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ORIGINAL ARTICLE

Common Mistakes Made in Clinical Research Ethics Committee Applications: Experience of a Training and Research Hospital

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Abstract

Introduction: It is the responsibility of the ethical committees to ensure that the studies carried out on volunteers are carried out in accordance with ethical rules. In this study, it is aimed to analyze the deficiencies in the 2018-2021 application forms of the Istanbul Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee.

Methods: The number of applications and revisions, the quality and type of research, area of application and acceptance rate were analyzed retrospectively in the archives of the ethics committee, in 598 files that were finalized between January 2018 and December 2020.

Results: In the examined period, the total number of applications has doubled as of the end of 2020 compared to January 2018 (131, 194 and 273 for the years 2018, 2019 and 2020, respectively), and almost all of the applications are non-pharmacologic clinical trials. Among these studies, the highest number of applications are individual research projects, and more than half of them are prospective (63.06%, 66.46% and 58.30%, respectively). The number of applications for which corrections were requested is 77 (58.77%), 107 (55.15%) and 107 (39.19%) according to years. Most of the corrections requested

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are method related. The highest increase in the number of revisions was in the misidentification of the research type (0.78%, 6.02% and 6.94% for 2018-2020, respectively).

Discussion and Conclusion: It was determined that the researchers had difficulties in the study methodology, informed consent and preparation of the scientific basis. Planning periodical Good Clinical Practices (GCP) trainings on an institutional basis under the leadership of ethics committees and that the specialty students have completed their current GCP training before starting their specialty thesis studies will ensure that the research projects to be carried out will be of higher quality in terms of ethics and science.

Keywords: Clinical research; clinical research ethics committee; clinical research ethics committee application form

The concept of ethics, which is defined as the principles of right behavior, basically includes the principles of beneficence, do no harm, respect and justice [1]. When the research to be conducted on the volunteers is evaluated in the perspective of these basic ethical principles, it should be considered that the volunteers are not harmed (do no harm), every effort is made to maximize the benefit to the volunteers (beneficence), the participation in the research is entirely on voluntary basis and informed consent, and where it is necessary to collect data about the subject, confidentiality is maintained (respect), and participation in the research is related to the expected benefits (justice) [2]. There is generally no disagreement on these ethical principles, as they represent fundamental human values. However, in certain situations there may be differences in the interpretation and application of these principles. Therefore, international ethical guidelines have been published by The Council for International Organizations of Medical Sciences (CIOMS) in cooperation with the World Health Organization (WHO) in order to eliminate these interpretation and application differences in studies to be carried out on volunteers [3]. In our country, for this purpose, in 1993, "Regulation on Drug Research [4]" (with its revision on 25.06.2014, with the name "Regulation on Clinical Trials of Pharmaceuticals and Biological Products") and in 2014, "Medical Device Clinical Trials Regulation" entered into force [5]. In the relevant regulations, the responsibility for observing ethical standards in research to be conducted on volunteers is defined separately for researchers, research institutions, national medicines regulatory authorities and funding institutions and organizations, which are the stakeholders of the study. Accordingly, research institutions should establish ethical review systems to ensure the protection of volunteers in research conducted by their staff and at their facilities, and to ensure that the research is conducted at the highest quality within the framework of science and ethics [6,7]. Ethical committees are formed within the institutions in line with this requirement. WHO has published an operational guide on the establishment of ethics committees, their functioning, their powers, and the establishment of regulations that provide standard evaluation. The "Good Clinical Practice (GCP) Guidelines" published in 1995 in our country (the last revision was published on 13.11.2015) is a guide for ethical committees [8]. Elements of ethical review, according to this guideline, include the scientific design and conduct of the study, the involvement, care and protection of volunteers, the protection of participant confidentiality, the informed consent process, and community considerations. Ethics committees carry out these examinations through the project file prepared by the responsible researchers. The sections that should be included in the relevant file are: project summary, general information, justification for the study, literature review, aim and purpose of the study, methodology, data acquisition and analysis, expected outputs in the study, duration of the project, project management, informed consent form, budget and financing institutions, responsibility sharing and resumes of researchers [9]. A well-designed and fully completed application file provides an overview of the entire proposed work and assists in the review of the work objectively [10,11], while the review process of incompletely filled application files is time-consuming and difficult [12,13]. Therefore, inadequately prepared application files will cause problems in terms of ethics committees understanding the purpose of the proposed study and approving the trial. In this context, it is very valuable for ethical committees to share their experiences and to emphasize the points to be considered in the applications to be made. In this retrospective study, it was aimed to analyze the deficiencies and frequently made mistakes in the application files given to the Istanbul Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee between 2018-2021.

