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A Retrospective Aspect at the Evaluations of a University Clinical Research Ethics Committee: The Unseen Reasons Behind the Disapproved Studies

Bir Üniversite Klinik Araştırma Etik Kurulunun Değerlendirmelerine Retrospektif Bakış: Onaylanmayan Çalışmaların Arkasındaki Görünmeyen Nedenler

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ABSTRACT

Objective: The process of conducting medical research on human subjects is secured by a number of regulations from its planning phase through its publication as an original article. Ethics Committees (ECs) play an important role in the follow-up and evaluation of the study. In this study, we present an evaluation of the experiences of the "Clinical Research Ethics Committee" of a university.

Methods: The characteristics of EC applications, reasons for rejection (technical, scientific, ethical), and files that did not reapply to the committee after the revision request were analyzed.

Results: One thousand and fifty-seven (73.96%) of the 1429 files were accepted with minor corrections at the first examination and 15 files were rejected (1.04%). Of the applications, 357 (24.98%) were returned to the EC agenda with major correction requests. Scientific reasons were reported in 19 (90.5%) of the rejected files, ethical reasons were reported in 12 (57%) and technical reasons were reported in 8 (38.1). The rejection rate increased to 8.24% when the same files were reevaluated and did not reapply to the EC after the revision request (6.8%).

Conclusion: ECs seek revisions for a significant portion of submissions and offer researchers scientific and ethical advice. The majority of the applications were approved by this consultation. In our study, most of the files that did not receive approval from the EC were actually those that did not return after the revision request. The difficulties associated with the legislation appear to be an important reason for researchers to withdraw their application files.

Keywords: Ethics Committee, attitude, research, legislation

ÖZ

Amaç: Gönüllü insanlar üzerinde klinik araştırma yürütme süreci, planlama aşamasından makale olarak yayınlanmasına kadar bir dizi düzenlemeyle güvence altına alınmıştır. Etik Kurullar (EK), çalışmanın takibinde ve değerlendirilmesinde önemli bir rol oynar. Bu çalışmada, bir üniversitenin "Klinik Araştırmalar Etik Kurulu"nun deneyimlerinin bir değerlendirmesini sunuyoruz.

Yöntemler: EK başvurularının özellikleri, ret nedenleri (teknik, bilimsel, etik) ve revizyon talebinden sonra komiteye yeniden başvurmayan dosyalar analiz edildi.

Bulgular: Bin dört yüz yirmi dokuz dosyanın 1057'si (%73,96) ilk incelemede küçük düzeltmelerle kabul edildi; 15 dosya ise reddedildi (%1,04). Başvuruların 357'si (%24,98) büyük düzeltme talepleriyle EK gündemine tekrar alındı. Reddedilen dosyaların 19'unda (%90,5) bilimsel nedenler, 12'sinde (%57) etik nedenler ve 8'inde (%38,1) teknik nedenler mevcuttu. Düzeltme talebi ile gönderilen dosyaların %6,8'inde araştırıcılardan EK'a dönüş olmadı. EK tarafından tekrar değerlendirilen dosyalarda ret oranı %8,24 olarak bulundu.

Sonuç: EK başvuruların önemli bir kısmı için düzeltme/değişiklik talep etmekte ve araştırmacılara bilimsel ve etik önerilerde bulunmaktadır. Başvuruların çoğu bu öneriler doğrultusunda onaylanmıştır. Çalışmamızda EK'dan onay alamayan dosyaların çoğu aslında değişiklik/düzeltme talebinden sonra geri dönmeyenlerdi. Mevzuatla ilişkili zorluklar araştırmacıların başvuru dosyalarını geri çekmelerinin önemli bir nedeni gibi görünüyor.

Anahtar Sözcükler: Etik Komite, klinik araştırma, mevzuat

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INTRODUCTION

The processes from the planning of medical research for human benefit to its publication in a scientific journal are secured by a number of regulations (1,2). Ethics Committee play an important role in the follow-up of this process and evaluate the research both scientifically and ethically (3). The job descriptions and structure of ethical committees were defined in detail because of national and international regulations/declarations (3,4). In our national legislation in Türkiye, "Clinical Research Ethics Committee (EC)" should have the qualifications to evaluate the scientific, medical, and ethical aspects of the proposed research. It is also stated that the EC should take decisions independently and should be approved by the ministry of health (MOH), Turkish Medicines and Medical Devices Agency (TITCK) of the MOH to start their duties (3,5). In addition, due to the legislation in our country, there are different research ECs (such as social sciences research ECs) that are established by each research institution to evaluate research outside the legal framework (not under the supervision of the MOH).

