

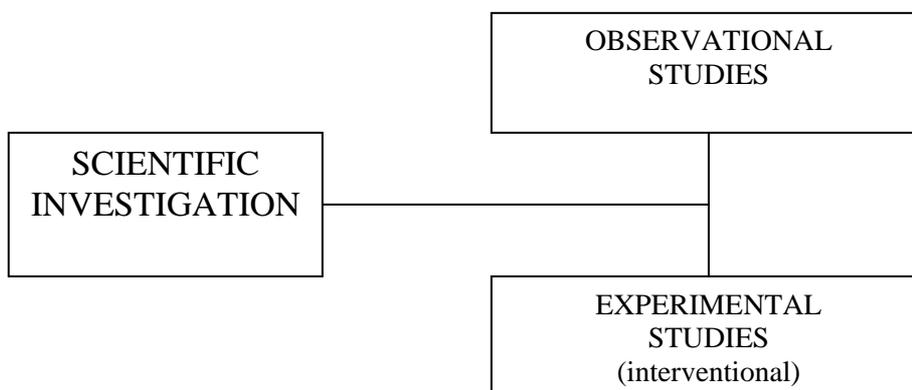
ETHICS OF CLINICAL TRIALS*

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INTRODUCTION

Broadly, we can affirm that an investigation can be observational or experimental. In the first case the investigator only observes a natural phenomenon while in the second, he/she intervenes in order to modify such phenomenon or to create an artificial phenomenon. Clinical trials correspond to this second group.

A clinical trial is a study involving human beings that tries to determine if an intervention, including procedures of treatment and diagnosis, can improve the health of the person. It can involve a medication, surgery, therapy, a preventive procedure, a therapeutic device or service, which is already preventive or diagnostic. This definition corresponds to the habitual concept of “clinical investigation.” A clinical investigation implicates the application of any practice that affects the health-sickness process in a human being having a cognitive objective; it is to say, with the intention of obtaining knowledge of the aforementioned practice. They include all those procedures that influence the promotion of health, the prevention of illness, its diagnosis, treatment or prognosis, and the rehabilitation of patients.



The objectives and the design of the investigation must involve an improvement in the therapeutic expectation. The purely promotional investigations (those which tend to meet market quotas), those already accomplished, those of repeated products, or those of products that promote a scarce increase in therapeutic capacity must be considered to have limited scientific contribution and minimal social value, with which their chance of being considered, should be specially calibrated in terms of the avoidable risks that the participating subjects assume.

According to The Medicine Law of Spain, a clinical trial is oriented toward some of the following purposes: a) to make known the pharmacodynamic effects of the

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experimental medication or to recover data concerning its absorption, distribution, metabolism and excretion in the human organism; b) to establish the medicine's effectiveness for a therapeutic, prophylactic indication or determined diagnosis; and c) to know the profile of the medication's adverse reactions and to establish its security.

In light of the possibility of adverse effects, the process of experimentation begins with previous basic preliminary experimentation, that comprehends the laboratory studies, analytical studies *in vitro*, and later, trials on animals, destined to confirm the effect of the medicine, the purity of the product and its toxicological state.

Nevertheless these procedures, the trials with animals are considered insufficient for diverse reasons: for example, the difference of the psychological processes between humans and animals, the fact that there are illnesses impossible to reproduce in animals or the variety of responses that exist among species.

In general, the preclinical studies are designed to confirm the effects of the medicine and its innocuousness, investigating the lethal dose, the acute, sub-acute and chronic toxicity, such as the capacity of teratogenesis, mutagenesis and carcinogenesis(1).

TYPES OF CLINICAL TRIALS

1. Free or Open Clinical Trial

The value of the effects of the new therapy is determined by comparison with previous experiences relative to the evolution of the disease and to the effect of other treatments; for this reason, these comparisons frequently are denominated "historical controls." The problems with this class of studies are

- a) The illnesses, their virulence and their clinical course vary with time.
- b) The diagnosis also varies with time.
- c) The hospitable installations tend to improve, as well as the care applied to the patients

2. Controlled Clinical Essay

The effects of the new treatment are compared with the evolution of the persons that have not received any therapy or that receive habitual treatment. Comparing these effects with those of the placebo has the purpose of providing evidence of a determined therapeutic effect (generally phase II) while comparing it with an active medication, has the purpose of showing a difference in the benefit/risk relationship in a concrete clinical situation (generally phase III).

The members of a parallel control group should present similar characteristics in terms of illness, age, sex, demographics and social competitors.

3. Controlled, Randomized Clinical Essays

One method of establishing a control group is randomization that consists of arbitrary selection of who is going to be in the control group and who is going to benefit from the experimental therapy. The randomized clinical trial is the methodical gadget most representative of medicine in the 20th century in its biological slope. The trial supposes that interventions, medicines or devices are compared in order to assert whether one or more are better than their equivalents, if they add any advantage or promote any benefit. The scientific confirmation of the treatments' efficiency is needed and it is

accomplished by comparative measurement using statistics; the periodic confirmation of efficiency of determined treatments is now viewed as a reasonable necessity and these necessary experimental and clinical tests are now done even to guarantee preexisting therapeutic practices.

The controlled clinical tests are at times necessary to confirm that an observed effect, like the decrease in mortality rate of an illness, is the result of a particular intervention rather than the result of an unknown variable in the patient population. In controlled clinical tests, a group receives the experimental therapy, while a control group receives no treatment, a standard treatment or a placebo (a pharmacological or biomedical substance or procedure inert to the condition of the patient). This allows researchers to determine if the experimental therapy is more effective and secure than the standard therapy or the placebo.

The randomization is based on the theory of probability and demands the selection of the subjects at random. In order to exercise randomization, ethics demand security, for example, that a patient has identical probability to receive the investigated drug, the previously used drug or the placebo with which it is compared; the same in the event that new surgical techniques are investigated. In experiments of this nature, placebos and new techniques cannot be exposed to people whose condition is presumed to worsen in cases where the most effective therapy known up until now is not used.

There are illnesses—such as psychiatric diseases like paranoia, schizophrenia, general paralysis and Alzheimer’s disease—that are impossible to observe or reproduce in animals; in cases such as these the experiments with drugs are initiated in animals, only to see their innocuousness to corporal structures, and only after experiments are carried out in human beings, rigorously following the rules of the clinical method. At times, however, when it is a question of serious illnesses that can lead to dementia or has a dementia component—like Alzheimer’s disease or schizophrenia respectively—, it is reasonable by analogy to skip the investigation in animals, provided that the step practiced is known to be more innocuous and controllable than the harm it pretends to cure.

TYPES OF CLINICAL TRIALS		
FREE OR OPEN	CONTROLLED	CONTROLLED RANDOMIZED
With historical controls	With control group: <ul style="list-style-type: none"> • Placebo • Active medicine 	With control group: <ul style="list-style-type: none"> • Placebo • Active medicine
Unreliable		Random distribution: <ul style="list-style-type: none"> • Simple blind • Double blind

PHASES OF CLINICAL TRIALS

Normally the development of clinical trials in human beings is structured into four phases (*1, p. 29-31*), which are distinguished in terms of their objectives in relation with the clinical development of the medication. The phases serve to describe the state of the experimental development of a compound as much as they characterize a determined type of study.

Phase I. Clinical Pharmacology.

It consists in the introduction of a drug in a human being (after it is tested on animals). Paul Ehrlich, at the beginning of the 20th century expounded that experimental pharmacology was necessary but not sufficient, requiring experimental therapeutics in humans before clinical therapeutics.

It is necessary to carry out clinical trials before the approval of new drugs or medication in order to know the best pharmacological action of products that are going to be utilized, as much in their pharmacodynamic over different organs, as in the pharmacokinetic aspect of the molecule (absorption, distribution in the organism, excretion), as the future dosage of the medicine in terms of pathology, or the collateral effects. These clinical trials:

- Can be used in “normal” volunteers to determine the level of toxicity and the pharmacological effects (how it is absorbed, distributed, metabolized, and eliminated in the organism).
- Can be followed in early studies of dose levels and, in some cases, to obtain initial evidence of their effectiveness.
- Serve to observe the general effects of the substance and to obtain data about the appropriate doses and the toxicity of the new medicine so that their effects are not confused with complications or symptoms of the illness.

