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Institutionalisation of Bulgarian ethics committees: history and current status

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Abstract

This paper provides an overview of the institutionalisation of the ethics review process in Bulgaria in accordance with the worldwide trend in establishment of ethics committees. Historical and current politico-legal changes influencing the work of ethics committees are analysed. The paper focuses on ethics committees which review biomedical research involving humans, with an emphasis on their composition, functions, training of members, and decision-making processes. Recent positive changes addressing insufficient training of ethics committees' members are highlighted. Recommendations are made for enhancement of the ethics review process and improved transparency.

Background

The formation of ethics committees (ECs) in healthcare started in the 1960s at almost the same time in the United States of America and Europe. Among the motivating forces for the institutionalisation of ECs were the brutal medical experiments on camp prisoners during the Second World War and the Tuskegee syphilis experiments on untreated Afro American men in Alabama, USA (1932-72) (1). Such practices inspired the creation of the Nuremberg Code, which introduced the concept of voluntary "informed consent" (2). This was followed by other international ethical guidelines and standards for conduct of biomedical research involving humans, such as the Declaration of Helsinki, the Belmont Report, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice (ICH/GCP), and the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organisation (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subjects (3-6). The common element of all of these documents was the requirement for ethics review and approval of clinical research by an independent review committee before the commencement of the research. These committees needed to demonstrate independence from political, institutional or professional influences, as well as competence, efficiency and timely review of research proposals (7).

Today, ethics committees across the world have different names: research ethics committee (REC), human research ethics committee (HREC), institutional review board (IRB), and local ethics committee (LEC). Their common main purpose however, is to ensure that the research is conducted in accordance with guiding ethical principles and that the rights and welfare of research participants are protected.

In the last two decades Bulgaria experienced a major transition in its healthcare from a centralised system to an open market, similar to the other transitional countries in Central and Eastern Europe. The expansion of clinical research in these countries including Bulgaria, undertaken by large international pharmaceutical companies, has led to the establishment of ethics committees (8). Their purpose is to provide ethics review of submitted research protocols involving humans and to ensure the safety and wellbeing of participants.

Historical overview of the establishment of Bulgarian ethics committees

The ethics review of research involving humans in Bulgaria started in the mid-1980s, but there was no formal regulation until the early 1990s (9). In 1995, in response to the increased volume of clinical trial proposals from international companies, the Ministry of Health passed the Law of Drugs and Pharmacies in Human Medicine, which regulated all aspects of the conduct of clinical trials (10). A separate document, Regulation N 14 of the Ministry of Health (11), contained detailed guidelines for the establishment, composition and functions of the Local Ethics Committee (LEC). The regulatory body for registering all LECs across the country and monitoring compliance with the standard operating procedures (SOP) was the Bulgarian Drug Agency (BDA) (12). Ethics committees were established in all major Bulgarian hospitals. They were assigned the job of reviewing clinical trial protocols submitted to them and providing opinions about the ethical aspects of the research. This process was the first step towards institutionalisation of ethics committees in Bulgarian healthcare.

However, due to the top-down approach in the establishment of this new advisory body in hospitals, there was uncertainty among health personnel about the EC's role and decision-making power. Further, because ethics committee members did not have formal training in the ethics review process, they were often inadequately informed (9). Moreover, conflicts of interest existed in some ethics committees because the chair of the committee was the director of the hospital. In addition, hospitals selected as sites for a clinical trial and clinicians participating in the trial gained financially from taking part in the research. (They had, however, to show evidence of compliance with international ethical guidelines for conducting research involving humans.) Only a few members of the public had access to information about the existence and role of ethics committees.

Major developments in the regulation of research involving humans took place after 2004 when Bulgaria began harmonising its laws with European legislation in preparation for European Union (EU) membership. The new laws and regulations were introduced when Bulgaria joined the EU in

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2007. The Rules of Good Clinical Practice were approved by Regulation 31 of the Ministry of Health (13). In April 2007 the Law on Medicinal Products for Human Use replaced the Law of Drugs and Pharmacies in Human Medicine (14). This new law is in compliance with Directive 2001/20/EC, Directive 2005/28/EC and the ICH/GCP Guidelines (5, 15-16). All clinical trials conducted in Bulgarian healthcare facilities must comply with the above-mentioned documents and the Declaration of Helsinki (3). Another important amendment is that a new ethics committee for multi-centre clinical trials was established by the Minister of Health. Existing local ethics committees now review only single-site clinical trial applications.

