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Toward independent clinical trials in Latin America. Comments on "Four words regarding clinical trials"

Hacia la investigación clínica independiente en América Latina. Un comentario a "Cuatro palabras sobre 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.

The article in question (1) puts into discussion the relevance of the clinical research carried out by the multinational pharmaceutical industry in Latin America. I share the ethical qualms and the profound concern over the powerlessness of our patients, professionals, institutions and control mechanisms when facing the development of projects with commercial interests (2). There is no doubt that the best response is the consolidation of ethics committees independent from the pharmaceutical industry, with an institutional base and with members trained in clinical and bioethical research. Currently, in the province of Buenos Aires, the recategorization of bioethics committees is being undertaken with great effort, outlining the necessary skills and level of training as well as the conditions necessary for protocol assessment to take into account the scientific interest of the protocol and the protection of patients' rights (3). Similar efforts have been undertaken in the province of Cordoba with good results (4).

One of the main weaknesses preventing an adequate analysis is the lack of training or of previous participation in clinical trials, as well as lack of instruction in clinical research in undergraduate and graduate courses.

The invasion of multicentric research studies funded by the industry in Latin American countries has had multiple effects on various levels. As the authors highlight, we should not believe that all they offer is virtuous and beneficial, as the official rhetoric of its promoters asserts. But I am afraid that it would be a mistake of equally negative consequences to assume that all is fraud, corruption and manipulation in multicentric clinical research.

I shall provide some information that may contribute to the debate in this sense.

A brief history of recent clinical research

Clinical research and controlled trials, from their initial implementation in the European postwar period in a study organized by Bradford Hill to test streptomycin in patients with tuberculosis and funded by the British Medical Research Council (5), have permitted an extraordinary growth of solid scientific proof with which to evaluate the benefits and risks of pharmacological and non-pharmacological therapeutic interventions. Evidence-based medicine (EBM) is unthinkable without reliable scientific proof of the usefulness of interventions. Even though EBM may be criticized from different perspectives and with good reason, a medicine that is not based in scientific proofs or that ignores them is no alternative.

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In the field of cardiology, it is illustrative to recall that, in 1975, the treatment of heart attacks during the first hours and throughout its progress was prolonged rest. Mortality during hospitalization was 12-15% and in the first year 5% of the patients died; the percentage was even greater in higher-risk groups. Currently, we have interventions that reduce in-hospital mortality by half and long term mortality by 80%, thus extending patients' lives by 10 to 12 years (6). Implementation of thrombolitics, primary angioplasty, aspirin, beta blockers, angiotensin-converting enzyme inhibitors, statins, anti-aldosterone treatment in the event of cardiac insufficiency, among other interventions, have arisen from large scale, multi-centered controlled trials, often with Latin American participants. The first trials were promoted by non-profit collaborative networks such as the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico* (GISSI) directed by the Mario Negri Institute of Milan and the ISIS group of Oxford University, following in the footsteps of Bradford Hill, with very limited support from the pharmaceutical industry. This model of large-scale multi-centered studies was later taken up by the industry as the principal way of introducing new drugs to the specialty of cardiology, generating the immense corporate complex of current clinical research. Cardiovascular mortality in Argentina has been decreasing in the last decades, and we can hypothesize that part of this improvement is due to the medications or interventions mentioned above (7).

The same could be said regarding other areas of cardiology such as cardiac insufficiency or primary prevention in high-risk groups, as well as regarding other pathologies with high mortality.

As a product of the expansion of useful treatments in cardiovascular pathologies, it is extremely difficult to introduce new drugs that considerably reduce morbility and mortality. This has led to the proliferation of me-too studies, trials with an ethical limit of non-inferiority, and to the selection of efficacy criteria that are not based in mortality, which are in many cases disputable or controversial (8). This strengthens the idea expressed by the authors of evaluating each individual proposal in terms of its relevance to potential findings beneficial to the community.