On occasions it is not ethical to utilize healthy subjects, as in the case of either especially toxic medications or those intended for treatment of very serious diseases. These trials are open, with regards to the number of subjects but they are not controllable.

The clinical trials in phase I can present ethical difficulties for its accomplishment. For example, in the informed consent for oncology studies of drugs in phase I, the following should be explained (even though frequently it is not done) to cancer patients.

- 1) The purpose of the study is to find the highest dosage that the person can tolerate without becoming extremely sick.
- 2) The risks of the study include that the dosage of the drug is going to be increased until the subjects get extremely sick. It is impossible to predict the collateral effects that will be experienced.
- 3) As for the benefits, the study is not performed for the treatment of cancer of the subject. Based on previous experiences, the probability of feeling better or living longer as a result of participating in this study is close to zero. The study is done with the hope that it will provide information that will improve the treatment of others in the future.

Phase II. Clinical Investigation.

Clinical investigation consists of random and controlled clinical trials, designed to demonstrate the effectiveness in a preliminary form, to establish the dose-response relationship and know the variables used to measure the efficiency of the drug and the relative safety of the patients that suffer from the illness for which the treatment is supposed to be effective. Normally this is accomplished with the use of a limited number of patients that are tightly monitored. These investigations are designed to

study the therapeutic effect and also the tolerance and toxicity in the context of the illness.

Phase III. Clinical Trial.

Clinical trials are those with a wide number of patients, some controlled and others not. They are accomplished after the effectiveness has been basically established or, at the very least, established to a certain degree, and have the purpose of gathering additional evidence to determine effectiveness for specific indications and in order to have a more precise definition of the adverse collateral effects. These trials:

- are accomplished attempting to reproduce the conditions of habitual use and considering the alternative therapeutics available.
- are carried out in a sample of patients broader than that of the previous phase, and representative of the general population that would receive the medication.
- are preferably controlled and random.
- tend to obtain conclusions about the activity of a medication in the context of the sickness, assessing the effects on the quality of life, treatment or survival.
- allow to carry out comparative analysis if an accepted medication already exists.

Phase IV. Clinical Trials Post-Commercialization.

These types of trials are accomplished with a product after their commercialization. They can be similar to those of phase I, II and III if they study some aspect not yet appraised or conditions of distinct use from those authorized, as it could be a new indication. They are preferably controlled and random. Their principle objective is to investigate collateral effects not well known and other safety standards. Examples of these trials are:

- 1) Additional studies to explain the occurrence of adverse reactions, to explore specific pharmacological effects or to obtain more information of a circumscriptive nature. In phases I and III, a maximum of two or three thousand people are studied, which does not make it possible to detect adverse reactions of a low frequency. Some of these reactions are produced after very prolonged exposure or with periods of long latency.
- 2) Long-term studies of importance to determine the effects of the drug on morbidity and mortality.
- 3) Clinical trials in populations of patients not adequately studied before launching the medication on the market.
- 4) Clinical trials considering the directions for which the drug will be used, once available.

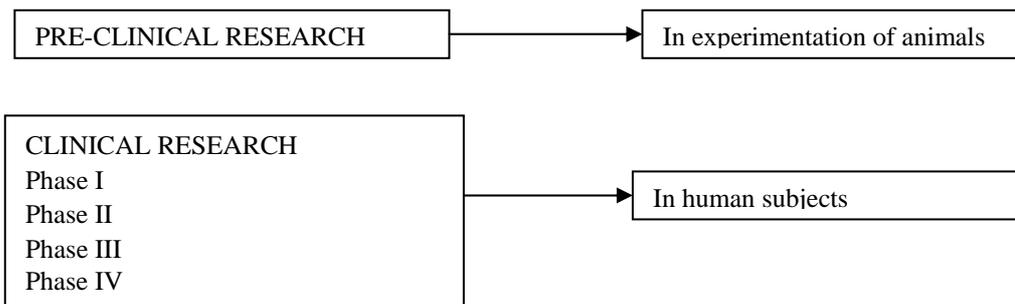


FIGURE PROCESS OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D)

R&D Stage	Research & Discovery	Pre-clinical Development	Phase I	Phase II	Phase III	Registration	Phase IV
Main Activities	Basic exploratory investigation is used to identify objectives, initial investigation is accomplished with new compounds in the laboratory (high throughput screening (HTS), identification and track optimization for selection of more promising compounds.	Selected compounds are studied in animals under Good Laboratory Practices for toxicity and safety; in parallel, specific analytic methods are developed for larger development	Later, the successful compounds are tested in humans in 3 phases of clinical studies: <ul style="list-style-type: none"> Phase I – Safety and tolerability in healthy volunteers. Phase II – Studies of safety, efficiency and bioequivalence in small groups of patients. Phase III- large studies with distinct universes to demonstrate proof of efficiency, safety and value. 			If results of clinical studies are satisfactory by quality, efficiency and safety, a regulatory expedient is presented to the regulatory authorities for approval	Post-marketing studies are initiated with thousands of patients after the launching of the medication to identify whichever collateral effects were not previously foreseen
Rate of success*	Less than 1 %		70 %	50 %	50 %	90 %	N.A.
Time	4-6 years	1 year	1-1.5 years	1-2 years	2-3 years	1-2 years	Several years

* The success rates reflect the quantity of projects that successfully pass to the next stage of R&D.

Source *Platform of Pharmaceutical Innovation*, International Federation of Pharmaceutical Manufacturers & Associations, Fédération Internationale de l'Industrie du Médicament (2004)

What Does it Mean to Investigate with a Placebo?

Carrying out research with a placebo consists of applying a substance or pharmacological proceeding, biomedically inert to the condition of the patient, with the intention of using it as a control to determine the efficiency and safety of an experimental therapy in a clinical trial. The placebo effect refers to the benefits to health, physiological or psychological that are produced by a treatment that should not have any effect. A placebo can take many forms. Sometimes a lump of sugar or another inert substance is used, when a medication is tested. It can also consist of a simulacrum, for example, in acupunctural studies, the placebo group can receive the same application in locations superficially separated from the specific points. An active substance can also be used but one that produces unexpected beneficial effects, like for example, the use of antibiotics for respiratory illnesses of viral origin.

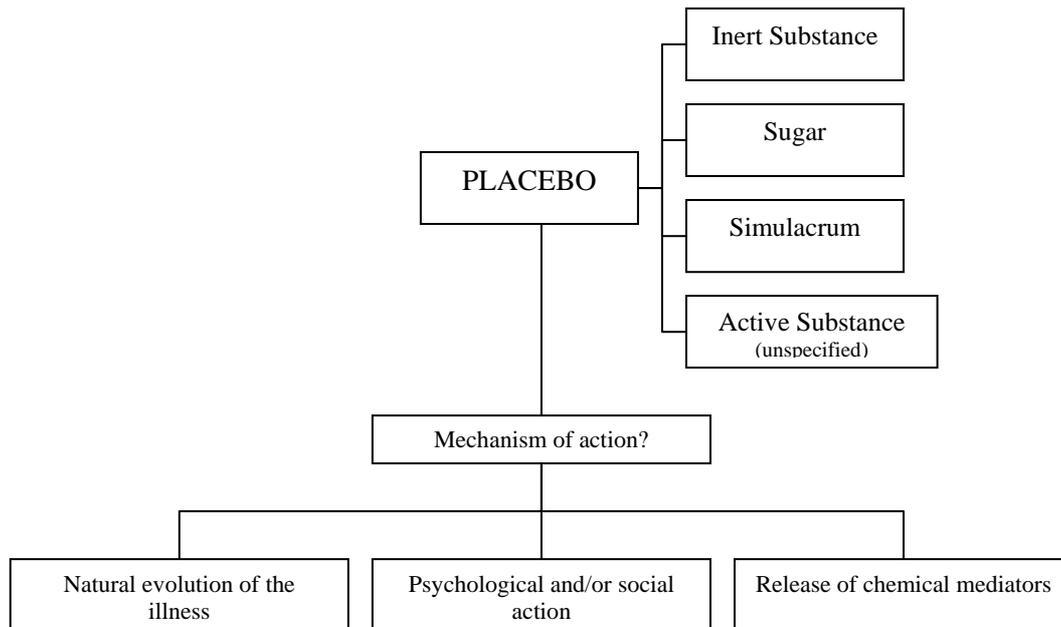
Considerable controversy exists about whether the use of a placebo has any consequence in the medical results. Hrobjartsson and Gotzsche argue that the importance of the placebo effect has been exaggerated; their study reveals that at some times it is confused with regression or the clinical tendency of some illnesses to regress

spontaneously (2). The placebo effect can be overestimated if there is only limited knowledge about the variations of the symptoms of the illness studied. In an illness, there are factors that can be incorrectly attributed to the placebo effect: spontaneous improvement in some patients, fluctuation of symptoms, improvement of medical care during the study and bias in the measure of subjective scales of improvement (3).

