Ethics in a scientific approach: the importance of the biostatistician in research ethics committees

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ABSTRACT

In medical practice and research it is necessary to consider the rights of the researcher or physician and of the subject or patient, to conform to scientific standards and to examine the appropriateness with respect to laws and moral values. Research ethics committees have an important role to play in ensuring the ethical standards and scientific merit of research on human subjects. Research of no scientific value is also against ethical principles. To obtain valid and reliable results from biomedical research, it is a scientific and ethical obligation to make use of the science of statistics. Therefore, for research to be evaluated using biostatistics intensively from ethical and scientific points of view, a biostatistics expert is necessary on research ethics committees. Developments in Turkey are used as examples.

Science tries to produce valid and reliable information, and scientific information is obtained through scientific research. Improvement in science and in scientific research depends on confidence: scientists have to conduct research that commands the confidence of the scientific world. Nowadays, publication of many papers of high quality is accepted as evidence of a scientist's success. This situation can lead scientists to take shortcuts to obtain new scientific data and outcomes. Ethical issues have increased in parallel with the increasing amount of scientific research. The pressure for scientific research and publication can overrule the principle of honesty, and actions contrary to scientific ethics can take place. Research ethics committees also have a responsibility to examine this phenomenon.

The aim of research ethics committees is to evaluate the appropriateness of ethics and scientific standards of biomedical research on humans. When evaluating research projects from an ethical and scientific point of view, such committees should also considered whether statistical methods have been used properly. To do this, biostatisticians must sit on the committees, because the correct use of statistics increases scientific quality. One of the conditions for the planning, administration and evaluation of research is that it must conform to appropriate scientific rules and at the same time be ethically acceptable. Ethical values ought not to be separated from science, but they certainly can be.

THE IMPORTANCE OF RESEARCH ETHICS COMMITTEES AND THE NECESSITY OF BIOSTATISTICIANS

When moral principles lag behind technological and scientific developments, new ethical problems can emerge. Mechanisms to correct this situation include the provision of ethical education to adopt ethical principles, the guarantee of an ethical approach through laws, and inspection. In the past, unethical medical trials carried out on people caused discomfort and conflicts in both the scientific world and the community, so control mechanisms became necessary. Throughout history, although ethical values have been determined, problems have still been observed in practice. It is necessary to consider the rights both of the researcher or physician and of the subject or patient, applying scientific standards and inspecting their appropriateness to laws and moral values in both medical practice and research. Therefore, to evaluate the scientific quality of clinical practice and drug research, ethics committees providing consultation services were formed.[1]

Research ethics should be seen both as an abstract concept limited by science and as a reflection of general ethical values in a specialist field. Although knowledge is in itself impartial, it is no longer seen as such in social practice and with the move into technology. Therefore, the community should also adopt the practice of requiring ethical approval of the researcher who will reveal scientific knowledge. It is very important to use biostatistics principles and methods properly in all steps, from planning to evaluation, in order to impartially present information obtained through research. Research ethics committees have an important role to play in ensuring the ethical standards and scientific merit of research involving human subjects. Despite the institutionalisation of ethical problems about trials on human subjects, these committees collectively form ethical and legal controls for patient and subject, researcher and research institution.[2]

Three important obligations are placed on the ethics committee. First, and most importantly, the committee must ensure that the rights of research participants are protected. To achieve this, comprehensible and complete information about any benefits or risks of the research must be provided and consent must be obtained without any pressure and with the subjects' free will. Second, the research ethics committee has an obligation to society, which provides the resources for research and will ultimately be affected by the results. Third, the research ethics committee has an obligation to the researcher. Meeting these obligations helps to ensure high ethical and scientific standards of research.[2–4]

Research ethics committees are the basic guarantee that the participants' safety, health and rights will be protected, that the interests of

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science and the community will never overrule these and that any potential misuse will be prevented. This guarantee occurs by evaluating research protocols prior to the research itself, as defined in the Declaration of Helsinki and national arrangements. Research ethics committees evaluate the appropriateness of protocols by ethical measurements, and also examine the aim, reason, approach and methodology of research from a scientific point of view. Research of no scientific value will also be contrary to ethical principles, so the ethical and scientific paths are inseparable. Whenever it is considered that errors may be made in planning, administration and evaluation, consultation with a biostatistician on assessment of the research project in which statistical analysis is needed should play an important role in the scientific evaluation. For this reason, biostatisticians must be a part of ethics committees.

