Fallibility of the Ethics Committees in Medical Research

La falibilidad de los comités de ética en la investigación médica

INTRODUCTION

Nothing is more difficult than facing the spirit of times, that is, the trends and laws set as valid at a given time. And that is the case when the relevance and infallibility of ethics committees in the work of clinical research and healthcare practice are questioned. It is true that the participation of bioethics committees in research regulations has been an essential contribution to proper research development; however, its vague sense of omnipotence hides some shortcomings that are rarely reproached. It is generally believed that the bioethics committee's primary focus of assessment is on making proper informed consents. However, an ethics committee should basically assess the risks and benefits of clinical trials; therefore, its members should be well versed in research. Without deep knowledge and understanding of the research dynamics, design, and topic to be studied, it will be impossible to acknowledge the risks and benefits patients will face. There is a long list of possibilities for a biased clinical trial to circumvent the good intentions of a bioethics committee, while its members, worried about the quality and transparency of an informed consent, are not aware of it. Researchers attempting to induce a positive result for a new study drug might be using one of the following designs (1):

- Compare the study drug against a treatment known to be inferior;
- Compare the new drug against too low a dose of a competitor drug to reduce its effectiveness;
- Compare the new drug against too high a dose of a competitor drug to increase the toxicity of the latter;
- Reduce the dose of the new drug to decrease its toxicity, even if effectiveness is affected;
- Compare the study drug against placebo to increase chances of effectiveness;
- Show results exclusively in terms of relative risk, which is more impressive than absolute risk reduction or number needed to treat (framing effect); (2)
- Conduct trials of new drugs with very small samples to show there are no differences with the control treatment (low sample power);
- Conduct trials of new drugs with very large samples to show differences with the control treatment when the benefit is very poor;
- Use multiple endpoints in the trial and then select those that give the most favorable results;
- Do multicenter trials and then select only results from centers that are favorable; and
- Conduct subgroup analyses and select the most favorable results.

Most of the situations listed above can be directly interpreted, but the last proposal requires some explanation. The bias is based on the fact that if mortality is significantly decreased in one subgroup but overall mortality is not changed, logic dictates that some subgroup of patients must have had an increased mortality. (3) For instance, suppose mortality associated to a new treatment is 40%, similar to that of the control group. We then select a favorable subgroup with only 30% mortality with the new treatment, while the control group mortality remains the same; therefore, it is obvious that in the experimental group there will be a subgroup with mortality >40% to compensate the rate of the subgroup with lower mortality rate. Therefore, one subgroup will benefit from the new treatment and another subgroup will be worse, compared with the control group.

It is common that most ethics committees in clinical research are unable to see these subtle biases in the design. However, recognizing the methodological gimmicks is part of the ethical assessment of a protocol, since it is ultimately a question of comparing risks and benefits of the trial for the patients. But there are even more subtle biases, such as those arising from effectiveness and safety requirements for a new drug. Regulations to approve a new drug or intervention are often demanding in their safety requirements but also flexible in assessing effectiveness. A new cancer drug is not required to improve cancer survival but to demonstrate an indirect effect, for example, in reducing the size of the tumor. A drug to treat AIDS would meet the effectiveness requirements just by increasing the number of CD4 lymphocytes in blood. Instead of demonstrating that a cardiovascular drug reduces mortality due to coronary heart disease, regulations merely accept that the drug lowers cholesterol. This situation is called use of indirect endpoints, surrogate endpoints, to determine the effectiveness of an intervention. In theory, for a surrogate endpoint to be an effective substitute of the clinical outcome, the effects of the intervention should reliably predict that clinical outcome, but that is rarely the case. (4, 5) On the other hand, how demanding are the regulations on the safety of the new treatment? That will depend on

how safety is defined: In terms of its lack of toxicity? And what if it is neither toxic nor effective, and deprives the patient of an already known and effective treatment? In this context, how can we still argue that the drug is safe? Once again, the interpretation of risk and benefit should justify the opportunity of the trial.

Another aspect to consider is the relationship between ethics in research and the study relevance. A deep-rooted belief is that it is better when the trial is large and multicenter. The larger the number of patients recruited in a controlled clinical trial, the larger the number of patients used to determine the effectiveness of an intervention in a trial with control and experimental groups, because the expected effect of the new drug or intervention is so little that it requires those large samples. And if these ostensible effects are so small, is it ethically justified to carry out the trial? It should be taken into account that the larger the trial is, the lower the researcher's expectation is about the beneficial effect of the new drug. In any case, a small beneficial effect may be of relatively minor significance, but may help many patients if it were an important intervention in public healthcare; that is, it could potentially benefit many people.

