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The precautionary principle in biomedical research, safety, post-research obligations and alleged therapeutic efficacy of experimental drugs. Violations of patient dignity

Principio de precaución en investigación biomédica, seguridad, obligaciones post-investigación y eficacia terapéutica supuesta de las drogas experimentales. Violaciones a la dignidad de los pacientes

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It is commonplace to assert that a new drug must have more therapeutic benefits than risks associated with taking it. However, from the selection of the drug that will be placed under experimental study to the design of the protocol, from the implementation of a trial to the analysis of data, from the approval of a drug by the regulatory body to its sale on the market, the search for profit on the part of the pharmaceutical companies comes into tension with the need for new drugs to prevent and treat diseases. In this sense, the work of Ugalde and Homedes (1) provides a thorough and interesting, albeit worrying, look at the present situation.

So long as the efficacy and safety of experimental drugs are uncertain, they should be subject to study in humans according to the principle of precaution. This approach is applicable in environmental ethics but must be extended to include biomedical research as well.

Ramón Alcoberro (2) explains that the concept of "precaution" does not necessarily entail a negative view of technoscience nor a restriction of research, but it does require being conscious of the responsibility implied in each and every phase of the technoscientific process. Making decisions in conditions that are unknown or uncertain demands an attitude of precaution, which is different from one of prevention (when we are aware of the risks and their probabilities) or of precautionary prevention (when we are aware of the risks but not their probabilities) (3). Taking into account the body of known information and the information provided by Ugalde and Homedes, we still have a way to go before the precautionary principle becomes a rule in the pharmacological clinical trials tested in humans.

Examples of the absence of the precautionary principle include the limited demands the regulatory agencies place on the Clinical Trial Data Monitoring Committees (CTDMC) (4,5), also referred to as Data and Safety Monitoring Boards (DSMBs) (6). These entities are defined as:

> [an] external board established by the sponsor to evaluate, in pre-established intervals of time, the progress of a clinical study, the data regarding safety, and the critical points for evaluating efficacy, in order to *recommend* whether the study should be continued, modified, or stopped. (7) (Italics added)

For the Food and Drug Administration (FDA), the CTDMC are required solely in emergency studies in which it is not possible to take informed consent. The committees are only recommended in other studies, for example large, randomized multisite studies which are intended to prolong life or reduce the risk of a

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major adverse health problem such as a cardiovascular event or cancer recurrence. Generally, according to the FDA, the CTDMC are not necessary in the majority of clinical trials. The World Health Organization (WHO) describes at length situations in which DSMBs may be required but it does not portray them as essential. In Argentina, provision 6677/10 of the National Administration of Drugs, Food and Medical Technology (ANMAT, from the Spanish *Administración Nacional de Medicamentos, Alimentos y Tecnología Médica*) states that "the sponsor may convene an independent data monitoring board" (7), but currently does not require it. In this way, we can find extended trials aimed at relieving minor symptoms, but that entail serious and unexpected consequences in the experimental stage; as the general risk-benefit analysis rests completely on the sponsor, in the research process as well as in the determination of the continuity or the termination of the study, the analyses and the decisions made are biased.

On the other hand, the independence of the CTDMC is controversial because in spite of being "external to the sponsor," the members are appointed and paid by the sponsor. Indeed, in addition to the safety controls implemented in clinical trials and grounded in the precautionary principle, it is necessary to discuss a higher level of rigor, authority and independence related to the CTDMC.

Ugalde and Humedes criticize the pharmaceutical industry's claims that the foreign capital benefits the country in which the research takes place. The Argentine Chamber of Medical Specialties (CAEME, from the Spanish Cámara Argentina de Especialidades Medicinales) expresses a similar idea in an article entitled, interestingly enough, *"Estudios clínicos, industria sin chimeneas"* [Clinical trials, industry without chimneys] (8). It may be added that the "canned" research of sponsors from the industry (in which the design, protocol and analysis of results are not carried out by the "researcher") not only mistakes the role of a researcher with that of a recruiter of patients, thereby often redirecting human resources that could be devoted to research studies based in local needs, but also, in some occasions, as happened in the COMPAS study highlighted by the authors, turns the medical professional into a "Body Hunter" (9), infringing not only the patients' but also the doctors' dignity.

Sponsors as well as many researchers state that patients recruited for a research study benefit from better medical care. It is true that, as a consequence of the research process, patients have more medical check-ups, but if the patient was already receiving proper medical care these added visits do not provide additional benefits. On the other hand, if the patient was not receiving proper medical care (as happens in marginalized populations in which access to medical care is limited), the patient will be under more control during the study, but his or her medical care will truly improve if the researcher commits to comply with the requirements of Article 33 of the 2008 Declaration of Helsinki which states:

> At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study *or to other appropriate care or benefits*. (10) (Italics added)

This means that beyond the results of the study, patients should enjoy the same beneficial accessibility provided by the sponsor and the researcher after the study is concluded. The opposite situation would mean that the patient was used as an instrument (thereby affecting his or her dignity) for the period of time that the research was conducted. In the same publication of the CAEME mentioned previously, it is stated that:

> ...the primary beneficiaries of this [research] process are the patients because they can access the *most advanced* treatments that are *not yet available* [and that] those who participate in a clinical trial have access to services with high quality standards in terms of medical interventions and professional care during and after the development of the study. *Moreover, they receive early and extended access to medications that may completely change the prognosis of their disease.* (8) (Italics added)

This confusion between a tested treatment and an experimental drug (whose therapeutic efficacy and adverse effects are unknown), if transmitted to the patient in the informed consent, would amount to a deception that could induce inappropriate participation in the study. Provision 6677/10 of the ANMAT, in the section regarding to notifications, states that "it shall not be indicated in an explicit or implicit way that the product being researched is effective and/or safe or that it is equivalent to or better than other existing products" (7). The industry text cited above evidently transgresses this criterion, leading to a clear violation of the patient's dignity.

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