Ethic and clinical research education before multi-centered trials in Argentina: A personal confession

In his best-known work (9) Lefanu comments on the total freedom and paternalism with which drug research was conducted in patients with different pathologies in university hospitals immediately after the war, from which came most of the pharmacological groups currently acknowledged as valued therapeutics. This research was carried out paying scarce attention to the standards already existing as regulatory guidelines. The same situation persisted in Argentina until the start of multi-centered trials in the second half of the 1980s. As an intern at the Hospital Italiano de Buenos Aires and then Head of the Coronary Unit of the Hospital Argerich, I took part in multiple studies based on the ideas of the medical groups conducting them, totally ignorant of the need for informed consent, ethics committees, or anything of the kind. In Argentina, it was also uncommon to request informed consent for interventions or diagnostic procedures, as the medical practice remained sheltered from the lawsuit industry. At the beginning of the 1990s, I held the position that in Argentina we should avoid requesting the signature of patients and relatives to include them in protocols regarding acute pathologies, which of course inspired horror in the organizers of multi-centered trials and would have not been accepted by the Food and Drug Administration (FDA). At that time, there were neither reliable nor adequately trained regulatory authorities; the protocols were presented locally and if after 90 days there had been no response, the study was conducted. The authorization often came through after the trial ended.

I would like to provide an explanation of the position I held at the time, which is now amusingly outdated and almost anti-humanitarian. In those days, we were completely isolated from the malpractice lawsuit industry, and trust was still maintained in the paternalist medical institution. In our hospitals and clinics the practice of asking for signatures to authorize procedures did not exist. Relatives were only asked to sign if an intervention was to be performed on critical patients with unknown

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results. I remember receiving a desperate call from one of my aunts, who told me that they would not operate on her husband's hip fracture if she did not sign, because he had a history of severe coronaropathy. "They are asking me to sign" was a synonym for doubt that he could survive the surgery. In the context of a patient suffering from precordial pain and the decision to compare thrombolytics, for example, reading a three-page consent form and assessing its content was absolutely impossible. Therefore, in my opinion, if the physician briefly explained the essence of the protocol to the patient before a witness, verbal consent was sufficient.

We did not get paid for the studies at that times and I truly did not imagine that someone would try to lie in this context. It seemed cruel and artificial to ask for a signature, which also arose from the confidence in the physician's word in a difficult situation. At that time, a journal editorial used the phrase "ethical imperialism" to refer to the imposition of American standards on the medical practice of other countries with different medical cultures (10).

The dynamics of the multi-centered trials led to the creation and training of regulatory authorities, as well as the gradual creation of private and hospital ethics committees. Research regulation did not arise from the demands of ethicists, but rather from the collateral effect of the need for the validation of local authorities in order to develop international multi-centered studies.

Multi-centered studies with local ideas and voluntary networks

We started to overcome our lack of training and experience in clinical research with new local projects, at least in cardiology: the Multi-centered Study of Streptokinase in the South American Republics (EMERAS, from the Spanish *Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur*) (11), the Study Group of Survival in Cardiac Insufficiency in Argentina (GESICA, from the Spanish *Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina*) (12), Enalapril in Unstable Angina: A Multi-Centered Study (ENAI, from the Spanish *Enalapril en angina inestable*) (13,14), the GEMICA study (from the Spanish *Grupo de Estudios Multicéntricos de Infartos con Amiodarona*) (15), among others, included thousands of patients in non-profit trials, motivated by the requests of physicians and with little support from the industry. These studies were conducted in the 1990s according to the customs of the time and perhaps would not comply with the ethical requirements we currently demand, but they resulted in the creation of a small critic mass of physicians trained in clinical research. Nevertheless, we still lack adequate structures for the training and economic support needed for independent research.

The authors remark that the industry is not interested in pathologies that, due to their prevalence or distribution, will not provide benefits to the industry. But what is worse, we must acknowledge, is that the State and the community are not interested in them either, because they have not yet been addressed with the seriousness and the structure they require.

