the national regulatory body (ANMAT) and ratified judicially (7). Even so, the transnational pharmaceutical industry still imposes industrial-business logic in clinical research as a source of foreign capital for the country, an opportunity for the transference of technology and way of establishing investments. As Ugalde and Homedes correctly assert, "the governments of the region have accepted the industry's rationalization" (1). In Argentina, the transnational pharmaceutical laboratories propose improving the balance of trade by bringing more clinical trials into the country (8), and from the economy and business sectors within the executive power mechanisms are created to foster such proposals (9). The previous comment regarding the smallness of the spaces open to critical reflection regarding these issues is thus made evident, as they are unable to introduce such issues into the political agenda of the government.

Risk or benefit

The previous commentary does not serve as impediment for considering the randomized clinical trial to be a (or the) paradigm within the medical research. The most widespread precautionary measures regarding clinical trials address methodological concerns deriving

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from the existence of factors that threaten the quality of the information acquired. Ugalde and Homedes go even further to detect mistakes that escape purely methodological considerations. As a complement to the observations of these authors and, fortunately, removed from such lukewarm methodological objections, it is possible to find within the core of medical empiricism excellent analyses that grant a comprehensive view of limits and risks in the assessment of randomized and controlled clinical studies. A highly circulated publication among cardiology practitioners of Argentina regarding evidence in cardiology dedicates an entire chapter to the detailed analysis of what is true and what is false in medical publications (10). Using as a basis a "classification of falsehoods" it takes on considerations of fraud, manipulation and concealment of information, physio-patological truths and clinical falsehoods, etc. Regretfully, pragmatic doctors tend to constrain themselves to a methodological trust in a statistically significant p-value of less than 0.05 or 0.01 as criterion of truth, and to the opinion of experts from well-regarded journals (10).

And what of the benefits of clinical trials? This is the second term, the other half of the question asked by the second binomial. On this subject I prefer to reiterate the conclusions of Ugalde and Homedes: "In the dichotomies science/profit and risk/benefit, clinical trials presently represent more profit than science, and, for the poor participants, imply more risks than benefits" (1).

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