Materials and Methods

Ethics Committee Structure and Operation

Istanbul Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee was established as Istanbul Ethics Committee No. 1, with the approval of the Turkish Medicines and Medical Devices Agency (TİTCK) dated 30.04.2009 and numbered B.10.0.İEG.01.11.00.01, and accepts research files from this date. The committee, which still continues its activities with 15 members (Table 1), holds 24 meetings per year in fifteen-day periods. Meeting dates are determined annually and announced on the committee's website. The evaluation of the application files by the committee is carried out in five steps: 1) receiving applications (days 1-9 following the last meeting); 2) the assignment of the application file to two rapporteur members in the appropriate field of expertise by the member responsible for the notification (10^{th} day) (In case there is no expert member suitable for the subject of study in the committee, an external rapporteur is determined); 3) submission of reporter evaluations in writing to the secretariat of the committee (11^{th}-14^{th} days); 4) the application to be discussed and decided at the meeting in line with the opinions of the rapporteur (day 15); 5) notification of the relevant decision in writing to the responsible researcher (16^{th} day).

Applicants are provided with advice on preparing informed consent by a member of the Ethics Committee and on data analysis (statistical analysis) by an independent professional, if they so desire, before their application.

Table 1. Number of ethics committee members and areas of expertise

Area of Expertise	Number of Members *
Pediatric Diseases	1
Gynecology and Obstetrics	1
Pharmacology	1
Biomedical	1
Microbiology	1
Internal Diseases	1
General Surgery	1
Ophthalmology	1
Family Medicine	1
Public Health	2
Cardiovascular Surgery	1
Cardiology	1
Lawyer	1
Civilian member	1

Type of Research

The study conducted with the files of the Istanbul Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee, is of the cross-sectional research type.

Research Universe and Sample

The study was carried out on 598 application files that were decided in the archive of the ethics committee between January 2018 and December 2020.

Data Collection

The research data, which are the number of applications and files with corrections, the budget situation, the centers participating in the research, the nature and type of the research, the application area, the acceptance rate and the research team, were collected with the file scanning information form and analyzed retrospectively. Data usage permission was obtained from the ethics committee before data collection.

Data Analysis

The data were analyzed using the SPSS 22 program, and frequency and percentage distribution were used as descriptive statistical criteria in the evaluation of the data.

The deficiencies in the application forms were classified under eleven headings and evaluated [14,15]: study type/application type, study title, purpose, research team, method, duration, scientific basis, informed consent, budget, technical deficiencies in the application file.

Results

The types of studies submitted to the ethics committee are given in Table 2. As can be seen from the table, the total number of applications has doubled in three years, and almost all of the applications are non-drug clinical studies. When non-drug clinical studies were evaluated within themselves, the highest number of applications belonged to individual research projects of academicians. More than half of these applications were prospective (63.06%, 66.46% and 58.30% of non-drug trial applications for the 2018-2020 period, respectively). The least application file was composed of master's/PhD thesis studies (Table 3).

When the applications made to the ethics committee were evaluated on a clinical basis, the highest number of applications were made from the Cardiology Clinic (7.63%, 20.87% and 23.19%, respectively, by years). The highest increase in the number of applications in the examined period belonged

Table 2. Types of studies submitted to the ethics committee

Study Type	YEAR					
	2018		2019		2020	
	n	%	n	%	n	%
Clinical Drug Study	0	0	1	0,51	0	0,00
Observational Drug Study	0	0	0	0,00	2	0,73
Medical Device Research	0	0	1	0,51	0	0,00
Observational Medical Device Study	0	0	0	0	1	0,36
Non-Drug Clinical Study	111	84,73	161	82,99	235	86,08
Survey Study	20	15,26	31	17,01	35	12,82
Total Number of Applications	131	-	194	-	273	-

