Chapter

Evaluation of the Research Protocol by Ethical Committee

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Abstract

Nowadays, the submission of a research project to an ethical committee and its approval is mandatory. However, researchers often overlook this obligation, because they are too engaged in the design and the process of construction of the study, because of the common tight deadlines, and many times because some devaluation of the role of the committee. Based on our experience of 10 years working in an ethical committee, we propose a way to get close researchers and evaluators, respecting their own aims but bringing them together as partners in the investigation process, protecting patients' values, at the same time that makes it possible to implement strategies to answer to the research question and to create useful knowledge. Our aim is to smoothen the way researchers look to the ethical committee and, at the same time, to make them understand what really is at stake. Ethics should be a commitment for all and not an obligation.

Keywords: ethics, ethics committees, research, ethical analysis, beneficence, personal autonomy

1. Introduction

Medicine is born from the human need to survive to diseases. At first, someone within the tribe began to realize the constellation of symptoms and signs that defined the diagnosis, for which a proper treatment could make the difference in the course of the disease. The so-defined medical act gave him the mastery over life and death. The awareness of this power has given rise to a set of self-regulating norms, early transmitted to the disciples who applied to learn the noble art of healing. This ethical code became known as the Hippocratic oath of the School of Kos, in honor to Hippocrates, the father of scientific medicine, known for having received himself the knowledge from the hands of Asclepius the Greek god of medicine [1].

Based on a solid knowledge derived from the scientific method, medicine commits itself to the patient and society in simple but basic principles of beneficence, non-maleficence, justice, truth, confidentiality, and respect for the human being. This commitment should be enough to ensure unblemished medical practice, both in the care and, no less important, in the research and experimentation.

But the twentieth century and the horrors exposed by the Holocaust of the Second Great War came to demonstrate that it was not enough.

On August 8, 1945, the countries that formed the Allied Forces in World War II signed the constitution agreement of the International Military Tribunal, to

prosecute the Nazi officers on charges of committing peace crimes, war crimes, and crimes against humanity (Control Council Law No. 10: Punishment of persons guilty of war crimes, crimes against peace and humanity). The initial trial in the city of Nuremberg, Germany, was followed by 12 other trials until 1949. The first of these trials became known as the medical case and resulted in the conviction of 16 of the 23 defendants for their involvement, among others, in research projects (high-altitude experiments; freezing experiments; malaria experiments; mustard gas experiments; sulfanilamide experiments; bone, muscle, and nerve regeneration experiments; bone transplantation experiments; seawater experiments; epidemic hepatitis experiments; sterilization experiments; vaccination experiments for yellow fever, smallpox, typhus and other rickettsiosis, paratyphoid A and B, cholera, and diphtheria; poison experiments; and incendiary bomb experiments) [2].

The question wasn't the possibility of conducting research in human beings but the way and circumstances under which it was done. This court had to define what were the permissible medical experiments, in accordance with ethics, morals, and law. The 10 principles emanating from this court formed the first code of ethical appreciation for research involving humans [2], later developed and extended in its application by the World Medical Association's Declaration of Helsinki (1964) [3]. Nevertheless, ethical evaluation was still a commitment of the investigators. The case of Tuskegee, USA, syphilis experience (1932–1972) has warned of the need for direct follow-up and the establishment of independent committees able to ensure the appraisal, evaluation, and guidance of research protocols, as proposed by the following Belmont Report [4]. The increasing complexity of ethical problems with the advance of knowledge has dictated the structuring of responses at the national level. In 1983, in France, President François Mitterrand established the "Consultatif National d'Ethique Committee," the first ethics committee for health and life sciences, with the mission to opine on ethical and social problems arising from progress in the fields of biology, medicine, and health. The increased specificity of experimental research in the new treatments has led to the establishment of research ethics committees with the highest technical capacity to fulfill their mission (US Institutional Review Boards, and the Ethics Committees for Clinical Research in Europe).