Nevertheless, the placebo effect is real. There is scientific evidence proving that the placebo has an analgesic effect that corresponds with the production of opiate neurotransmitters, since antagonistic substances of the opiates nullify the placebo effect (4,5). Also, a placebo can exercise a motor improvement, depending on the release of dopamine in the cerebral cortex, which raises the level of energy and helps with recovery. It has been demonstrated that patients with Parkinson's disease release dopamine in the cerebra in response to the placebo, the same as if an active drug was used (6). Furthermore, recent evidence suggests that the expectation of clinical benefits accelerates the response to placebo as a response mechanism of the organism when it is waiting for recompense (7). Diminishing anxiety can make symptoms disappear that are caused by responses by the body to tensions; the confidence in the treatment increases the possibility of the placebo effect. Each time it is more strongly demonstrated that the placebo effect operates through psychosocial mechanisms, like faith, confidence, conditioning or anticipation. These produce physiological responses that diminish the symptoms of the illness. A recent study shows that there is little difference between the majority of common antidepressants and the placebo effect (8).

One way of explaining the placebo effect is to indicate that those who suffer from symptoms that are repeated by enduring a chronic sickness are often depressed and the depression produces symptoms that the patient attributes to the sickness that he/she endures. The promised hope that receiving treatment produces can make the depressive symptoms disappear and the patient would experience an improvement that could explain the placebo effect.

For the proponents of alternative medicine, the mechanism of action can be the same that produces the placebo effect. The placebo effect appears to be related to similar effects that certain alternative therapies produce like: meditation, devotional practices or religious beliefs. The fact is that the mind and body are not two independent structures contrary to the Cartesian way of thinking; there is an evident interaction between the two.



Scientific Merit of Placebo Use

The randomized clinical trial constitutes one of the methodical advances more representative of the experimentation with new therapies and procedures. The comparisons of two treatments can be of equivalency or superiority. The first type tries to establish if the results show a similar efficiency in both treatments; the second type tries to study if one treatment proves to be superior in efficiency, in the sense that it attaches some advantage or it promotes some benefit. In order to demonstrate scientific reliability, clinical trials are designed to compare the effects of interventions that are investigated —be it therapy, prevention or diagnostics—in subjects assigned to the experimental group, with effects that are produced in subjects of the same population assigned to the control group. Normally, the control group can receive a treatment of proven effectiveness and the results can be compared with the procedure being researched. Yet there are circumstances when the use of a control by placebo in order to obtain scientific validity is necessary; in these cases it is always a question of demonstrating that the treatment in trial is superior to the placebo, on the contrary there is no demonstration of efficiency.

The use of a placebo has various benefits, since it is considered that it generates valid scientific data and, on the other hand:

- 1) It grants a larger grade of objectivity in the measurements.
- 2) It provides protection against possible subconscious desires of the patient to please the researcher.
- 3) It controls attitudes of the patient or the physician that could influence the results of the study.
- 4) It provides some level of protection against fraud, when a patient or a physician has financial or other interests in demonstrating a particular result.
- 5) It requires a smaller sample size to obtain significant statistical differences. Therefore, it invests less time and resources.

It is known that context is important in medical treatment. The words and attitudes of physicians and nurses can have a great impact on the patient; therefore, any investigation can have a hidden placebo effect. The fact that simulating an intervention already produces a difference is not the same as not receiving any treatment. The simple contact with a professional that produces respect can alleviate the anxiety. The benefits of any therapeutic intervention in the clinical practice can be increased by the placebo effect and, on the contrary, adverse responses to the placebo as a consequence of mistrust toward physicians can also be produced(3). Using a placebo as a control eliminates this possible bias, since the results could be very different with the same medication in one study center than in another.

Ethics of Placebo Use

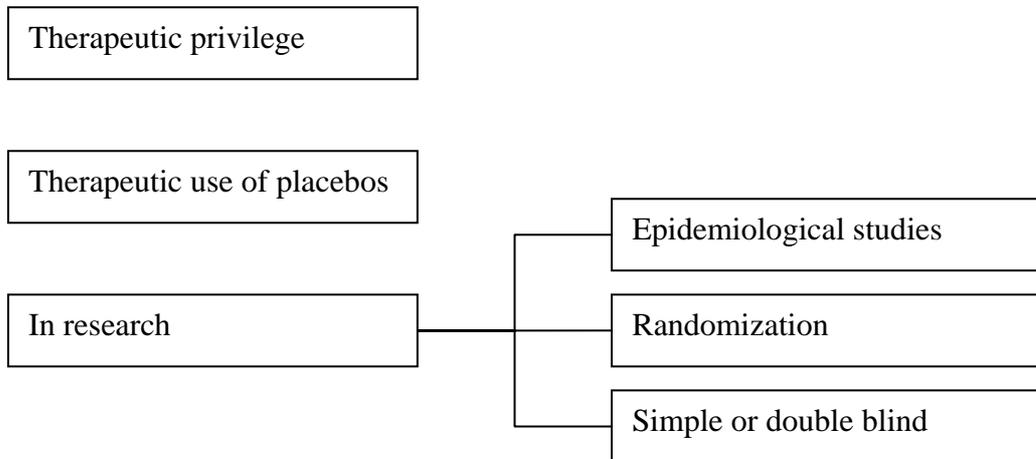
The conflict that a patient involved in a study can fall into a placebo group has serious repercussions for the researcher, for the subject of the investigation and for the study itself. Experimentation using a placebo as a control is inconsiderate of the individual treatment, sacrificing the individual for the good of the society. If the complete information of the procedure is actually given, it is probable that patients will not accept to participate, unless they are guaranteed that they will not receive the placebo.

Research involving human beings is not ethical if the results of the experimentation do not provide useful knowledge. Using placebos in clinical trials has given rise to a lot of worry about ethical dilemmas. There are three questions that need to be answered in order to evaluate the ethicality of placebo use:

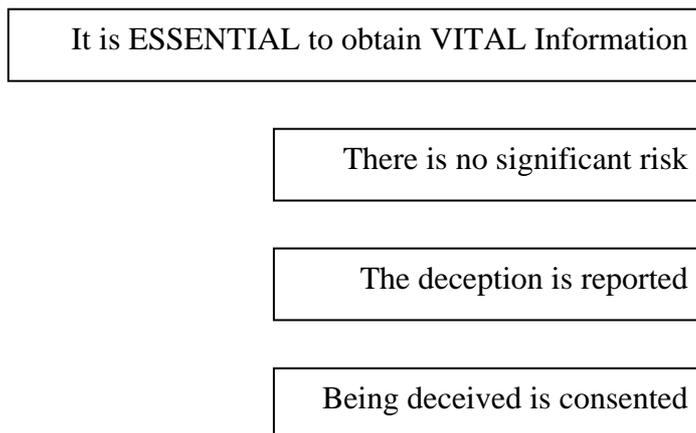
- 1) Will the use of a placebo help to answer relevant scientific questions?
- 2) Is it ethical to hide information from the patient?
- 3) Is it ethical to deny treatment to a patient?

It should be demonstrated that concealing information has scientific merit and would not cause damage to the patient. It should not interfere, for example, with other treatment that the patient is receiving; for this it should be established appropriate restrictions for recruitment of patients to allow that they can renounce to participate in the research at any moment for medical reasons. For that hiding partial information be ethical, generally the patient must be told that he/she is going to participate in a randomized study, that would be assigned as much as the placebo group as the group treated with a medication on trial and that he/she will know to which group was assigned once the study has concluded. The patient should know that information is to be hidden from him/her for purposes of the study.