All ECs are required to protect the rights, safety, and well-being of volunteers by guaranteeing that research is conducted to high ethical and scientific standards (6). In addition, it fulfills its responsibility to science by supporting research for the benefit of society. Although it is not directly included in the legislation, in fact, ECs protect investigators from possible risks. Each EC can take three types of decisions after evaluation: (1) acceptance, (2) a reasoned refusal, or (3) a decision to re-evaluate after amendment/correction. A scientific or ethical problem to be identified by the EC may cause possible harm to the researcher beyond harm to the volunteer or society. Perhaps it could put the investigator in a difficult position due to the law. Therefore, clearly stating the correction/amendment requests or rejection reasons contained in the reports of the ECs will also provide a guide for the solutions to possible problems.

When the literature is evaluated, the ethical and scientific reasons underlying the revision request and rejection decisions of the ECs have been revealed by many studies, including the rejection rate percentage (7). However, another important point is that the investigators withdrew the application files after the initial evaluation by the EC. Looking at the examples given from the literature, although the percentages of rejection and/or reasons for rejection of the ECs can be viewed, it is observed that the application was withdrawn by the researcher following the evaluation and reporting of the EC at a serious rate; the real cause of this withdrawal is not known. In this five-year period study, we want to evaluate not only the decisions of a university "Clinical Research Ethics Committee" but also the decisions of withdrawn or did not return to the EC following the first application and the first reporting of research files. The unique value of this article is that it sheds light on the reasons why researchers cannot fulfill the requests of the EC beyond the apparent reasons for refusal.

MATERIALS AND METHODS

The application files submitted to the Gazi University Faculty of Medicine Clinical Research EC between January 1, 2014, and December 31, 2018, were evaluated retrospectively. This research was approved by Gazi University Clinical Research Ethics Committee (approval number: 491, date: 07.08.2020). The research data were obtained from the information in the digital database and meeting notes. Research applications were evaluated in the following aspects: total number of applications, faculties of applicants, characteristics of the research, EC decisions (approved, rejected and requests for changes / corrections), reasons for refusal, number of applications withdrawn after the EC assessment, characteristics of the withdrawn applications, and decision-making time.

The reasons for rejection by the EC were evaluated in 3 groups. The main criteria under these three headings are summarized in Table 1. According to the criteria presented in Table 1, the reasons for refusal were categorized as scientific, ethical, and technical reasons and converted into numerical data.

Statistical Analysis

Descriptive statistics were used to evaluate the data obtained by transferring the data to the SPSS database. Number (n) and percentage (%) values were used for variables determined by number.

RESULTS

A total of 1429 applications were submitted during the 5-year period. Of these, 1221 were single-center research, while 208 applications were conducted in multi-centers. Of these, 1383 were national and 46 were international. When the research was evaluated due to their places of application, 1035 of them were from the Faculty of Medicine, 237 of them were from the faculty

Table 1. The reasons for rejection taken into account in research applications

Reasons for refusal		
Scientific reasons	**Ethical reasons**	**Technical reasons**
(1) The design and methods of the study are not sufficient or valid and reliable in order to achieve the objectives and hypothesis of the research. (2) Insufficient scientific and evidence-based justification for the purpose of the study, which is not supported by resources. (3) Lack of an expert/competent researcher on the subject	(1) Insufficient application of the principle of respect for the person/autonomy (Autonomy) (2) Insufficient application of the principle of respect for society (3) Insufficient application of the principle of justice (4) Failure of adequately applying the principle of not to give harm (5) The expectation of the utility principle is not sufficient	(1) Missing/incorrect forms (2) Incorrect application form (3) Missing permission letters