2. The ethical principle

The ethics committees are now multidisciplinary boards, including medicine, nursing, social work, law, pastoral care, healthcare administration, and various specialty areas. Their role includes the ethics education, policy formation and review, ethics consultation, and research ethics [5]. In clinical investigation, every protocol must be submitted previously to the beginning of the study for consideration, comment, guidance, and approval. The ethics committees must be independent of the researcher, the promoter, and the sponsor and transparent in their function [6].

The ethics committees for health, especially in the context of clinical research, are thus born not from an internalization of the need for self-regulation but from an external, regulatory, and legal imposition. Since the beginning, they assume a problem-solving police nature that they rarely escape, as their mission includes the laws and regulations as well as applicable international norms and standards. It is common that the ethics committees focus much attention on legal and procedural aspects, answering to this feature, more than applying an individualistic appraisal of the factual project. Consequently, the researchers look at them more as obstacles to the execution of projects than as partners in their implementation.

Ethic must be above the law, respecting it, but discussing it and framing it towards the specific case [7], keeping in mind the protection of the human being. The primacy of ethics, which compromises us all, is certainly not the primacy of the ethics committees, as if they were the exclusive holders of the absolute truth, or its juridical version. The ethical appraisals must return to the Hippocratic matrix of the basic ethical principles to find their guiding path, combining the need for innovation and development in health, through research strategies, with respect for the human being in his or her dignity and vulnerability, in health or in illness, in the daily care they need, or in participating in a research project.

The ethical principles were defined in 1971 by Thomas Beauchamp and James Childress [8]. Beneficence, non-maleficence, justice, and autonomy had become the basis of bioethical decision-making in the last 50 years. Despite the heated discussion about their interpretation, importance, and role of each one, they remain the most internationally accepted. Nevertheless, there's some controversy about their inability to answer to all the challenges posed by the complexity of current biomedical decisions.

The same principles were adopted by clinical research as a key for ethical evaluation, ensuring the protection of the rights of participants. But there are several differences in their application.

Beneficence refers to the promotion of the best practices to improve the patient. However, many times, the beneficiary of the results in a research project is not the participant but the all other population that will receive the medicine under tests [9]. The principle of non-maleficence derives from the Hippocratic sentence of "primum non nocere," which means that doctor abstains from practice that put patients under danger. Although we may argue that the risk of harm is under control, we cannot guarantee for certain even in observational research. The principle of justice and equity reminds us to provide the best treatments to those who really need them. The randomization of the sample removes any selective allocation criteria. The autonomy respects the patient's freedom of choice, based on a sufficient given information. The informed consent freely expressed gives legitimacy to the inclusion of participants. Although the guaranties of the possibility of self-exclusion, no one really wants that to happen, which may compromise the very principle. The definition of autonomy has evolved over the last years, as the boundaries for information and self-determination, leading to structured forms almost widely accepted, but depersonalized and eventually far from the participant.

Over time, other ethical principles have been defined and applied in scientific research. As ethical principles, by definition, require action, new procedures have been adopted to ensure respect for the participants in investigation protocols.

In 1978, the Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [4] described the ethical principles for research in human beings: beneficence, justice, and the respect for the person. The respect for the participant implies that researcher must recognize the subjects' autonomy to their own will and assume the duty to protect the most vulnerable.

In the 1998 Barcelona Declaration, a panel of experts defined the principles of autonomy, dignity, integrity, and vulnerability [10]. Autonomy comes up as an ideal to reach. Dignity is an intrinsic value of the individual, meeting himself with others. Integrity is the right to inviolability, implying the respect for privacy, personal ideas and expectations, and for patient's understanding of his own life and illness. Vulnerability expresses the susceptibility to be hurt. It is commonly understood as the condition of a patient before the threat of disease. In investigation, vulnerability refers to the fragility of participants before the methods. It implies the duty of not to harm the integrity of the participants and, at the same time, to protect their integrity. Classically, we consider children, pregnant women, and elders, but there

are many other ways of turning vulnerable, such as the invitation to participate in a research of the doctor to his patient.

More than the statement in the ethical issues of a paper, assuring that the authors were committed with Declaration of Helsinki and Oviedo Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine, researchers should incorporate the ethical principles since the formulation of the research question and in the entire definition of study design and results analysis, in the assumptions they make, and in the decisions they take.