Current situation of Bulgarian research ethics committees

There are currently two types of ethics review of biomedical research involving humans in Bulgaria. One is for clinical trials of new medicines involving humans (predominantly internationally funded trials) and biomedical research including human use of medicines (conducted by MEC and LECs) and the other is for clinical and non-clinical biomedical research applications excluding clinical trials of medicines (conducted by university research ethics committees) (17).

The ethics review of *single-site clinical trials* is conducted by LECs established in all healthcare facilities by their director. Currently 150 LECs are registered with the BDA (12). The composition of LECs has not changed since the first legislation was introduced in 1995. They have seven to 12 members with different medical specialties, both males and females, at least two members with a non-medical degree and at least one person who is financially independent of the institution. Members are predominantly middle-aged physicians (49 years (±1.4) with a range of specialties and experience, lawyers, health administrators and few representatives from nursing, psychology, philosophy or ethics backgrounds (9). Since 2007, the operating procedures of LECs require preliminary ethics training and continuing education of all LEC members, overseen by the Chair of the LEC. Members of the LEC must attend a training course and obtain a certificate to fulfil this requirement. This is an essential step towards addressing the insufficient training of ethics committee members, an issue faced by ethics committees worldwide (9, 18). How this will influence the quality of the ethics review process is still not known, but it is a positive change in the work of Bulgarian ethics committees. The law also allows the involvement of external experts according to the needs of the LEC; however, there is limited information available about the extent of their involvement and the type of expertise required by the committees. The most commonly invited experts are medical specialists (60%) and lawyers (35%). The least likely to be invited are nurses (5%) and other non-health professionals (3%) (9).

The main function of LECs is to review ethical aspects of proposed clinical research, with particular attention to participants' rights, security and wellbeing, especially those of participants from vulnerable groups. Other functions include monitoring of research, preparation of guidelines, and ethics education. Most LECs fulfil their main function very well, but at the expense of the other functions (9). Some LECs prove to be more efficient than others, depending on the size and location of the hospital. One explanation of the ethics committees' efficiency is that review of clinical trial protocols is important and also brings prestige and financial benefits to the hospital and investigators involved in research. Ethics committee meetings are held monthly and decisions are made by open vote. Despite the WHO recommendations, consensus is not accepted for decision making, because of the constraints of the SOP which require a final decision to be made by simple majority of the eligible to vote members of EC (19).

LEC approval is necessary for research to start, however it is not sufficient due to the advisory nature of the approval. Other bodies such as the BDA must also provide inputs. For example for phases I, II and III clinical trials approvals from the following two bodies should be obtained: the Department of Clinical Trials at BDA and the Specialised Committee for Approval of Clinical Trials based at the Ministry of Health (14). This adds another layer to the ethics review process and can delay the research. Second, decisions of the LEC are only advisory. In the future their role and authority could be enhanced by making their decisions binding, as is the case in other countries (e.g. Australian RECs). This would also reduce the time required for the ethics review and final approval by removing the unnecessary intermediate levels of approval.

Recently the workload of LECs has been reduced substantially because of the limited number of single-site clinical trial applications. The majority of clinical trials conducted in Bulgaria are international multi-centre trials and these applications are reviewed by the Multicentre Ethics Committee. The role of the LECs in multi-centre clinical trials is limited only to receiving copies of research-related documentation for record keeping purposes, site-specific approval allowing the hospital to take part in the study as a clinical site, monitoring, and notifications of adverse reactions (19).

Multi-centre clinical trials are reviewed by the Multicentre Ethics Committee (MEC) whose composition and functions are identical to those of LECs. Since the MEC's establishment in 2007 all applications for multi-centre clinical trials across the country are submitted to this committee located in the country's capital, Sofia. Members of the MEC must deal with a large volume of applications, and a workload that is beyond the current committee's capacity. This sometimes delays the approval process. If the workload continues to increase, it may necessitate the establishment of a second MEC located in another Bulgarian city.

Local ethics committees and the MEC are overseen by a central ethics committee reporting to the Council of Ministers. This committee has a predominantly advisory and arbitration role (to provide opinion when approached by LECs, the MEC or by contracting authorities) in the ethics review process of clinical trials (14).