INTENTIONAL RESERVATION OF INFORMATION
(intentional secret)



The DECEPTION is justified only if:

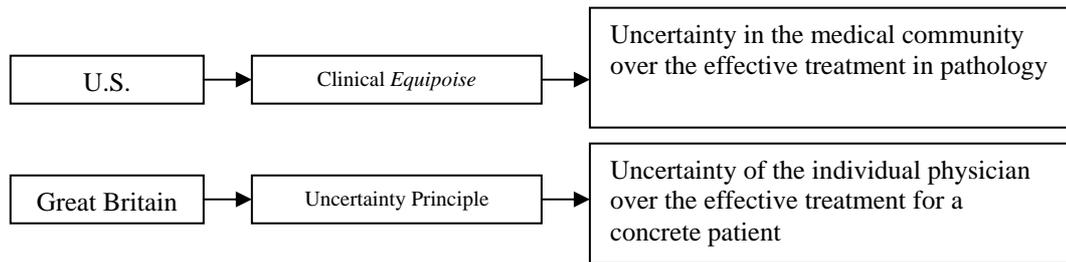


The researcher is obligated to justify why it is necessary to use a placebo as the control, both to the subject and to the scientific ethical review committee. In the design of a clinical trial to prove the effectiveness of a new medication, when there already exists a medication of proven effectiveness, the trial should be carry out comparing the efficiency of the new medication with that of the already existent one, unless it is ethically justified to use a placebo. The use of placebos in trials of small samples has been criticized, since the measurements are subject to considerable statistical error and the study does not serve to answer if the new treatment is effective with respect to the treatments of proven effectivity. It is necessary to consider that, for the pharmaceutical companies, it is cheaper to use placebo designs with small samples and avoid comparing their medication with others that could compete with their medication(9). On the other hand, it cannot be known if any new medication is effective, when its effectiveness is inferior to the standard treatment, if it is not compared with the placebo. Also, it is necessary to bear in mind that a study made with a placebo as the control and another with the active treatment as the control is not possible, since they are made in different times and with different patients.

Dr. Freedman has incorporated the notion of “clinical uncertainty (*equipoise*),” which is considered as the moral foundation for controlled and randomized clinical trials. Ethically speaking, in order for a clinical trial to be initiated, there should be uncertainty about the preferred treatment for the determined disease within the community of experts in the medical practice(10). Also, at times, when therapies are evaluated for which there are great doubts concerning its pure therapeutic advantage, it is necessary to reformulate the therapeutic character of the medication, for example, if it were to have potentially harmful collateral effects. When there is *equipoise*, the clinical experiment is ethical. If it is known that the treatment is superior to the placebo, then it is inappropriate to include a control group with a placebo. *Equipoise* has been defined as a state of equilibrium. Clinical *equipoise* requires that the therapeutic index (balance of benefits and risks) comparable to each treatment and with a standard therapy (if it is not included in one of the treatments) be calculated in a controlled and randomized trial. The use of a placebo is ethical if there is proportion between the treatment to be investigated and the placebo, taking into consideration what is known about its efficiency and collateral effects; to be investigated the expected benefits should surpass the risks. The uncertainty can be maintained in different levels, either as a lack of consensus within the scientific community or as uncertainty of the individual doctor. For Freedman, for being *equipoise*—and the use of the placebo in the clinical trial could be accepted—authentic uncertainty in the medical community should exist, instead of insisting in the evidence that there is equivalency in the treatments as for a preference during the duration of the trial, which is impossible to attain(12). However, there is no agreement in terms of a minimum number of physicians with uncertainty.

It is necessary to bear in mind that very rarely there is true neutrality at the beginning of an investigation; nobody would begin an investigative intervention if there were no expectation of improvement in the treatment or if they did not doubt the standard therapy’s ability to function. But having an expectation is not the same as having knowledge, for which one can be in a state of *equipoise* despite having optimistic expectations. A placebo can be used ethically even though there is no *equipoise* when delaying the treatment that does not entail a substantial risk and if, when patients on placebo, their health deteriorates due to the illness, they could proceed to the treatment group(12). In the United States, it is preferred to use the term “clinical *equipoise*,” which reflects collective uncertainty or a state of “no resolution of disputes” as the ethical base for accepting a randomized controlled study. In England, on the other hand, the use of the word “uncertainty principle” is favored, according to which a patient can receive experimental treatment if—and only if—the physician responsible has uncertainty over which of the possible treatments is more appropriate for this patient. This patient should not receive experimental treatment if the physician responsible has reasonable certainty, for either medical or non-medical reasons, that such a treatment is inappropriate for this particular individual in comparison with receiving or not receiving another treatment that can be offered(13). Furthermore, this could run the risk of withholding therapy to persons in cases in which it can be presumed an aggravation to their illness. A physician convinced that a treatment is better than another for a particular patient, ethically he/she cannot choose at random what treatment to give to the patient; the physician should maintain his or her faithfulness and do what he or she believes is the best decision for the patient. For this, the physician that believes to know the answer should not make the decision to enter the patient in a clinical trial. If the physician has uncertainty concerning what treatment is best for the patient, offering him or her the chance to participate in a random trial is

acceptable and does not violate his or her duty. As it will be seen, the Declaration of Helsinki emphasizes the priority of the medical obligations over those of the researcher.



For some authors, the uncertainty principle does not constitute a solid moral base to perform controlled randomized trials, because a physician could be wrong in including a patient in a trial. However, truthfulness should not be confused with the truth. Truthfulness is a propriety applicable to the subject while the truth is applicable to a statement. Someone can be truthful and nevertheless, he/she may say something false. In other words, anyone can be truthful when he or she believes to be telling the truth. The ethical demand is of truthfulness. In the same line of thought, one is correctly acting when he or she believes to be doing the best for the patient.

On the other hand, the concept of equipoise explicitly recognizes that it is not the individual physician but rather the medical community that establishes the standards within the medical practice(14). A physician can offer a patient participation in a trial when there is an honest professional disagreement among medical experts concerning which is the preferred treatment(11). The second part of the clinical equipoise establishes that: "...the trial should be designed in such a form that be reasonable to hope that, if it is finished satisfactorily, the clinical equipoise will be placed in question." In other words, the results of a successful trial should be sufficiently convincing as to resolve the dispute among physicians(11). For others, the morality remains as much with the individual as it does with the collective group and, as the individuals, the medical community also fails. In the case of controlled clinical trials, the medical researcher has a double role, with contradictory obligations and conflicts of interest. Hellman and Hellman (15) consider that: "It is impossible to reconcile the clinical act (based on the principle of major interest of the patient) and the act of research (the promotion of knowledge)." The patient always has the right to the better treatment and in the randomized clinical trial, it is very difficult. As the experiment advances, it is made evident which treatment is better.

Both roles have the intention of benefiting the patient, but that of the scientist is directed toward unknown future patients, while that of the physician is directed toward the current patient. The separation of the figures of physician and researcher has been proposed as a efficacious form of protecting the rights of the participants in the clinical trials. At first, the physician, to be ethical should do what he or she believes is best for his or her patient; it does not matter whether his or her certainty comes from scientific studies, from the personal or anecdotal experience, or whether his or her opinion agrees or disagrees with the point of view of the medical community; the responsibility resides in the physician who carries out the trial(16). However, how many inconveniences can a person suffer for the purpose of investigation? In part, the Declaration of Helsinki of 2000 in its 29th paragraph caused problems of interpretation, since it was indicating that only the use of a placebo would be permitted when there did not exist a therapy of

proven effectiveness, but the World Medical Association retracted this affirmation in 2001.

Paragraph 29: “The possible benefits, risks, burdens and effectiveness of a new procedure should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”

In the Note of Clarification of the World Medical Association the conditions for which the use of a placebo is legitimate are determined, including if there is at disposition a proven therapy.

- *“Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or*

- *Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition which would not imply an additional risk and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.”*

These conditions continue to produce conflict, which has seen reflected in the recent CIOMS guidelines (2002), which do not manifest an interpretive agreement for this.