ETHICAL AND SCIENTIFIC EVALUATION BY RESEARCH ETHICS COMMITTEES

To achieve medical progress based on research, it is essential to carry out experiments on human subjects. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and to understand the etiology and pathogenesis of a disease. The 13th item of the Declaration of Helsinki[5] states:

> The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence.

With this last change, it can be possible to intervene in the method of research. Thus, we can say that ethics committees must evaluate biomedical research from two perspectives: ethical and scientific.

Ethical evaluation

The ethical principles that must be considered in biomedical research involving human subjects are autonomy (informed consent is related to this), beneficence (non-maleficence is related to this), justice and confidentiality. These principles constitute the moral aspect of research on humans.

The principle of autonomy requires researchers to obtain informed consent from the research subject and protect them from the risks of the research. The principle of beneficence is based on showing a favorable risk/benefit ratio appropriate to the aim of research. The justice principle demands that the burden and benefits of research are equally distributed. The necessity of the principle of confidentiality is to hide the identity of subjects in order to show respect for the rights of the individual.[6] There must be a balance between the benefits society derives from research and the interests of individuals. Aspects of balance concern consent, the patient's right to autonomy, the researcher's duty to act in the patient's best interests, justice and confidentiality. The principles underlying these requirements are in accordance with the tenets of human rights.[7]

The life or immunity of a patient (or other subject) may be harmed by the limitless carrying out of experiments with treatment and scientific aims, if they have not been tested before and their effects on humans are not known for certain. It is necessary to provide some fundamental conditions to validate any physical invasion, both ethically and legally. The first condition is to have acceptable consent of the subject.[8] The consent is valid only if the researcher has ensured that the subject is informed, is in no doubt about the experiment and its results, is not being taken advantage of in any physical, spiritual or materialistic way and has not given consent under pressure. The second important fundamental condition is not to harm or imperil the life of the subject by medical trials.[9] On the other hand, because research fundamentally includes unknowns and uncertainty and as such fundamentally carries risks, no research can guarantee not to harm a participant. However, risks ought to be minimised and precautions should be taken. In accordance with the principles of justice, the benefits and distresses of research must also be distributed equally between all groups and classes in society without considering age, sex, economic status, culture or ethnic distinctions.

Ethical problems can be seen in all stages of research, from planning to presentation. These are of three main types.

Ethical problems arising during planning and application of the research

The aim of the research

To what degree the research serves social and scientific requirements is one of the important ethical problems. Experiments on humans are possible only by collecting knowledge about the people or by their physical participation in the research. In the first case, the issue is raised of effects on private life and on the structure of the culture, while in the second, the amount of physical intervention is the priority.[10]

Ethical problems that can be seen at this stage should be considered from the point of view of autonomy relating to informed consent and beneficence. Primarily, the aim of research must be to provide a contribution to society and science while protecting the subjects' interests.

For example, if we know that the well-known treatment methods are effective or efficient, trying a new, unknown or uncertain treatment would be ethically inappropriate according to the principles of beneficence and non-maleficence.[11] But if we expect that the new treatment might be more effective than the present one, ethical conduct requires researcher to obtain the informed consent of the subjects and to ensure that they comprehend it fully.