I believe that the current challenge, in order to establish clinical research that meets the needs of our patients, in collaboration with universal scientific developments and with the highest academic standards, requires the achievement of several objectives:

1) The consolidation of ethics committees independent from the pharmaceutical industry, preferably linked to the university and academic care facilities, conformed by physicians trained in clinical research, bioethicists and members of the community. These committees would necessary receive payment due to the complexity of the tasks of supervision of adverse effects, protocol modifications, amendments.
2) The development of public settings of bioethical debate in which the conceptual guidelines for difficult decisions can be discussed. I think for example of myocardial infarction, perhaps the most studied pathology in controlled trials, and for which study results have had the greatest impact in decreasing mortality. I have heard and read the opinions of bioethicists about the lack of ethics in researching patients with severe pathologies (difficulty in respecting the principle of autonomy, etc.); if such opinions

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had prevailed, today we would have thousands more deaths per year only in Argentina, deaths that were avoided with the results of these trials. This is a complex dilemma whose solution must not be lack of research.

3) The creation of new courses and master's degree programs in clinical research, with practical experiences in existing projects and objectives related to public health, in order to reach the critical mass that will allow us to address health problems with competence and scientific fundaments.

4) To establish work hours and positions dedicated to research in public hospitals and academic institutions. This objective necessary implies that part of public funding for research be directed towards clinical research.

An epilogue on new drugs to escape the paradox

In one paragraph the authors highlight the suggestion made by another author to readers and future users to wait seven years before taking a recently patented drug, with the aim of accumulating experiences about its safety. The authors then rightly state that that if this suggestion were implemented no experience would be accumulated and, thus, new drugs would simply not exist. To escape this paradox that refers us to Achilles and the tortoise, I send a decalogue for the introduction of new drugs in chronic pathologies for which drugs already exist (16). This decalogue attempts to contemplate the real context in which this problem occurs and the precautions we can take into account in its inclusion.

Decalogue for the prescription of new drugs for chronic use

1) Due to the complex network of interests involved, new drugs should be regarding with a critical eye. Blind trust in the FDA, the European Medicines Agency (EMA), the National Administration of Drugs, Food and Medical Technology (ANMAT, from the Spanish *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*), medical sales representatives, experts and the agreements should be avoided.

2) It is probable that only ineffective drugs or interventions will be innocuous. All active drugs interfere with a number of biological mechanisms of which we are only familiar with a part, sometimes a minor part. We should remember that the word phármakon in Greek means both medicine and poison.

3) The chain of events arising from the prescription of a drug is so important that any decision about it must be considered carefully and responsibly.

4) Due to the particular condition of chronic pathologies, it is advisable to prescribe drugs only when non-pharmacological measures were unable to resolve the medical issue. This suggestion is applicable to any medical field, and especially to psycho-affective problems.

5) Drug selection should be based on pragmatic trials when they are available.

   a) Prescription on the basis of the drug action mechanisms should be limited to patients with rare pathologies not solved by other interventions.

   b) For common pathologies, a drug whose main effect is a new physio-pathological mechanism should not be considered revolutionary until such a time as there is information available from "pragmatic" clinical trials; that is to say, until it is shown that they have improved essential aspects of the disease such as quality of life and survival rates.

6) The inclusion of a new drug in place of an effective "old" drug should not be guided by any criteria other the welfare of the patient.

   a) The availability of free samples, dependency on medical sales representatives or the industry, and interest in demonstrating to the patient that new drugs are used should not be logical criteria for choosing new drugs.

   b) It is only worth testing a new drug when the available therapies are not able to control the problem or do so at the expense of unacceptable collateral effects. Even if an unforeseen risk is discovered with a new drug years after its implementation, this risk will have been assumed in benefit of the patient, as an attempt to alleviate an illness that could not be controlled in another better way. If the prescription of the new drug was due to arbitrary criteria or because the drug was "in fashion," this risk would be deemed unacceptable.

7) A contribution should only be considered revolutionary when the drug in a pragmatic trial solves a problem for which there is no alternative strategy.

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When a historical alternative already exists, it is preferable to wait for a direct comparison, given that indirect comparisons in several opportunities have not been confirmed after the relevant comparative trials have been performed.

8) It is not advisable to suspend the administration of drugs with known capacity to extend life and prevent serious medical events when there is a slight suspicion of minor collateral effects. "Not every cough comes from ACE inhibitors and not all sexual dysfunction comes from beta blockers."

9) The conscious use of placebos may be a powerful evidence-based weapon.

10) It should not be considered ethical to be rewarded by the industry for prescribing a drug.

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