The use of a placebo as control is ethically justified, in agreement with CIOMS guidelines 2002(13), when there is no treatment of proven effectiveness or it has been demonstrated that the standard therapy is not better than the placebo; when the omission of an intervention of proven effectiveness would expose, to the subjects, at most, a temporary bother or a delay in the relief of the symptoms; and when the use of an intervention of proven effectiveness as a control would not produce scientifically reliable results and the use of a placebo would not add any risk of serious or irreversible damage to the subjects.

On the other hand, for debilitating or fatal illnesses, in the absence of therapy, it is not ethical to use a placebo. Its utilization is preferable to the continuing use of treatments of unproven efficiency and security, especially when they cause serious collateral effects(17). The use of a placebo in clinical trials requires not only an ethical evaluation but also a scientific and legal analysis.

CIOMS 2002

Guideline 11

Election of the control in clinical trials
As a general rule, the research subjects in the control group of a diagnostic, therapy or prevention trial, should receive an intervention of proven effectiveness. In some circumstances, it can be ethically acceptable to use an alternate control, such as a placebo or “absence of treatment.”

A placebo can be used:

- when there is no an intervention of proven effectiveness;
- when the omission of an intervention of proven effectiveness would expose the subjects to, at the most, a temporary bother or a delay in the relief of the symptoms;
- when the use of an intervention of proven effectiveness as a control would not produce reliable scientific results and the use of a placebo would not ad any risk of serious or irreversible harm to the subjects.

Use of control by placebo in developing countries

The use of experiments with a placebo in developing countries is especially controversial. It is possible that exists a treatment of proven effectiveness but that it would not be locally available for administrative and economic reasons. The controversy comes from the fact that, in communities where there is no access to treatment of any kind, the concept of the best available treatment—as is defined in developed countries—does not have any meaning.

The trials regarding the infection of HIV/AIDS controlled by a placebo in order to study the maternal-fetal transmission of HIV in African countries constitute an example(18). The subjects that participated in the investigation were given the placebo, even though a treatment of proven effectiveness was becoming habitually supplied to pregnant women in industrialized nations; and even though, for ethical reasons, this procedure was not possible to be carried out in the United States. Regime “076” of AZT (which is very costly) was used but, in reduced dosage, orally instead of intravenously, and at the end of the pregnancy instead of in the middle. The Public Citizen for Health Research Group criticized this study, citing that the investigation would infringe upon principles of the Nuremberg Code, CIOMS and the Declaration of Helsinki: “In any medical study, every patient- including those of a control group, if any- should be assured of the best proven diagnostic and therapeutic method” [...] “ethical standards of the sponsoring agency’s country should prevail when research is conducted in another country” [...] “the ethical standards employed should be no less exacting than those in the sponsoring agency’s country.” As far as it is concerned, the National Institute of Health of United States, sponsor of the study, responded saying that 1) The “standard of attention” for HIV positive women in developing countries is absence of treatment. 2) a trial controlled by a placebo can be carried out with much fewer human subjects and can be completed in less time than could a study controlled by AZT. 3) The current regime of treatment with AZT is not available nor will it ever be for developing countries. 4) If the cheaper experimental regime proves effective, it could be employed in developing countries.

The requirement that the medication in research be made “reasonably available” for the investigated population is an ambiguous expression. In practice, the criteria for putting certain medicines at the reach of developing countries can be sufficiently difficult and pharmaceutical companies would not be ready to invest in research that could prove

very costly. In this respect, in the controversy over the HIV/AIDS clinical trials controlled by placebo to study the maternal-fetal HIV transmission, even though the experimental therapy was less expensive, its cost were not at the reach of African population either. Therefore, it is necessary to establish dispositions in agreement with host country health authorities in order to make available the cost of treatment.. For developing countries it can be of advantage to carry out clinical trials in their population for prevalent diseases in the country and with the goal of finding effective therapies less expensive to the reach of the average population; in this way it will be possible to speak of a benefit for the country.

A cause of concern is that developed countries could exploit developing countries in order to avoid ethics of research restrictions. As a minimum, studies should consider the points of view of the countries were research is taken place.

The problem of cost-effectiveness has originated two opposite positions. There are those who support to carry out interventions in countries of low resources which could be less effective that treatment employed in countries with greater resources, but less expensive. This, with the argument that a research effort should not be rejected, only in the basis of being considered contrary to ethics by developed countries, if it offers appropriate public solutions for developing countries. The countries in which the research is carried out should be the ones who take the decision according to their local conditions, always providing clear general norms for the protection of individuals and vulnerable communities.

Others, by the contrary, argue that these trials may constitute an exploitation of poor countries by the rich ones, and, therefore, by themselves are contrary to ethics, since economical factors should not carry weight *a priori* in ethical considerations. Developed countries and the pharmaceutical industry –in the opinion of this group– should provide effective available treatments for comparison purposes. Furthermore, some low resources countries has been able to make available to their general population some established and effective treatment for some diseases of expensive treatment, such as for HIV/AIDS.

As it can be seen in the commentary to CIOMS 2002 guidelines (11) this was a conflict not completely solved, although some effective protections against exploitation are established.

The new CIOMS guidelines specify that: “...the scientific and ethical review committees must be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population (12)”. An exceptional case for accepting a comparator less effective is that a health authority of the host country determines that the intervention in study could be made available for the population and not the established effective intervention for being too costly or for having management difficulties (12). Another ethical issue is that, even though the clinical essay is carried out in developing countries, experimental subjects are generally poor, while those with more resources will be the ones benefited.

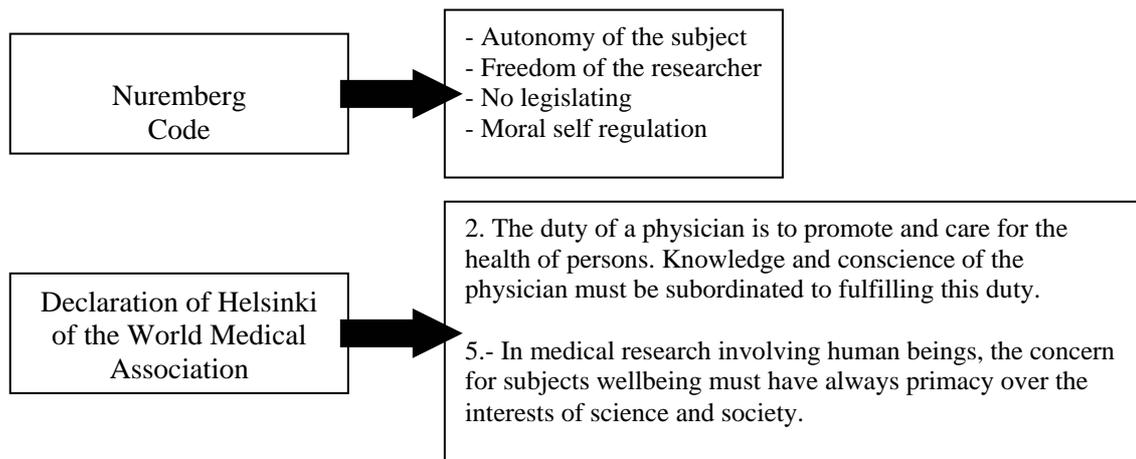
Special designs of placebo control

There are special designs to diminish the damage produced when not receiving treatment because of being the subject in the placebo control group. These are:

1. Studies of short duration, in which a delay in treatment does not imply a substantial risk.
2. Studies in which, if the patient deteriorates while being in the placebo control group, it is allowed to move to a group receiving treatment. A cross-over design can be used, in which the conditions of the experiment are changed, so that the placebo control group becomes experimental and vice versa. This design has been criticized since, generally, the placebo effect is greater in those who receive first treatment, a reaction that is interpreted as a conditional response to receiving treatment.
3. Studies in which treatment is added at a particular time in the investigation. A design add on is employed, in which treatment is introduced after when the study therapy and the standard treatment have different active mechanisms and when a no fully effective intervention is tried to be enhanced or when the effective intervention have intolerable collateral effects (12).
4. A escape treatment design, in which changing to active treatment is allowed if intolerable symptoms occur.