THE DOUBLE STANDARD

When there is little evidence that one therapy is better than another to treat a certain condition, physicians could use one of the treatments with all their patients without providing an explanation for their decision. However, if due to the absence of evidence a physician randomly indicates a treatment to half of the patients and a different one to the other half at random, he should request authorization to a bioethics committee, ask for written consents, and even approve the regulations of the government agencies on clinical research. Even worse, if he were an innovative (and not very responsible) professional, he could choose a brand new treatment of scarce clinical experience just because he feels it will benefit his patients. Instead, his responsible colleagues, who are aware of the uncertainties at stake, should ask for permission if they want to compare this new treatment with a traditional one, and thus elucidate which option is the best. This paradox is known as the "double standard" of the codes of ethics regulating research but not medical practice. When there is uncertainty about a treatment, that is, when the opinions of two physicians are different based on controversial evidence, the bioethics committees should accept that it is reasonable and even mandatory to conduct a controlled clinical trial with the honest approval of the scientific community supporting the controversy, since in principle, there would be no ethical barriers to conduct the research; what is more, not conducting the trial could be unethical in itself. (6)

INVESTIGATION IN POOR COUNTRIES

A basic dilemma for poor and developing countries is how to include financial needs and local political aspects in research ethics. In theory, clinical trials in the pharmaceutical industry may benefit poor countries by improving their facilities, facilitating access to cheaper alternative treatments, and providing higher standards of health and medical care. But are companies interested in trying cheaper treatments, or treatments of interest for local public health? It is also true that clinical trials are often very demanding in medical resources, so that in countries with deficient healthcare systems they can confiscate their scarce health resources. The regulations that would ensure "the most effective treatment or health methods demonstrated" for the control group have been changed for lower income regions, ensuring the control group "the best treatment or health method available in normal circumstances, in their countries or health environment". With this regulation, researchers from many clinical trials can justify low-quality treatment to experimental subjects from poor countries, where the level of local health care is low in comparative terms. (7)

NEW VERSUS OLD DRUGS; PUBLIC HEALTH VERSUS INDIVIDUAL HEALTH

The bioethics committees that evaluate protocols do not make a clear distinction between, on the one hand, research that studies the therapeutic effects of a new drug or procedure that may have already been approved but of which there is little clinical experience, and, on the other hand, research that evaluates the new use of a drug or procedure of which there is a vast clinical experience. The demand should clearly be greater in the case of new drugs or procedures than in the second case. Undoubtedly, this differentiation would facilitate the accumulation of evidence of what is already known. The bioethics committees could also tolerate certain ethical slips when experimentation is carried out aiming at public health (where there could be a lot of compensation), rather than when the investigation does not follow the logic of public health but that of the sponsoring pharmaceutical companies.

THE PROBLEM OF THE PLACEBO-CONTROL GROUP

Although the most refined practice of a controlled clinical trial requires the comparison of a new intervention against a placebo-control group, on many occasions it is unreasonable or ethically unacceptable to deprive patients of an alternative and partially effective treatment, and instead administer placebo. In principle, placebo should only be used in the control group when no other effective treatment is known. However, this situation can be overlooked in case of low-risk conditions in which the omission of a conventional treatment would not cause damage to the experimental subject. Nevertheless, the dilemma arises when it comes to determine what a low-risk condition is and who decides whether it is reasonable to omit its treatment. Although the golden rule of ethics is that

placebo should not be used in the control group if a treatment is available, the regulations for drug approval often require the comparison against placebo in order to demonstrate an effect, even if it is inferior to that of the traditional treatment. The only concern is to know the safety of the new drug and at least one limited or partial effect. For example, fluoxetine showed to be slightly more effective than placebo for the treatment of depression. If it had been compared with tricyclic antidepressants, its effectiveness would have been lower, even though with fewer collateral effects. (7) There is a certain intrinsic perversity in the clinical trials with control group that include placebo. The Declaration of Helsinki points out that the experimental subjects should have guaranteed access to the best recognized or existing treatments for each study. What happens then with the use of placebo? Requiring a treatment-control rather than a placebo-control group is particularly relevant when imitation drugs (known as me too drugs) are being tested, since these non-inferiority trials require a very large sample size with enough power to reduce beta error. The development of these me too drugs is known as "gradual therapeutic progress", since it provides a marginal benefit compared with the already known molecules. In fact, the placebo-control group, instead of the best recognized treatment, increases the chance of detecting a statistically significant difference in the experimental group, when this difference exists and is small. Perhaps, the main goal is to demand that new drugs prove to be better than existing drugs, and not simply better than nothing. This would promote the development of more active and beneficial drugs, rather than the proliferation of imitation molecules with a strictly commercial purpose.