The appropriateness of the research method to ethical principles with regard to place, time, the subject and science

The aim of the research must be harmonious with the method that will be applied. The criteria for the inclusion or exclusion of subjects in the experiment must be clearly explained. There must be an appropriately selected control group for true comparison, with the characteristics of the subjects distributed equally between the study and control groups and observations carried out with the necessary objectivity. One of the most important problems seen in research is that the researcher either consciously or unconsciously does not remain neutral and objective.[12]

Care must be taken to act appropriately regarding the principles of beneficence and justice at this level. To obtain valid research results, any bias in the subject selection will affect research results negatively from either the scientific and reality aspect or may not be ethically acceptable.

Ethical problems relating to the financial support of research

The interests of society must be a primary concern when conducting research. The companies providing financial

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resources for research that will be profitable for them may not support research that does not match their interests and expectations, thus showing bias and misleading society by preventing or delaying publication when unwanted results appear.[13] The other problem in this regard is that research relating to treatment services can find financial resources more easily than that relating to public health protection. This situation can be seen as evidence of research being supported by those who aim to profit from it.

This raises the issue of beneficence. Drug development and marketing has become a multi-billion-dollar industry and financial interests are bound to influence the design and planning of clinical trials. In research supported by a company, the partial reflection of results and non-explanation of negative ones may lead to the research subject being misinterpreted, other researchers' time being wasted, and even to patients being harmed.

Ethical problems arising in the evaluation of research results

One problem frequently seen is the non-evaluation or lack of comment on the results of subjects who were not included in a study, who were removed from a study or whose records were lost during the study. To mislead and defraud by knowingly changing results or by inventing or excluding some part of them is just as unacceptable ethically as scientifically.[14 15]

Results obtained from inappropriate use of scientific methods, whether it is known or not that the research results are affected, can be misleading. There are two important questions to be answered when evaluating clinical research. 1) Can I believe the data presented? 2) Can I use the results on my patients?[16] It is important that errors be avoided in clinical research. In the 20th century, the increase in the use of statistical methods and the sensitivity of these methods have facilitated understanding of the problems that cause errors. Inappropriate or incorrect usage of scientific methods in research may cause the results to differ by as much as 50%.[12] In such a case, using a medicine that has a good effect according to the research will not provide the expected benefit.

Ethical problems on publication of research

Problems may be encountered when research is published in many places, when there is repeated publication, when publication is prevented or delayed or when there are problems relating to the author.

It can be seen that scientific and ethical evaluation are inseparable parts of the whole, so that when evaluating research involving human subjects from an ethical point of view, it should also be evaluated from a scientific aspect.

Scientific evaluation

To obtain valid and reliable results from biomedical research, it is a scientific and ethical obligation to make use of the science of statistics. A biostatistician's routine professional activities are likely to have important ethical consequences. This is due in part to the fact that good medical practice and scientifically valid medical research both require as precursors high quality statistical design and data analysis. Statistics is the basis of scientific method.[15 17] Statistically appropriate planning, administration and evaluation of biomedical research based on science forms one of the conditions of ethical acceptance. It must be emphasised that although failure to conform to the principles of medical ethics in biomedical research will not render research outcomes invalid, failure to conform to biostatistics ethics will invalidate them. Outcomes obtained from research that has no scientific value or doubtful validity and reliability will not be useful and may be harmful.

Important errors that may affect the outcomes of biomedical research are listed as follows:

- Failure to define the aim of the study adequately or to show the appropriateness of the method to achieve the aim
- Failure to define the subject inclusion and exclusion criteria
- Failure to have an appropriate control group for true comparison
- Failure to have the important clinical features distributed equally between the study and control groups
- Failure to carry out observations objectively
- Failure to evaluate the results of subjects removed from the study or whose records were lost, or to comment on them in the study.

These errors affect research outcomes, diminishing the validity and reliability of the research and thus making it scientifically misleading.

The unwitting use of biostatistical methods together with conduct contrary to scientific ethics will lead to misinterpretations and partial or false results, thus violating the principles of medical ethics of beneficence, non-maleficence and justice.