Informed Consent

When giving consent, the research subject must understand the likelihood of receiving placebo instead of treatment and, also, why placebo used is required. In no case a person should be deceived so that he/she believes is receiving treatment instead of placebo. Dr. Robert Levine states that “in case that a placebo control is justified for a particular study, the patient should be informed rightly on the risks involved of withdrawing from an active therapy (19)”. The researcher should not place the patient into a position in which his/her health and wellbeing is compromised, even if the patient accept it. This because, even though he/she has been informed, the physician is who, in general, knows better treatment options; furthermore, the patient is given the option to participate or not in a trial, but no over which treatment would be studied (20). This requirement is based in the ethics of beneficence, clearly delineated in the Helsinki Declaration. In this sense, the Declaration surpasses the ethics of autonomy of the Nuremberg Code, since it establishes that the requirement of informed consent is a necessary condition but not sufficient to guaranty the legitimacy of a study. In other words, the Nuremberg Code emphasizes the autonomy, while the Declaration of Helsinki emphasizes beneficence and non maleficence.



There could be reasons for withholding information to the patient, but these must be sufficiently justified by their scientific validity and necessity to reach research objectives, and it must be shown that it would not cause unjustified damage to subjects and would not interfere with the health care of the patient. Also, there must be an adequate plan to discontinue research with particular subjects, if it is necessary, and to inform subjects about the results of the study. Never an information must be withhold with the purpose of encouraging subjects cooperation. Furthermore, withholding information may cause serious biases in research when this has to be with which treatment to follow. Withholding information is not the same as intentional deceiving. Subject could be told that he/she is going to participate in a randomized study in which he/she has the possibility of either falling into the placebo control group or the treatment study group. It is not ethical not informing to the patient that he/she could receive placebo instead of treatment.

In the case of randomized, double or single blinded studies, subjects must be explained, in simple terms, the meaning of randomized and blindness and why this method is used, who can identify the persons assigned to treatment (possessing the key code), when and under which conditions the key code could be revealed and when will be given information to the subject about the treatment, clarifying if the information will be given at the end of the study or when the subject end his part (21). Fulfilling the requirement of informed consent, in this type of study, implies to tell the patient that, intentionally, some information is being withheld and the reasons why is done so.

MONITORING

It is necessary to specify in the research protocol the way in which data and results will be monitor through the study. This can be undertook in several ways: by the principal investigator, by the sponsor, by a specialized group or by an Independent Data Safety Monitoring Board (DSMB), as it is generally done in phase III clinical trials in the United States. It must be specified who will have the responsibility of analyzing facts and will determine if the study should be modified in order to minimize risk to current or future subjects, or if the study must be ended. Is it necessary to determine the times for reviewing data and the norms for ending. The ethical review committees must

establish requirement criteria for DSMBs and for avoiding biases for potential conflicts of interest. The ethical review committees should not be the primary mechanism for monitoring, but they must secure that a mechanism is in place. The protocol of the study must describe the basic parameters to be used for monitoring data.

The Data Safety Monitoring Boards are multidisciplinary, generally composed by three to six experts in at least two fields:

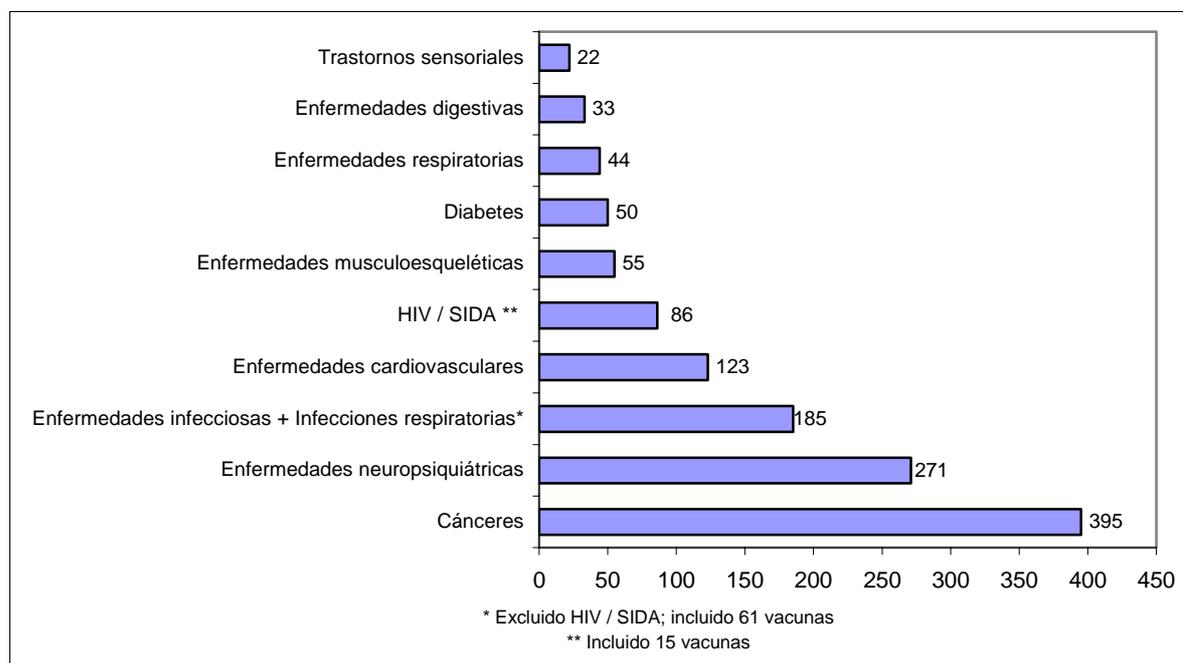
- 1) Medical issues (disease, medicaments, devices, proceedings results measures)
- 2) Methodological issues (design of clinical trials, management of data and statistical analysis).

For some studies experience in biomedical and research ethics is required. DSMBs may supervise proceedings, quality of data obtained, management, safety of participants and scientific integrity; they must be independent. without professional or financial interests on the results of the study. In general, these Boards are necessary for huge populations, in multi-centre studies, when there are proceedings of high risk, when it is expected a high mortality rate or there is a high expectative of early ending. These Boards are required generally for phase III clinical trials and habitually they review data in established intervals determine by the study protocol for deciding if the study could be continued. One study could be terminated for lacking efficacy, for being futile or for lack of safety for participants, being the risks too high.

MULTI-CENTRE STUDIES

Multi-centre studies are every time more frequent in clinical trials carried out by pharmaceutical companies; in this way studies are carried out more quickly since more patients can be included simultaneously. On the other hand, disease conditions could differ depending on the country where research takes place. For example, with respect to AIDS, there are differences in the transmission route of the virus between Africa and the United States and, also, there is differences in the specific viral subtypes. For this reason, it is not true that a successful vaccine in United States would be successful also in African countries. Furthermore, there may be differences in the state of health; for example, in some countries most of the population suffers malnutrition and, as a result, the medicaments may have different effects.

FIGURE: NUMBER OF COMPOUNDS IN DEVELOPMENT ACCORDING TO MAIN DIAGNOSTIC CATEGORIES



Source: PhRMA, Medicines in Development Surveys 2003 / 2004.

Nevertheless, resource inequalities between sponsor countries and developing countries where research is carried out are in general so huge that there could be easily exploitation, for which rigorous safeguards should exist to protect vulnerable populations. Countries should have their own norms and legislation to protect their populations and to review the protocols for their scientific and ethical validity and their relevance for local health priorities.

One ethical guidelines for international research is that a treatment who has been proved efficacious must be made available for the community in where the research is taken place. This has been established by the Declaration of Helsinki 2000 and CIOMS guidelines 2002. Nevertheless, in order to decide which research is important for the community before is carried out, developing countries must define by themselves first their priorities on the health field. The best solution is that the sponsor meet with the communities of potential countries and select those studies of maximum benefit for the health and wellbeing of the population of each country.