of health sciences, 58 of them were from the Faculty of Dentistry, and the remaining 99 were from other faculties (Figure 1). When the applications were evaluated in terms of research types, 1323 (92.58%) non-interventional clinical trials, 55 clinical drug phase trials, 15 non-drug clinical trials, 9 medical device studies, and 27 observational drug studies (Figure 2). When the research applications were evaluated in terms of EC decisions, it was seen that 1057 (73.96%) of the 1429 files were accepted with minor corrections at the first examination (Figure 3). We also report minor corrections. Before the next meeting's agenda, the EC approved the conduct of checks. Almost all of the files in which minor correction requests were made, correction/amendment requests were made on informed consent. Fifteen files were rejected in the first evaluation (1.04%). Of the applications, 357 (24.98%) were returned to the EC agenda with major correction requests (Figure 3). After the major correction request, 6 more files were rejected, and the number of rejected files increased to 21 (Figure 4). In 97 of the 357 applications sent back to the researcher with a major correction request (6.78%), the researcher did not make a correction and reapplied it to the EC, which defined the files as inconclusive. When 21 rejection files were evaluated together with these 97 applications, it was observed that 8.24% of the applications did not receive approval from the EC within the 5-year evaluation period. When these 97 files were examined in detail, it was seen that the basic correction request was incorrect in 48% of them. These files also required approval from the Ministry of Health of the Republic of Turkey after approval from the corporate EC. Other applications that did not reapply to the EC after correction were noted for methodological errors, problems in insuring volunteers, and budget problems. Of the 21 rejected applications, three were Phase 3 trials, 11 were non-interventional, and 7 are herbal product or food supplement research (Figure 5). Scientific reasons were reported in 19 (90.5%) of the rejected files, ethical reasons were reported in 12 (57%) and technical reasons were reported in 8 (38.1) of the rejected files (Figure 6). More than one reason for refusal was also recorded in the same file. The average decision-making time of the EC was 23.6 and 5.2 days; in the case of files with a request for correction, this period was 52.1 and 4.3 days.

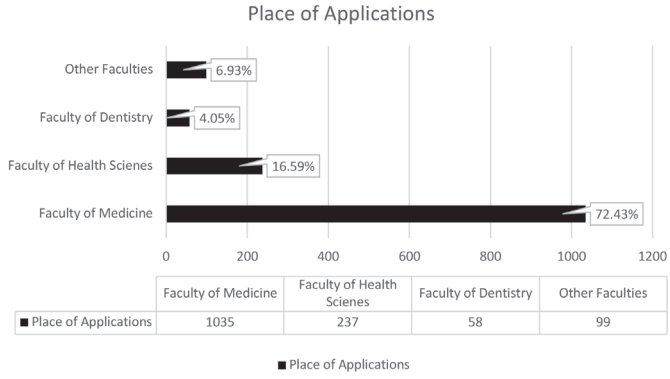

Figure 1. Distribution of the researches according to the places of application

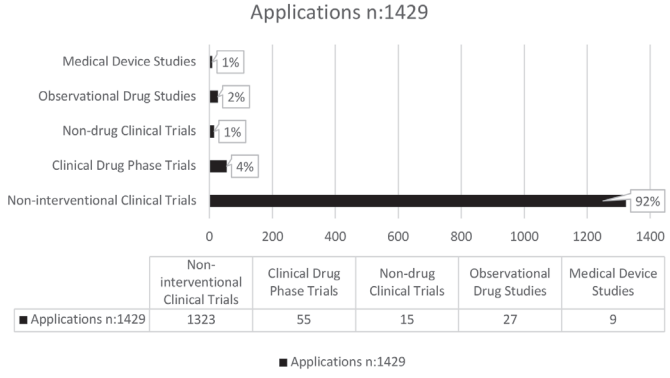

Figure 2. Distribution of total applications according to application types

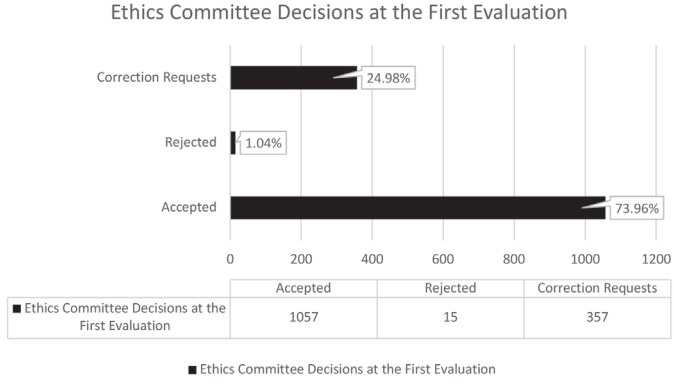

Figure 3. Decisions of the Ethics Committee as a result of the initial evaluation of a total of 1429 applications