3. Checklist of the ethical appraisal

The ethical appraisal of a research protocol often starts with a descriptive characterization of the study. Checking the presence or absence of certain elements in the protocol may assist this task. **Table 1** presents the checklist of ethical appraisal. It does not pretend to be a definitive tool of decision, since the ethical appraisal of a research protocol is not an assignment that may be reduced to a checklist. This table should be perceived as a summary tool to help structure and guide critical thinking regarding ethical research assessment.

Overall the research protocol proposal is assessed for its merit and integrity alongside with the description of appropriate and rigorous methods and procedures committed to non-maleficence. The use of sound scientific methods is warranted. Although this is not the main focus of the consideration it is important to assure that the use of resources and enrolment of participants is based on solid scientific grounds. Additionally, appropriate academic conduct in terms of references

Ethical appraisal			
Research team	Yes	No	**Merit and integrity**
Individual researchers curriculum vitae			• Research team CVs are expected to demonstrate capacity to develop the study • Relevance and feasibility of the study is expected
Problem	Yes	No	
Coherent rationale supported by literature			
Questions	Yes	No	
Clear and answerable research questions			
Design	Yes	No	**Appropriate and rigorous**
Experimental			• Coherence between research questions and research design is expected • Efficient resource allocation is expected • Appropriate bias identification and mitigation strategies are expected
Pre-post intervention			
Control group			
Observational			
Cohort			
Case–control			
Cross-sectional			
Qualitative			
Validation (e.g., scale development)			
Mixed methodology			
Other			

Ethical appraisal			
Participants enrolment	Yes	No	**Non-maleficence**
Clear description of the procedure to enroll participants			• Consideration of benefits and costs (risks) weighting for individual and for community interests is expected • Commitment to respect the integrity, dignity and autonomy of participants is expected • Appropriate informed consent presentation is expected • Appropriate procedure of data protection is expected • Appropriate procedure for adverse event reporting is expected
Data collection	Yes	No	
Gathering data from people			
Questionnaire			
Individual interview			
Group interview (e.g., focus group)			
Biological sampling (blood, urine, saliva, sputum, feces, semen, tissue or other bodily fluids)			
Gathering data from clinical records			
Anonymized or pseudonymized data			
Written informed consent from participants			
Data storage	Yes	No	
Safety measures for database management			
Participant safety	Yes	No	
Written informed consent from participants			
Procedure for reporting of adverse events			
Identification of possible risks or harm to participants (e.g., stress or anxiety)			
Insurance (intervention studies, if applicable)			
Data analysis	Yes	No	**Merit and integrity**
Exploratory			• Detailed explanation of statistical analytical plan is expected (viz., identifying all variables and statistical tests use) • Commitment to report and make results public is expected • Declaration of any conflict of interest is expected
Prespecified			
Reporting	Yes	No	
Publication or registry of the protocol			
Compromise to send a report of the research			
Intention to publish the study			
Funding	Yes	No	
Funding protocol (if applicable)			

Table 1.
Checklist of the ethical appraisal.

and authorship authorizations in the use of tools and instruments for research is required. The main focus of attention is usually placed in all the interactions with participants. From first contact where the study is presented to enrollment in the study followed by all the activities required to the end of the study and eventual subsequent follow-up.

4. Common mistakes

The ethics committee of the Northern Regional Health Administration of Portuguese Health Minister was created in 2009 as the first ethical committee in primary care in Portugal. The Northern Regional Health Administration covers a population of about 3.5 million people and have about 9000 collaborators (2776 physicians and 2829 nurses). We have a large experience, counting over 1200 processes evaluated till the end of 2018 (95% research projects in primary care settings). Also we contributed to ethical education among providers implementing several courses on ethical topics, particularly focusing ethics in research.

During this period the discussion on ethical issues increased considerably among physicians and researchers, accompanying Portuguese legislative changes in ethical committees and access and protection of personal data. Ethics does not belong to any one in special: it is a commitment of all. Nevertheless, belonging to an ethical committee forces us to think globally and to decide case by case. In our monthly meeting, we have evolved continuously both in knowledge and in practice. Every project is a challenge for discussion, and every problem is an opportunity to think over about the way to improve ethical awareness, in an increasingly globalized and informed world, but somehow with less time to stop and think. As a result, more than 80% of projects were approved without ethical constraints.