Difficulties of multi-centre studies:

In order to secure the validity of multi-centre studies for each place where the research is taken place, it is important that as far as it can be:

1. Proceedings be identical in all places.

2. Genuine informed consent (voluntary and informed) must be obtained. Problems in understanding may occur when sponsors of research do not know the cultural traditions of the country where it takes place. For example, in some communities it is a custom that the elderly take decisions for women and children. Due to cultural reasons, communal leaders must be asked authorization to carry out research, but this does not exempt from getting individual informed consent of potential subjects. Another problem is that sometimes the information given is not understandable in the cultural context where the research is carried out and in others it is not possible to sign a document. In many occasions the population is not prepared to understand the complex medical language so that their consent to participate in research may be compromised. Many times what is informed is not the most relevant for subjects or the information may be too long and complex. Researchers must try to solve this type of situations, clarifying the content and answering all questions requested by the subject even if they do not appear relevant. In some occasions, subject may incur in the so called “therapeutic misunderstanding”, thinking that the research physician is acting as his/her practitioner physician. The fact that some subject may be illiterates must also be considered. In these cases, providing written information makes no sense, neither asking to sign the consent form, rather a verbal informed consent must be obtained with witnesses to credit the fulfillment of ethical requirements of the procedure.

Finally, there is possibility of covered coercion through recompenses or undue inducement.. Differences, mainly economical, between sponsors and members of host community may be so large that what may be an adequate incentive for a person in the sponsor country, it may constitute a coercion mechanism for someone in a marginal social group. The ethical review committee has a key role in evaluating the risks and benefits of participating in research, also in view of incentives offered.

3. Bioethical principles and rules must not be violated, which may occur sometimes in open way (not obtaining informed consent from research subjects) or in covered way (obtaining consent in a language different to the subject’s one)

4. Equity in the selection of research subjects must be assured. The principle of justice is easily violated. Many times samples are not obtained with equity so that risks and benefits are shared by all. When research is carried out in the population of developing countries, their interests and future access for potential beneficiaries must be taken into account.

Studies are well known in which, for example, drugs for certain pathologies are proved in communities where these are not an important health problem. Ninety per cent of research funds are destined to ten per cent of world population. This makes urgent to rethink research priorities in developing countries, where infectious diseases, such as malaria and tuberculosis, are the most prevalent. Without doubt, external sponsors (from developed countries) have other necessities and goals, for which it is desirable that each country establishes their own priorities in health care research, and that any research externally funded that does not adjust to these priorities, must be stingily evaluated by a local ethical review committee.

Nevertheless, developing countries should not undervalue their possible participation in some research projects which do not fall into their health care priorities; for example, in the field of genomic medicine (genetic diagnosis, gene therapy). In agreement or not, developed countries have started to develop, since several decades, lines of research in this and other similar fields. Without doubt, there are clear purposes and goals in these projects whose results, soon or later, in one way or another, will affect developing

countries as well. For this reason, these communities should not be absent in the round table discussion about these topics. The best way to face a potential danger is to recognize it and to anticipate its consequences. If developing countries avoid these type of discussions, because of considering they do not enter into their health care priorities, they will leave open room for others to decide what and how to do it.

An ethical framework based on four principles must be established which in conjunction with the social, cultural and economical context must be taken into account. These principles are: the duty to relieve suffering, duty to respect persons, duty to be sensible to cultural differences and duty not to exploit vulnerable populations. International guidelines (Helsinki, CIOMS) are very general and result ambiguous. For this reason, it is recommended that each country establishes its own norms and operational guidelines in order to apply international guidelines in a clear way. In this sense, it is important that professionals involved in research, as well as project reviewers, would be trained continuously for interpreting adequately norms and guidelines¹.

5. There must be health care standards. In general, an universal standard of care must be offered instead of the available treatment in the region. Nevertheless, sometimes this is not appropriate because it can not be carried out in the social context or, if its is done, would not produce relevant results or would not be effective for the health system of the country. In order to determine which health care standard should be provided, *Nuffield Council*(22) recommends to consider the following factors:

- a) An appropriate research design which responds to the research question.
- b) The seriousness of the disease and the effect in the treatments proven
- c) The existence of a universal health care standard for the disease.
- d) The health care standard in the sponsor country and in the country where research takes place.
- e) The health care standard that can be funded in the sponsor country and in the country where research takes place
- f) The health care standard which could be effectively provided in the country while the research is done
- g) The health care standard which will be provided in the country where research has taken place in a sustained way.

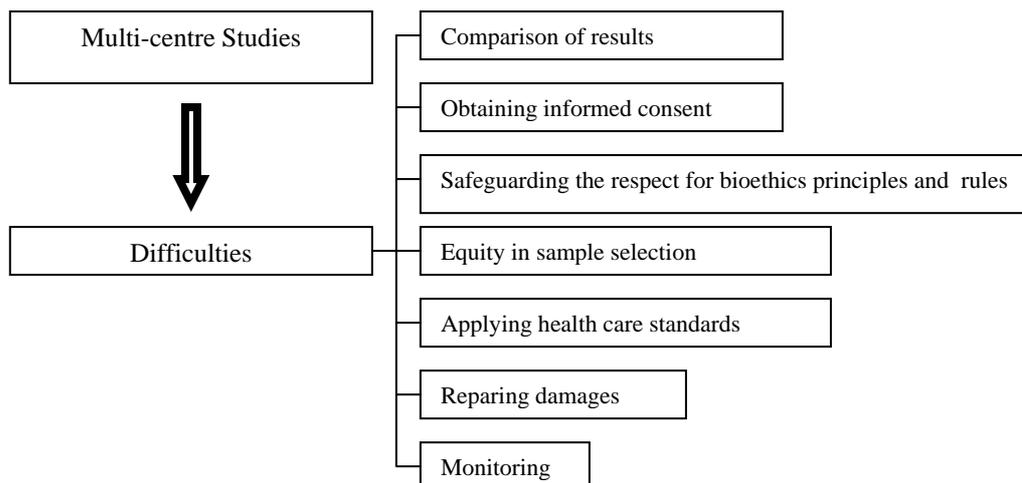
According to Ruth Macklin(23), in order to protect populations of developing countries from the risk of exploitation by international research sponsors, one must recur to the concepts of “distributive justice” and “justice as reciprocity”. The concept of “distributive justice” requires that the risks and benefits of the studies be distributed with equity (to give to each one what he/she needs) among all persons or societal groups. The concept of “justice as reciprocity” requires that research subjects would receive benefits for participating. It would not be justified that if a patient subject has received placebo, when the research is ended he/she would not receive the medicament that the study has proven it has a therapeutic effect. There is exploitation when rich or powerful persons or agencies take advantage of the poverty, weakness or dependency from others, using them to serve their own goals (those of the rich and powerful) without adequate benefits for compensating individuals or groups dependable or less powerful.

¹ Mac Adam, K. Conference given October 27, 2003 in the Bioethics Academic Unit of the Faculty of Medicine, University of Buenos Aires.

Considering the CIOMS guidelines requirement that research products be made available in the country where research is taken place, there are several questions: in case the sponsors have the duty to provide treatment, to whom they must give treatment? For how long?. These and other inquiries must be decided by sponsors, investigators, ethical review committees and local authorities “before” initiating research. We must remember also that , generally, several trials are needed in order to show the actual effectiveness of a medication. Even, there is possibility that results be contradictory in different groups in multi-centre studies. Therefore, one must be very cautious when offering treatment which “appears” better “provisionally”. In order to affront these questions, once more, it is obvious the need to develop, in quantity and also in quality, ethical review committees. At the same time, sponsors must engage in funding resources for the ethical and scientific training of investigators and health care professionals of host countries.

6. The researchers, during the study, must assume the responsibility of caring for those who suffer adverse effects for participating in the research. There should also be compensation for adverse effects posterior to research ending. Lack of protection of persons in developing countries is evident in phase IV of clinical trials, when the drug is already commercialized, when the drug surveillance mechanisms fail. An example was pointed out by *The New York Times*. The Bayer unity, Cutter Biological, continue commercializing factor VIII (which carries a high risk of HIV transmission) in Latin American and Asian countries, when in United States and Europe was not marketed. Another press release in Argentine gave account of the marketing in this country of clozapina, terfenadina and astemizol drugs, when their selling was prohibited in the United States (24). The problem for the pharmaceutical industry is that to put into the market a new molecule costs about 500 million dollars and, if after six months it must be withdrawn due to adverse effects, monetary loss is huge.

7. Monitoring could be carried out. Monitoring and safety safeguarding of patients is very difficult to achieve in practice



ECONOMIC RELEVANCE OF RESEARCH FUNDING – THE CASE OF THE PHARMACEUTICAL COMPANIES

In some occasions, the profit logic which governs pharmaceutical companies may cause that biomedical research socially necessary but not profitable be disregarded.