DEVELOPMENTS IN TURKEY AS AN EXAMPLE

The first ethics committee in Turkey was established in 1986, and since 1993 there has been a legal requirement to obtain approval from an ethics committee before commencing any medical research and to continue under its supervision. *Regulations for medicine research* (Official Gazette 1993 Jan 29, No 21480), which was published by the Ministry of Health and Social Services, formed the turning point in the constitution of ethics committees in Turkey. *Regulations for the assessment of bioprofit and bioequivalent of pharmaceuticals* (Official Gazette 1994 May 25, No 21942) determined the systematic principles of clinical research. The rules and methods of observation that should be applied in laboratory practice and/or clinical research were determined by the *Guidelines of good clinical practice* and *guidelines of good laboratory practice* (Official Gazette 1995 Dec 29, No 51748) in order to ensure that research is carried out in accordance with international scientific and ethical standards.

With the *Regulations for medicine research*, aimed at evaluating and controlling clinical research in medicine from an ethical point of view, the committee that was formed at the Ministry of Health headquarters was defined as the Central Ethics Committee, and the committees that were formed within the institutions and establishments where the research would be done were defined as local ethics committees. According to these regulations, any person, institution or establishment wishing to do research on any medicine with a scientific aim must apply to and get permission from the Ministry of Health through the local ethics committee. To do research on humans, the approval of the ethics committee is a legal obligation.

The members, and their qualifications, of the Central Ethics Committee and the local ethics committees in training hospitals, were clarified in the relevant regulations. The membership was to include a clinician, a pharmacologist, a pharmacist, a biochemistry expert, a pathologist, an expert in the area of the study and a medical ethicist if possible. A biostatistician was not required to be present.

Although there are legal arrangements, there are some problems in the functioning and construction of ethics committees. These are:

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- The relevant regulations only consider research on humans with medicine.
- The criteria for ethics committees in training hospitals are not determined.
- There is no standardisation between local ethics committees regarding the decision-making process.
- There may be delays in the ethics committees' decisions.
- Some scientific qualities of the research are not taken into consideration by the local ethics committees.
- There is no provision for a biostatistician on the ethics committees.

It would undoubtedly be beneficial for ethics committees to have a common structure and function, with regulations internationally standardised. The last two items listed are relevant to the topic that we are considering here.

It is believed that the *Turkish national programme about taking on the regulations of the European Union* and the *Regulations for medicine research* and *Regulations for the assessment of bioprofit and bioequivalent of pharmaceuticals* (24 June 2003, No 25178) will be repealed, and a new regulation in accordance with the 2001/20/EC numbered European Parliament and directives will be published. With this aim, the *Draft of regulations for clinical research on medical products for humans* has been prepared. This regulation does not cover only medicine research, so the first problem that we listed above has been resolved. In addition, according to this draft, both a biostatistics and an ethics expert would be present on both the Central Ethics Committee and on local ethics committees.

Because evaluation of the scientific qualities of research is at the same time one of the conditions of ethical assessment, the proposal that biostatisticians be included on research ethics committees is a pleasing development.

CONCLUSIONS

Applications in biomedical research are full of countless statistics and ethical difficulties. In the protection of the scientific value of research, research ethics committees are a necessary and important part of the ethical evaluation. Where people are participating in research, it is a requirement to select ethically acceptable aims and the appropriate means to achieve these aims. The correct application of scientific methods in biomedical research will reduce the occurrence of unethical situations. Therefore it is essential to plan research in the best way and analyse data using correctly applied statistical methods to maintain ethical standards.

The planning, administration and evaluation of the research appropriate to scientific rules is also one of the conditions of ethical acceptance. Therefore, undoubtedly biostatisticians must take part in preventing and exposing intentional or non-intentional errors and in measuring the effect of the research and its outcomes.

Having a multidisciplinary structure of research ethics committees will assist in adequately evaluating every aspect and stage of research. As a biostatistician is most certainly needed in every research team, a biostatistician must also take part in ethics committees at the stage of assessment from an ethical and scientific point of view. It is a pleasing recent development in Turkey to have a biostatistician on research ethics committees, thus making it possible to evaluate research from both ethical and scientific aspects.

Competing interests: None.

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