However, many of the projects submitted for appreciation showed ethical constraints, reflecting the distance between research methods and ethical details:

1. Lack of informed consent. Some researchers think the informed consent is expendable. Others think that informed consent is just a signature in a paper sheet, overlooking the relevance of the information and the explanation to give participants the capacity of accepting consciously and freely [11].

2. The invitation to participate in the study. It's hard for a patient assisted in a clinic to refuse the participation in a study when invited by his/her doctor or nurse. It is not forbidden, but this vulnerability forces researchers to be more cautious in the way they include their patients in the study, for example, by asking another member of the team to talk with the patient. This is particularly relevant in the primary care due to the proximity of doctor-patient relationship.

3. Data collection. Clinical files keep a lot of health data of interest for research. However, these data are available for healthcare and not so much for investigation. The reuse of data implies a legitimacy that does not derive directly from assistance. The free informed consent of the patient or his/her agent is the right way to do it. Nevertheless, under certain circumstances, ethical committee may excuse the explicit consent, but special care must be taken to minimize, anonymize, and secure data.

4. Variables under study. It's common to see data collection forms including identification variables such as the patient's name, birth date, or health system number. This potentially jeopardizes the anonymization and confidentiality of the database. Rarely these variables are relevant for research and should be avoided or duly justified [11].

5. Use of questionnaires of other authors. Many questionnaires are protected by copyright and must be authorized by their owners. Even if they are on the public domain, the questionnaire has an intellectual property that should be respected. It's appropriate to obtain prior authorization from the original authors.

6. Absence of a well-defined statistical analytical plan. Quantitative studies may have an exploratory approach to data with all the limitations that poses for causal inference. Still, an exploratory approach may be helpful for theory generation. For the purpose of theory testing, prespecification of statistical analysis is warranted. Researchers should identify all variables in the study and specify the statistical modeling and testing that will be used. This is an important procedure to mitigate "p-hacking" practices [12].

7. Lack of feedback to the participants. Researchers should commit with the obligation of informing participants if they identify a health or social problem that needs intervention, during the investigations. Whenever it is appropriate, a definition of adverse event and a procedure for reporting and managing adverse events is expected.

8. Declaration of conflicts of interest. Although there's a general acceptance about the definition of conflicts of interest in its several dimensions of financial ties, academic commitments, personal relationships, political or religious beliefs, and institutional affiliations, many times researchers opt by an individual assessment choosing which characteristics are more prone to set up a conflict in the particular case. Everyone has some kind of conflicts of interest [13]. The transparency and truth is also an ethical duty.

5. Weaknesses of ethical review

Current trend of ethical review seems likely to make ethical approval less efficient and less sustainable both in terms of time and money [12]. We can identify potential types of weakness in different places and in different areas of the pathway of ethical review.

Ethics is not an exact science, including several lines of thought, from Aristotelian virtue to Kantian deontology, the deterministic theories, the situational view, the Buberian relational perspective, and many others. Different decisions may arise from different points of view [7].

The most frequent hazards in clinical investigation are the breach of confidentiality, the adequacy of informed consent, and the protection of personal data. Patients are often the weakest link in the research project, unable to control most of the procedures in the protocol. But they may be also the strongest piece as they have the power to drop off, conditioning a potential bias able to weaken the interpretation of the outcomes. It's crucial to implement good strategies to safeguard voluntary informed consent, allowing the responsible freedom of the participants, based on effective information, especially when researchers are involved in their healthcare assistance [14].

Nowadays, many researchers use a standardized form to submit their study proposals to research ethics committees. The form overcomes the problem of inconsistencies in the paperwork required by different committees or, sometimes, by different members of the same committee. However, this procedure is time-consuming, and many times a work overloads, forcing the researchers to adapt their study protocol to a closed predefined form. Instead of the original idea of simplifying the process, there's a real risk of increasing the paperwork.