The factors which affect pharmaceutical companies are: that the main customers be public health systems; the regulation of the process for approving a medicament; the policies for containing expenditures in health care through establishing reference prices for drugs, the promotion of generic drugs or the control of medical prescriptions; the regulation of patent rights duration for products (20 years, but due to management problems is reduced to 10 years); the state subsidy or tax reductions to research institutions; the financial cost for the development of new pharmaceutical products (it has increased four times in the last 10 years) and the increase in duration for the process of clinical trial of the medicament since its discovery to its final approval by administrative authorities (13 to 15 years).

FRAME 1. AVERAGE PERIOD OF EXCLUSIVITY OF PATENTS FOR NEW CHEMICAL ENTITIES APPROVED DURING 1997-2001

Year	Less Duration ^a	More Duration ^b
1997	10,8	13,4
1998	13,0	15,0
1999	8,6	10,2
2000	8,3	11,9
2001	6,5	9,1
Aver..., 1997-2001	9,8	12,3

^a Average amount of years between NDA approval (New Drug Approval Registration) and first patent expiration (or exclusivity)

^b Average amount of years between NDA approval and the last possible patent expiration (or exclusivity)

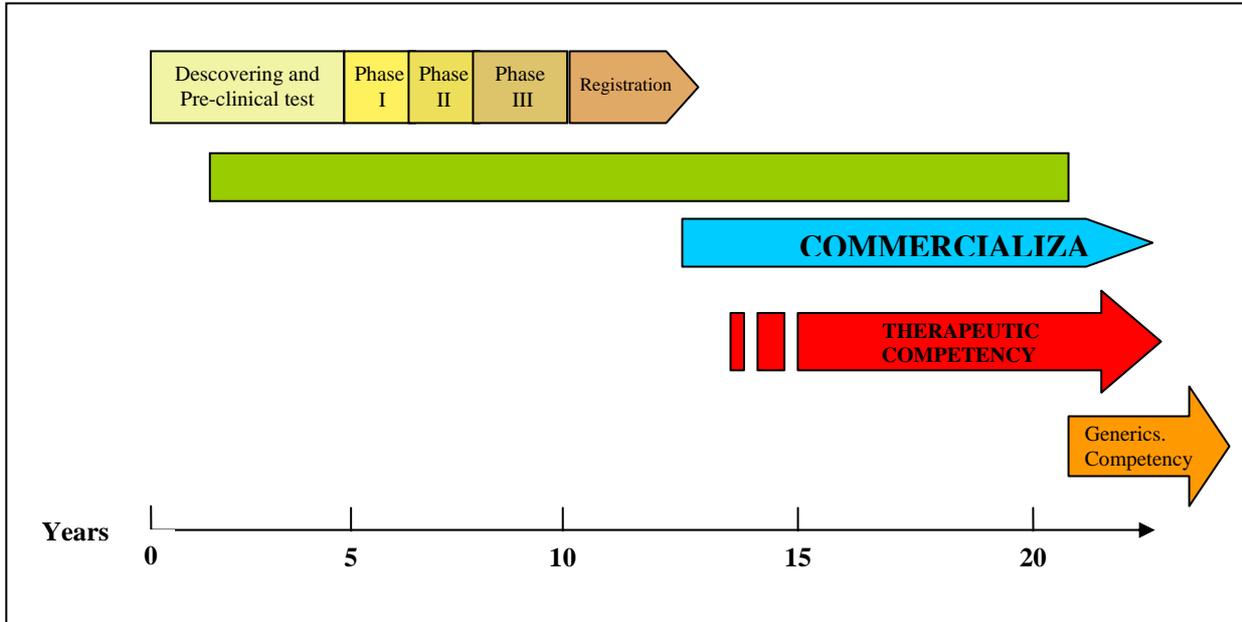
US Food and Drug Administration, Drug Approvals List, 1997-2001. US Food and Drug Administration, Electronic Orange Book.

In developed countries there are several pharmaceutical products of similar effects with different commercial names. Real therapeutic advancement require a huge investment and they are more risky under an economical point of view, for which the pharmaceutical companies invest regularly in imitation research

In the corporal field, the economic development of the drug market has changed, so that pharmaceutical companies can not increase more their prices. This has put pressure to reduce costs, creating more medicaments and reducing the time of introducing them into the market in order to maximize the patent protection.

FIGURE: REDUCTION OF THE EXCLUSIVITY PERIOD IN THE MARKET

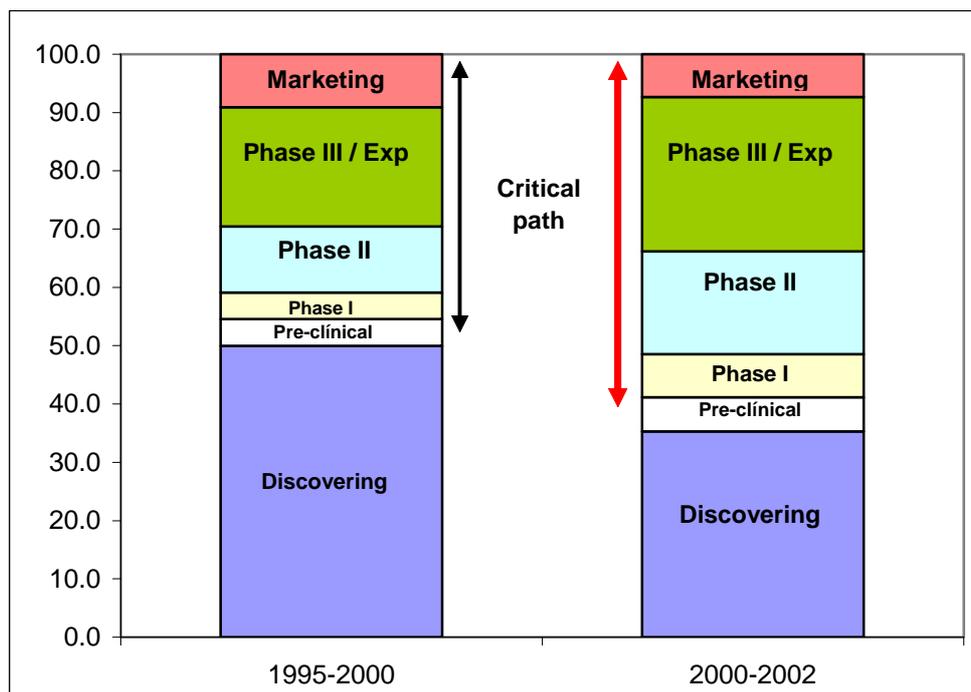
Source *The Platform for Pharmaceutical Innovation*, International Federation of Pharmaceutical Manufacturers & Associations, Fédération Internationale de l'Industrie du Médicament, Federación Internacional de la Industria del Medicamento (2004)



Sponsors look for other places for carrying out trials different from academic centers, where best experts are located, but there is an excessive burocracy which makes the process slow. Instead, hospital and private clinics are chosen, or developing countries, and networks are developed. In order to facilitate o accelerate the process *Contract Research Organization* (CRO) has been created.

Looking for expanding their market, the pharmaceutical and biotechnological companies are presently the main sponsors of clinical research for the development of new drugs and vaccines. These corporations are moving many clinical trials to developing countries to respond to the pressure to shorten the duration of the clinical trial and for getting more patients participating in studies which are cheaper, there is less tradition of respect for individual autonomy, population need more medical attention and there are state lax regulations. Generally, 3,000 to 4,000 patients are needed to fulfill all phases of the clinical trial. The costs increase extraordinarily if the clinical trial takes more time (the cost of developing a new drug has multiplied four times in the last 10 years). The problem for the pharmaceutical companies is that, for numerous legal reasons, patent must be asked when preclinical tests are still being done. The result is that once final approval for the medicament has been obtained and it is made available, half time of patent duration has past already (normally 11 years remain), for which time is reduced for recovering what has been expended in clinical trials.

**FIGURE INCREASE OF DEVELOPMENT COSTS
COST ELEMENTS OF R&D PROCESS AS PERCENTAGE OF TOTAL COSTS**



Source: Adapted from Windhover's In Vivo: The Business and Medicine Report. Bain drug economics model, 2003.

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