CONFLICTS OF INTEREST, MONITORING, AND REPORTING OUTCOMES

Bioethics committees usually do not require the declaration of conflicts of interest that the study sponsors and researchers could have, an aspect that in itself plays a key role in the subsequent development and in the evaluation of research outcomes. Also, and for different reasons, these committees have proven to be inefficient in monitoring the compliance with ethical standards during the course of the study. In turn, this lack of control causes the so-called communication bias, since the committees do not require outcomes to be reported at the end of the study, even if those outcomes were not the ones expected by researchers or convenient to sponsors. Ideally, the bioethics committee reviews the protocol, requires it to be included in a public registry of clinical trials, and clarifies the role of the study sponsors. However, the bioethics committee does not carry out the final step of evaluating the trial results, a procedure that is performed by the editors of scientific journals where the results are published. Therefore, the bioethics committee is familiar with the initial protocol but not with the final results, and the editors of journals are familiar with the results but not with the protocols. All bioethics committees should require the presentation of the final results of all the protocols they have approved. All the trial results should be made public, although this is not always the case.

INFORMED CONSENT IN CLINICAL PRACTICE AND MEDICAL RESEARCH

In the occasional analysis of our routine, we can ask ourselves what is the purpose and validity of the informed consent in medical practice. Some consider it an ethical standard of respect for patient autonomy, and others the physician's protection against potential litigation. As many studies reveal, autonomy cannot be dissociated from the patient preferences for information; (8) and as demonstrated by many judicial decisions, the informed consent does not protect the health care system either. Of both statements, I consider that the first one is the most serious. In defense of patient autonomy, the informed consent requires that the patient be informed of all the details, options, risks, complications, and prognosis of the procedure to be performed, regardless of what the patient himself wants to know. There is consensus in that an essential aspect in the process of providing information to facilitate decisions and respect autonomy is to know the patient preferences to receive such information, and to get involved in the evolution of the disease. (9) In general, the literature supports the concept that it is useless and even harmful to the patient to provide information not according to the preferences. (10) If this preliminary step of judging the preferences was not followed, the evaluation of the damage and the benefit of respecting patient autonomy would be highly debatable. A problem of conscientious objection could therefore be raised due to the compulsory use of the informed consent. In a recent local survey, the information preferences of about 800 patients were analyzed. They were asked what they preferred to know about their disease and how they wanted to participate in the decision-making process about it. (11) A high proportion of respondents, which varied according to sex, age, educational and socio-economic status, ethnic origin or cultural background, and perception of their own health status, preferred a paternalistic style of trust in the doctor regarding information and treatment options, and almost 10% preferred to received the minimum necessary information or "to know nothing" in case of a serious disease. Undoubtedly, the "to know nothing" preference suggests a potential risk of damage if too much information is to be provided to the unprepared patient, and it should be taken into account in order to require different levels of informed consent on the basis of what the patient wants to know. On the other hand, it is common to recognize the paternalistic role of the voluntary and informed consent in clinical research. A clinical trial can move forward only if participants understand what such re-

search involves. However, after the informed consent is obtained, the researcher rarely verifies the level of understanding of the experimental subject about the trial he is going to participate in. Signing the informed consent is often a brief procedure that complies with the regulations and exempts the researchers from potential responsibilities. This procedure scarcely helps patients know the true risks, given the gap of understanding most participants have, many of them with little instruction or formal education. Almost all research subjects understand they will undergo a treatment with either drug or option; however, that is not true. In fact, the main obstacle and obligation is to tell the experimental subject that there is a difference between treatment and experimentation, between health care and the research they will undergo.

CONCLUSIONS

There are some practical aspects that the bioethics and ethical research committees should analyze and modify. In the first place, if the bioethics committees aim at serving the patients' interests, they should be experts in research. Moreover, they will have to insist on the declaration of the conflicts of interest that link researchers with sponsors, as well as on the monitoring and presentation of final results, in order to avoid the bias of reporting positive results only. The committees should also accept that research goes hand in hand with clinical practice, and under that premise, they should facilitate and request its development, eliminating the double standard when comparing treatments with those in which there is a wide clinical experience. In these cases, the consent form will have to be flexible to avoid dropout of clinical trials that report minimal risk and great potential benefit, particularly for public health. Finally, concerning health care practice, adapting the informed consents to the information preferences of individuals, and not to imposed legal models, would be an honest application of patient autonomy criteria. Pharmacological and technological clinical research forms an intricate system of health and commercial interests and intentions. For bioethics committees to serve as impartial arbiters in this community-business relationship, they should learn to recognize the subtle biases in design, the rationale and relevance of the trial, the relationship between safety and effectiveness, and ultimately, between risk and potential benefit. The independent and autonomous bioethics committees are probably the only neutral institutions that have the practical possibility of improving clinical research not only because they are the interpreters of the regulatory frameworks that rule experimentation in human beings but also because they are obliged to protect the integrity and dignity of life. (12) If bioethics committees want to justify their existence, they should increase their intellectual commitment and humanitarian responsibility in order to conscientiously be less and less fallible.

Declaration of conflict of interest

Dr. Raúl A. Borracci is a member of the Bioethics Committee of the Argentine Society of Cardiology.
(See authors' conflicts of interest forms on the website/Supplementary material.)

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