Table 3. Nature of non-drug clinical trials

Study Type	YEAR					
	2018		2019		2020	
	n	%	n	%	n	%
Prospective	70	63,06	107	66,46	137	58,30
Individual Research	37	52,85	64	59,81	82	59,85
Medical Specialization	32	45,71	42	39,25	50	36,49
Master/PhD	1	1,43	1	0,93	5	3,65
Retrospective	41	36,94	54	33,54	98	41,70
Individual Research	31	75,61	46	85,19	81	82,65
Medical Specialization	10	24,39	8	14,81	17	17,35
Master/PhD	0	0,00	0	0,00	0	0,00

to the Ophthalmology Clinic (4,58%, 13.18% and 14.43% of applications for 2018 and 2020, respectively) (Table 4).

While the number of applications rejected in the examined period was 2 (1 medical specialization, 1 individual research) for 2018, and 3 (2 individual studies, 1 medical specialization) for 2020, no applications were rejected in 2019. The number of applications for which corrections were requested in the relevant period was 77 (58.77%), 107 (55.15%) and 107 (39.19%), respectively (Table 5).

The reasons for correction in the projects submitted to the Ethics Committee are shown in Table 6. As can be seen from the table, most of the corrections requested by the ethics

Table 4. Distribution of ethics committee applications on a clinical basis

Clinic	YEAR					
	2018		2019		2020	
	n	%	n	%	n	%
Cardiology	10	7,63	40	40,48	63	23,19
Ophthalmology	6	4,58	25	13,18	39	14,43
Family Medicine	4	3,053	10	5,15	28	10,26
Pediatric Diseases	12	9,16	12	6,18	16	5,86
Otolaryngology	5	3,82	18	9,28	22	8,06
Anesthesia and Reanimation	18	13,74	14	7,22	30	10,98
General Surgery	6	4,58	9	4,64	15	5,49
Other	70	53,44	66	34,02	60	21,98

Table 5. Rejection and correction rates in ethics committee applications

DATA	YEAR					
	2018		2019		2020	
	n	%	n	%	n	%
Application		131		194		273
Number of rejected applications	2	1,53	0	0,00	3	1.09
Number of applications requested for correction	77	58,78	107	55,15	107	39,19
Individual Research	54	70,13	69	64,49	75	70,09
Medical Specialization	22	28,57	37	34,58	30	28,04
Master/PhD	1	1,29	1	0,94	2	1,87

committee (24.2%, 33.77% and 42.36% for the years 2018-2020, respectively) were related to the method. In the evaluations regarding the methodology, it was observed that the deficiencies identified regarding the determination of the study groups increased in the examined period (While it was 4.68% in 2018, it reached 21.53% in 2020). Correction requests in the data collection method also increased in the period examined (1.56%, 7.60% and 10.42% for the years 2018-2020, respectively). On the other hand, it was determined that the correction requests made to the informed consent and budget categories tended to decrease in the examined period. The most striking increase in the correction categories in the examined period was the wrong determination of the research type and the use of the wrong application form as a result. It is quite remarkable that this type of error has increased approximately 7 times in three years (0.78%, 6.02% and 6.94% for the years 2018-2020, respectively).

The categories for which the least corrections were required, were the research team and the purpose categories (2.78% and 0.69%, respectively for 2020).

Discussion

Ethics committees established within health institutions can be classified as consultant ethics committees, health services/hospital ethics committees and research ethics committees, depending on the function of the committee and the institution they are located in [16,17]. The main duties of these committees can be defined as producing science and health policies, developing patient-centered service delivery, ensuring the safety of volunteers and researchers, and ensuring that ethical principles are taken into account in the production of scientific knowledge [17,18]. Istanbul Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee was established in 2009 and still continues its activities with its 15 members. The committee holds 24 meetings per year with fifteen-day periods.

In the study, it was determined that the number of applications in the examined period doubled as of the end of 2020, compared to the beginning of 2018. The majority of these studies, almost all of which are non-drug clinical studies, are individual research studies, and the least number of applications belong to master's/PhD thesis studies. It is thought that this may be due to the fact that master's/PhD thesis studies are often planned in a preclinical nature and submitted to the Experimental Animals Ethics Committees.