The informed consent is the key to legitimate the inclusion of the participants. However, its necessity may introduce some bias in the research. In primary care, socio-epidemiologic studies are common, and surveys frequently used methodological strategies. The requirement for a written consent will overload the paperwork

and may withdraw some participants, leading to lower response rates and conditioning the results [15].

One of the most important fundamental and central aspects of ethical review is the essential information necessary for ethical approval. That information can be written in form of questions [15]:

- Can the research protocol be modified to reduce potential hazards, without compromising its ability to answer the research question?
- Can the protocol study include solutions to minimize the chances that the remaining hazards result in harms?
- Are the hazards or the risk of resulting in harm disproportionately great in comparison to the importance of the new knowledge to be gained?

Another weakness commonly appointed to the ethical committees is the lack of expertise in specific scientific domains or in certain methodological approaches. The deliberations of research ethics committees require knowledge not only of ethical principles but also of different study designs and research topics. It is true that single members of research ethics committees usually do not have expertise in all of these domains for a given application. The way to prevent this weakness is to increase the number and the interdisciplinarity of the members of each research ethical committee. Portuguese health minister made recently an actualization of the regulation of health and research ethical committees, increasing the number of members to a maximum of 11 and imposing the obligation to integrate people from different areas such as medicine, justice, philosophy/ethics, theology, nursing and pharmacy, or even others as necessary [16].

There are also some concerns about the time to answer. One reason is the bureaucratic issues inherent to its internal functioning, not always well understood, many times perfectly expendable, but always present in our experience. The main reason, however, is more relevant. Some projects raise doubts that require further reflection and imply to postpone the decision, giving time to mature each one's opinions, based on each knowledge, sensitivities, experiences, and values, extended by self-education and, if needed, by consulting other experts.

There is a tendency to normalize the vision of the human being and his nature, leading to preconceived technical decisions, type "ready to wear." This is more common as the time goes by and the routine settles in. The decision must be always case by case. Each project requires specific consideration, which extends over time in the implementation process.

The most important factor for weakness in ethical committees, as in many other organizations, is the inability to recognize their own limitations. This blindness results in the lack of self-criticism and the affirmation that the decision is so perfect that everyone should accept without reservation. The solution is to maintain a deliberative environment in the ethical committees, with open dialog and real discussion on the different points of view, and the capacity to create consensus more that resorting to the decision by imposed suffrage.

6. Conclusion

Scientific inquiry and the production of new knowledge are central factors in the development of medicine and in improving the quality and quantity of life. It allows the generation of evidence about technologies and procedures offering information

useful for health reasoning and decision, whether with and for patients as individuals either for the population.

Thus, the emergence of a research question that does not yet have an established answer (often in the context of the clinical evaluation on medical consultation) is an opportunity to create new knowledge with the potential to improve the current situation.

Methodological strategies for hypothesis testing and for attainment of answers driven by research questions are known. Such procedures are expected to be sufficiently described and structured in the investigation protocol.

Good practices require the submission of a protocol to an ethical committee prior to the start of participants' inclusion.

Ethical committees are sometimes seen as an obstacle to the work of researchers. The most common criticisms arise from the difficulty in perceiving some scientific concepts due to a lack of training in that specific topic and a tendency to overvalue prejudices that lead to a certain paternalistic attitude towards patients and distrust towards researchers. The historically established police character of ethical committees also contributes to this depreciation.

On the other hand, researchers have a tendency to facilitate processes based on their perception of excellence of the expected results and to forget (or even not know) current regulations and laws.

Ethical committees are a fundamental instrument of self-regulation that seek a balance between the benefit of research and its results (that may be translated into more and better health) and the respect for the participant has a human being in his biopsychosocial dimensions.

In its Greek genesis, ethics derives from *ēthikós*, which means relating to one's character. Thus, ethics refers to the ability to live with you and with others respecting individual freedom and its limits by realizing that any act on our part will have a significant influence on the other and therefore must always be weighed.

This may be the key to solve the apparent dilemma. Introducing this consideration in the design and implementation of the research turns it into an ethical investigation that we all agree on.

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Conflict of interest

The authors declare no conflict of interest regarding the contents of this chapter.

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