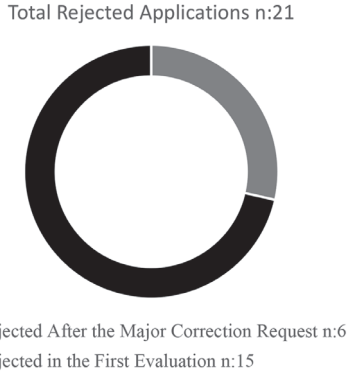

Figure 4. Distribution of the total 21 rejected applications according to the rejection time

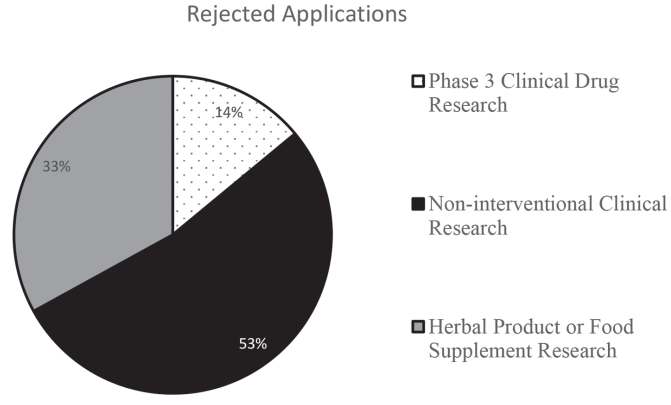

Figure 5. Types of rejected research

Figure 6. Percentage distribution of reasons for rejection in a total of 21 applications rejected by the Ethics Committee

DISCUSSION

In this study, in which the 5-year experience of the EC of a large university located in the capital of **Tü**rkiye was evaluated, the majority of applications (74%) were accepted at the first examination with minor corrections, and about a quarter requested major corrections.

When we have reviewed the literature, the evaluation of EC verdicts for 12 years in a study has shown 8% unconditional approval, 72% approved with minor revisions or conditions, and 20% major revision requested. It has been reported that no application was rejected in this study (8). In another study in which the decisions of the clinical research EC were evaluated, 1256 projects were reviewed. 68% of the projects were approved at the first meeting, and the decision-making period was days. It was stated that 97.5% of the applications were approved at the end of the process (9). In our research, 91.7% of all applications were accepted after revision. In another study by Bueno et al. (9), the reasons for revisions were inadequate use of language on the informed consent form (%32.2), the absence of enough information about the protocol on the informed consent form (%25.8), and related methodological and statistical issues of the protocol doubts (%77.1) have been reported. The results of this study are similar to our research. In our research, the reasons for rejection were largely scientific reasons, and in particular, insufficient and untrustable study design and methods to achieve the goals and hypotheses of the research. Bueno et al. (9) reported the lack of documentation and inaccuracy as a priority among other reasons for returning projects. They have also emphasized the need for explanations or consent for the participation of external organizations (incomplete signing of signatures), the non-compliance of the research team, and the lack of information about financial support in the research (9). Similarly, in our research, it was found that 48% of the files did not reapply due to revision request after the first application has been made with (incorrect) application forms that are not in accordance with the legislation. In addition, in our research, the most common problems observed under the heading of technical reasons for rejection are incomplete/erroneous forms, incorrect application forms, and missing permission letters from the necessary institutions, which includes 38.1% of all reasons for rejection. A survey conducted with multiple IRBs revealed that among the reasons for rejected studies and requesting revisions, problems with informed consent were identified. This was followed by the poor design of the studies, the fact that there were risks that could not be accepted by the subjects, and ethical or legal reasons (10). In another study, it was found that the researchers have received the most criticism regarding the preparation of the study methodology. Regarding the criticism of the method, it was reported that the inadequacy of statistical analyses and sampling errors were the most common. Similar to other studies, the leading correction requests have included reasons such as bias in consent, lack of mention of benefits, and lack of informing volunteers about the practices (11). In our research, almost all of the files that were decided both accepted with minor corrections and requested major revisions, there was a request for changes or corrections in the informed voluntary consent form. There were no rejected files owing to the informed voluntary consent form. Issues such as deficiencies/errors in the informed voluntary consent form, insufficient explanation of the expected benefit/harm from the research, and non-observance of the principle of justice were within the scope of ethical issues. In our research, ethical reasons account for 57% of the reasons for rejection, and these problems are encountered in one out of every two files. In our study, the rejection rate was found to be quite low, such as 1.5%. In 9 out of every 10 rejected files, the reason for rejection was scientific reasons. The rejection rate increased to 8.24% when evaluated together with the files that did not reapply to the EC after the revision request (6.8%). As a result, it was observed that around 8% of the files could not complete the EC process. When the literature was reviewed, there were also some studies in which the rejection rate found as 8% (5,6,9). In a study, according to the data of the EC of a university medical center, it was seen that 90.3% of applications were accepted and 9.7% were rejected. In this study, it was stated that a large proportion of the rejections were independent of the EC evaluation process, and only 1.2% of the protocols were unsuccessful after the review. The most common reasons were unacceptable risks and inadequate methodology (12). In our study, most of the files that did not receive approval from the EC were actually those that did not return after the revision request. The EC consists of files that have not completed the evaluation process. When these files are examined, it is seen that 48% of them are studies that require a second approval from the central authority (Ministry of Health) after receiving approval from the EC. If it is to be evaluated specifically in our country, interventional research (drug research, medical device research or various interventional procedures, non-drug clinical studies) must also receive approval from the central authority (Ministry of Health, TITCK) after approval by the EC. In this type of research, which requires the approval of the central authority, there are different and detailed application forms, annexes of the application and a number of procedures (13). The fact that the researchers found all these processes very long and tiring and that some conditions seemed impossible to fulfill may be a reason why they did not reapply to the EC. According to the results of our research, among the revision requests in these files, the obligation to ensure volunteers and budget problems drew attention. The existence of compelling conditions may have also caused the EC review process to be interrupted. In our research, the majority of applications are noninterventional. This result also seems to reflect the difficulties associated with the