When the applications were evaluated on a clinical basis, it was determined that the most applications were made from the Cardiology Clinic. The main reason for this is that the relevant applications were made to the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee, since there is no separate ethics committee in Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital.

When the characteristics of the application files in the examined period (2018-2020) are examined, it is seen that more than half of the applications are of a prospective nature, although their number has decreased in the relevant period. We think that the main reason for the decrease in prospective study applications, especially in 2020, is the difficulties in the continuation of prospective studies during the COVID-19 pandemic we have been experiencing as of 2019. Again, when the data is evaluated, it is seen that medical specialization projects are often of a prospective nature. This shows that prospective studies are evaluated as more original studies by thesis evaluation committees.

In the study, it was determined that corrections were requested for the majority of the files evaluated by the committee. Similar results were also presented in the study by

Table 6. Distribution of corrections in ethics committee applications (n=624)*

Category	Correction	YEAR					
		2018		2019		2020	
		n	%	n	%	n	%
Study type / Application type	Wrong choice of study type and use of wrong application form	1	0,78	23	6,02	10	6,94
Study Title	Study title is long, using abbreviations, research title is incompatible with the content	4	3,13	11	2,88	6	4,17
Aim	Insufficient explanation of the purpose of the study (primary-secondary) and inconsistency with the method	4	3,13	5	1,30	4	2,78
Research Team	Insufficient formation of the research team, lack of clear definition of duties and responsibilities	3	2,34	20	5,24	1	0,69
Method	Inadequate explanation of the study method (lack of scale reliability studies, not translating the scales into Turkish, deficiencies in describing treatment-interventions to be applied to study or control groups and randomization)	15	11,72	27	7,07	10	6,94
	Deficiencies in the determination of study groups (sample size, inclusion and exclusion criteria, not including study patients in another study, lack of information on how to form study and control groups, etc.)	6	4,69	66	17,28	31	21,53
	Insufficient explanation of data collection method (including outreach to volunteers, ORF deficiencies)	2	1,56	29	7,60	15	10,42
	Inadequate explanation of the data analysis method (lack of statistical method, incomplete explanation of how the data will be evaluated in retrospective studies, etc.)	8	6,25	7	1,83	5	3,47
Duration	Failure to specify study duration, start-end dates, and volunteer intake dates, deficiencies in defining primary and secondary endpoints	9	7,03	15	3,93	9	6,25
Study Centers	Errors in determining research centers	2	1,56	6	1,57	1	0,69
Scientific Basis	Insufficient support of scientific basis and method with resources (the absence of standard treatment guidelines, lack of Product Information and Instructions For Use of the drug, lack of CE certificate, label sample, user guide information of medical devices)	14	10,94	21	5,50	11	7,64

Table 6. CONT.

Category	Correction	YEAR					
		2018		2019		2020	
		n	%	n	%	n	%
Informed Consent	Not mentioning the bias and benefits in the consent, not disclosing the information to be used by the volunteers, irrelevant sentences, inconsistency with the method, lack of technical knowledge (number of volunteers, protection of confidentiality, 24 hours available phone information etc.)	30	23,44	53	13,87	16	11,11
Budget	Lack of disclosure of the source of the research budget or determination of the budget items, supporting declaration	22	17,19	40	10,47	10	6,94
Technical Deficiencies	Not specifying the unit where the research will be conducted, not adding data collection forms, incompletely filling in the commitments, incompletely filling the consent control form, missing signatures on the forms, incomplet research permissions	8	6,25	59	15,45	15	10,42
TOTAL		128		382		144	

* Application files received multiple criticisms.