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The second type of ethics review is for clinical and non-clinical biomedical research involving humans, human tissue, animals and genetically modified animals or microorganisms, as well as research using personal biomedical information. It doesn't deal with applications for clinical trials of new medicines involving humans and biomedical research including human use of medicines (as mentioned above these are reviewed by LECs and MEC). This review is undertaken by ethics committees at universities or research institutes called University Research Ethics Committees. Their composition is similar to that of LECs; however they are monitored by a Central Committee on Research Ethics at the Ministry of Education and Science (17). Their work is guided by international and national guidelines such as the United Nations Universal Declaration of Human Rights, the Declaration of Helsinki, the Bulgarian Health Act, and the Regulation 31 of the Bulgarian Ministry of Health (3, 13, 20-21). Although there is currently no legal requirement for those conducting biomedical research at Bulgarian universities to seek ethics approval (except for clinical trials involving humans that need to be approved by an LEC or the MEC), many international funding organisations and academic journals require it. (A similar situation existed in Sweden before 2004, when there were only 10 ECs acting as advisory boards, and researchers were not required by law to obtain ethics approval. During the implementation of Directive 2001/20/EC, these committees were replaced by independent ethics committees and all research projects conducted on humans in universities had to be approved by them (22).

This raises the question of the necessity of a formal legal requirement for an ethics review process for biomedical research other than in clinical trials - such as qualitative studies or medico-social surveys. Currently, some of the university ethics committees in Bulgaria consider only a few research projects at each monthly meeting. Most of the applications require expert opinion on the ethical aspects of research with minimal ethical impact (e.g. laboratory experiments with animals (23). There is a positive move towards making the work of ethics committees more transparent and available to the public. Major university research ethics committees have their standard operating procedures published on their websites and include the contact details of the EC's secretariat.

Discussion and conclusions

The worldwide trend in the establishment of ethics committees in healthcare had an influence on Bulgaria, where biomedical research, especially in the form of international clinical trials, gained momentum in the mid-1990s. The establishment of ethics committees in large Bulgarian hospitals using a top-down approach was the first step towards the institutionalisation of the ethics review process. According to international guidelines, ethics committees must demonstrate independence from political, institutional or professional influences, and provide competent, efficient and timely review of research proposals (7). Not all these requirements were met initially. In the first decade of the establishment of ethics committees, the training of their members was inadequate, and there was lack of clear guidance and consistency in their work. Some ethics committees performed their duties efficiently but others may have existed primarily to satisfy the legal requirement of the hospital conducting research.

During the preparation for EU membership there was a major change in the legislative basis underpinning the work of ethics committees. The composition of ECs remains the same; they are still dominated by physicians and lawyers, with minimal representation from other medical and non-medical professionals. The ethics review process would benefit from broader multidisciplinary representation and wider ethics expertise, which would enhance the decisions made by the committee.

A positive step towards increasing ethics committees' competencies and addressing the insufficient training of their members is the newly introduced compulsory preliminary ethics training and continuing education. In recent years, different certified training courses have been organised in the capital city.

Is this training sufficient? Has the quality of the ethics review process improved? The answers to such questions will come only from further research. The advisory character of ethics committees' decisions weakens their role, and the two layers of approval delay the start of the research. The situation could be improved by requiring only one approval, as is the case in other countries, and ensuring a timely ethics review process.

In 2007, LECs in existence at the time were assigned to review only single-site clinical trial applications and a new ethics committee for multi-centre clinical trials was established by the Minister of Health. This change left LECs without a specific role to play in the ethics review of clinical trials and led to an excessive workload for the new committee and delay in the approval process. Other EU countries such as Hungary and Portugal also experienced problems resulting from the centralisation of clinical trial assessment, evidenced by tensions between local ethics committees and the new central body (22). This too raises questions: Is centralisation of the ethics review processes the best solution for Bulgarian ethics committees? How will it affect the decision making process? Will this new system be effective?

To establish compliance with international ethical standards, the review of biomedical research other than clinical trials also needs to be made into a formal legal obligation.

Ethics committees play an important role, and they will continue to play an important role in the future. We need to look closely at their context and understand what they do. There have been a number of improvements in their work, making information about their role and functions available to the public. However, there is still need for further transparency of the ethics review process and the availability of this information in the public domain.

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Competence of ethics committees in patient protection in clinical research

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Abstract

Research Ethics Committees (RECs) are responsible for the protection of patients' rights and wellbeing. In this paper, we describe the findings of a survey of ethics committee members in a south Indian state. 29 members of 11 RECs responded to a questionnaire of 56 questions on their knowledge of and attitudes towards ethics review and the practices of the RECs to which they belonged.

Introduction

Research Ethics Committees (RECs) play a critical role in the conduct of good research. They are responsible for the protection of patients' rights and wellbeing. The Declaration of Helsinki (1) and the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (2) have set international standards for ethics review of clinical research.

In India, clinical trials are governed by Schedule Y in the Drugs and Cosmetics Act (3). Schedule Y requires that the study protocol be reviewed and approved by an REC, following the Indian Council of Medical Research's (ICMR's) ethical guidelines for biomedical research (4). The ICMR guidelines lay down various requirements for RECs, including their composition and