approval process for interventional research. On the other hand, it was seen that a significant part of the files rejected in our study were herbal product or food supplement research. In the legislation of our country, these studies require approval from the central authority after approval of the EC and are subject to drug-like review processes. There are detailed and compelling requirements for national and international legislation in drug research and other interventional research. It can be considered that researchers have difficulty fulfilling these requirements. Clinicians conducting research should be aware of the rules and regulations affecting human research (14). ECs should also guide clinical researchers to conduct high-quality studies with human participants.

In a study, it was stated that the consistency of the decisions of institutional ECs should be measured (15). Accordingly, it is important to undertake quality assessment and continuous improvement in decision-making. At this point, ECs should also evaluate their own decisions. In particular, rejection decisions must be in a way that does not cause suspicion. In our study, it was seen that rejection decisions were expressed with very clear and obvious reasons, and national and international legislation was cited for the justification of the decision. On the other hand, when there are changes in the structure of the boards, it is important that all board members are informed about the decision-making processes due to our national legislation. In addition, every board member should take the course of good clinical practice, including national/international regulations about clinical research. Our clinical research regulations and guidelines are regularly updated by the Ministry of Health.

Study Limitations

The main limitation of this research is the retrospective evaluation. Evaluation was performed on the limited available data. The evaluation could be performed over a longer period. Our starting point was in 2014. We took this point as the application of the new regulations which were revised at 2013 in our country. Therefore, a 5-year period was taken for the evaluation. Another point, we were particularly challenged regarding the status of the files sent to the upper approval authority. We have defined these as inconclusive files. As a result, we believe that we have received an answer to our research question.

CONCLUSION

As can be seen in both our research and other examples, ECs provide scientific and ethical advice to researchers with revision requests in a large part of the applications. With the help of this consultation, most applications were approved. The difficulties associated with the legislation appear to be an important reason for researchers to withdraw their application files. However, informing all researchers about national and international legislation will both save researchers time and reduce the burden of ECs.

Ethics

Ethics Committee Approval: This research was approved by Gazi University Clinical Research Ethics Committee (approval number: 491, date: 07.08.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: C.U., A.K.C., Design: C.U., A.K.C., Supervision: C.U., A.K.C., Resources: A.K.C., U.A., Material: C.U., Data Collection or Processing: A.K.C., U.A., Analysis or Interpretation: A.K.C., Literature Search: A.K.C., U.A., Writing: C.U., A.K.C., U.A., Critical Review: C.U., A.K.C., U.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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