Meral et al. [14] in which non-invasive ethics committee applications made in a university hospital between 2016-2018 were evaluated. The researchers stated the revision rates for the 2016-2018 period as 72%, 66.6% and 44.7%, respectively [14]. Again, Yıldırım et al. [15] determined the revision rate as 76.5% in non-invasive clinical studies ethics committee applications within a two-year period. Results similar to these correction rates determined at the national level, have also been reported in studies from abroad. It was also determined in the study in which the applications made to the UK National Health Service were evaluated. According to the study, it was stated that 64% of the files evaluated by the relevant department between 2005 and 2006 were requested to be corrected [19]. In the study conducted by Jones et al.,[20] in parallel with this study, it was determined that 56% of the applications made to a hospital ethics committee operating in England between 2008 and 2009 were requested for correction. These data show that researchers need to be informed about the preparation of ethics committee application files [9]. In addition, not allocating enough time for the preparation of application files or being careless can be considered as another reason. The fact that the mistakes made in the selection of the research type/application type increased approximately 7 times in the examined period, and the deficiencies in the methodology of the study in the category for which corrections were requested most frequently in the relevant period support this. As a matter of fact, fewer corrections required in applications planned as medical specialization thesis, is a result of the preliminary evaluation of the relevant projects by the thesis evaluation committees before they are submitted to the ethics committee.

In the examined period, it was determined that the most corrections were requested in the preparation of the study method in the applications of the ethics committee. Among the requested corrections regarding the method, the deficiencies in the determination of the study groups take the first place, followed by the deficiencies in the explanation of the study method and the deficiencies in the data collection method. As known, the value of the information obtained as a result of a scientific research depends on the objective evaluation of the data by obtaining the

right tools [21]. This can only be achieved if the study has a correct methodology. Contrary to the correction requests related to the method, it was determined that the correction requests made to the informed consent and budget categories tended to decrease in the examined period. It is thought that the main reason for this is the increase in the number of retrospective applications in the examined period, especially in 2020.

Although the deficiencies detected in the informed consent forms decreased in the examined period, this is the second most frequent category for which correction is requested. The reason for the decrease in the number of corrections in this category in the period examined is the increase in the number of retrospective studies, especially in 2020, as mentioned above. As it is known, there is no need to prepare an Informed Consent Forum for retrospective studies. The most common mistakes made in informed consent forms include not writing the form in a simple way that it can be understood by the volunteers (frequent use of medical terms, etc.), not explaining the benefit of the research, making biased explanations in a way that affects the free will of the volunteer in the formation of study groups, and not providing sufficient information about the procedures to be applied to the volunteers.

In the third rank, the category with the highest number of deficiencies detected is budgets. Although these deficiencies have decreased over time, the main reason for this is the increase in the number of retrospective studies over time. The basic correction items related to the budget are the lack of disclosure of the budget source, the deficiencies in the determination of the budget items and the supporting declaration.

The fourth rank correction category is the technical deficiencies observed in the creation of the application form and its annexes, and we think that the main reason for this is carelessness in preparing the relevant files, the responsible researcher not giving enough time to the file preparation and not consulting the ethics committee secretariat.

The subjects for which the least correction is required in the examined period are the determination of the study centers and the creation of the research team. The main reason for this is that most of the applications made to the ethics committee are single-centered studies. The main criticism of the research team by the ethics committee is that, especially in retrospective data analysis studies, in interpreting data outside the researcher's area of expertise, it is requested to include a researcher from the relevant area of expertise in the research team.

As a result, it was determined that the researchers had difficulties in the study methodology, informed consent and preparation of the scientific basis. As known, in addition to the ethical rules of the studies carried out on volunteers, the data obtained from the study must be of scientific quality. Therefore, the methodology of the study and the informed consent form the key point in designing a reliable and efficient research in which scientific and ethical problems are minimized. The prerequisite for this is that both parties (ethics committee and responsible researcher) have a good grasp of the regulations and GCP principles. As known, in all national and international regulations, it is among the duties of ethics committees to evaluate clinical research applications scientifically and ethically, taking into account the purpose, rationale, approach and methodology [6,7,22,23]. In this context, the planning of periodical GCP trainings on an institutional basis under the leadership of ethics committees and the requirement that residency students have completed their current GCP training before starting their specialization thesis studies will ensure that the research projects to be carried out will be of higher quality in terms of ethics and science.

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Ethics Committee Approval: Data usage permission was obtained from the Haydarpaşa Numune Hospital Clinical Research Ethics Committee (decision dated 06.09.2021 and numbered 2021/235)

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