Ethics in Research with Human Beings: from Knowledge to Practice

Sandro Gonçalves de Lima[1,2,3,4], Tatiana Albuquerque Gonçalves de Lima[2], Larissa Araripe de Macedo[2], Michel Pompeu Barros de Oliveira Sá[2], Marcela de Lima Vidal[2], Rafael Alessandro Ferreira Gomes[2], Laura Correia Oliveira[2], Ana Maria Aguiar Santos[3]

Sociedade Pernambucana de Cardiologia - Departamento de Epidemiologia[1]; Universidade Federal de Pernambuco - UFPE - Grupo de Pesquisas em Cardiologia[2]; Centro de Pesquisas Aggeu Magalhães - FIOCRUZ[3]; Realcor[4], Recife, PE - Brazil

Abstract

Background: In Brazil, resolution 196/96 and its amendments regulate the preservation of rights, respect and dignity of human beings involved in research.

Objective: To analyze the adequacy of Free Communications (FC) presented during the *XVIII Congresso Pernambucano de Cardiologia* to resolution 196/96.

Methods: During a cross-sectional study, interviews were carried out with the authors of the FC presented at the Congress and the abstracts of the studies were assessed in order to identify the need for previous approval by a Research Ethics Committee (REC).

Results: A total of 90 FC were presented and, in most of them (86.8%), medical files were the most commonly used source of data. Only 23.1% of the FC were submitted to the assessment of a REC and 15.4% of them used a Free and Informed Consent Form (FICF). Among the authors whose studies were not assessed by a REC, 65.6% stated that this conduct was not necessary and 18% of them were unaware of the need to submit the study to such assessment. The written authorization given by the institution where the FC were carried out was not obtained in 56.6% of the studies. Most of the authors (80.0%) stated that they had never read Resolution 196/96. The proportion of FC submitted to a REC was significantly higher among authors that had read Resolution 196/96 ($p = 0.005$). The FC design influenced the non-submission of the studies to a REC ($p < 0.001$). Most of the FC that were authorized by the institution where they were carried out were submitted to a REC ($p < 0.001$).

Conclusion: Most of the FC presented at the Congress did not follow the Brazilian regulations concerning the ethics in research. (Arq Bras Cardiol 2010; 95(3): 289-294)

Key words: Ethics, research; humans; knowledge; practice.

Introduction

In Brazil, according to resolution 196/96 of the National Council of Health, the research involving human beings is characterized by the direct or indirect participation of human beings, in totality or in part, individually or collectively, which also includes the handling of information or material[1].

Therefore, it is understood that the investigation of family cases of rare cardiopathies, reports of unusual cases, atypical presentations of known diseases, unexpected responses to usual treatments, among others, at the medical office or outpatient clinic, with the intention of submitting such information for publication, characterizes medical research and the formerly medical-patient relationship should now be seen as researcher-research subject relationship.

Mailing address: Sandro Gonçalves de Lima •
Rua Frei Jaboatão, 180/2802 - Torre - 50710-030 - Recife, PE - Brazil
E-mail: sandrolima@cardiol.br, slima@cpqam.fiocruz.br
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Thus, the information regarding treatments, recorded in medical files, as well as examinations carried out in these patients, are sources of research data. In these circumstances, it is common to erroneously admit that it is not necessary to use the Free and Informed Consent Form (FICF), as it was a medical procedure and not medical research[2]. For McCance, the definition of research is associated with the mental attitude of the one who performs it[3] and Ladimer[4] reinforces that, although traditionally connected, the experimentation and the medical practice must considered separately.

In national scientific events, it is still considered unnecessary to obtain the previous approval by a Research Ethics Committee (REC) for the presented research projects, differently from what is required when submitting the same studies to scientific journals. Such events are also characterized as a way to disseminate scientific knowledge, and therefore, it is necessary to request the adequacy of the studies to the national and international ethical patterns, before they are made public.

It is important to mention that the Free Communications are, in many cases, published in scientific journal supplements

with an international scope or Annals of Congresses, thus constituting references that can be cited in scientific studies.

Therefore, the present study evaluates the adequacy of the FC presented at the *XVIII Congresso Pernambucano de Cardiologia* to the Brazilian regulations concerning the Ethics in Research with Human Beings.

Method

The present was a cross-sectional study, where the analysis unit consisted of Free Communications that were approved for and presented at the *XVIII Congresso Pernambucano de Cardiologia*. Data collection was carried out in October 2008, during the aforementioned congress, through a questionnaire that contained open and closed questions, which was applied to the first author of each Free Communication or another author that had presented the work at the congress. When it was not possible to carry out the interview during the event, the authors were contacted later to answer the questionnaire.

The abstracts of studies that were approved and printed in the Annals of the Congress were independently assessed by two members of Research Ethics Committee (REC) with the following objectives: 1) to analyze whether the studies presented at the congress involved human beings (according to the concept adopted by Resolution 196/96); and 2) whether, according to the data presented in the abstracts, it would have been necessary to submit the projects to the REC.

The need to submit the study to a REC was considered when there were two favorable decisions regarding such indication. The abstracts that did not have enough information for the assessment to be carried out were excluded. The information concerning the institutions involved in the researches, the sources of data and the place of recruitment of the research subjects were obtained from the study abstracts.

Pearson's Chi-square or Fisher Exact tests were used for the analysis of the associations, when necessary. The level of significance was set at 5.0% and the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, release 12.0.

The research was coordinated by the Department of Epidemiology of SBC-PE, after being approved by the Scientific Director and the President of SBC-PE. The study authors' identities were kept anonymous.

This research project was submitted to the approval of the REC of *Centro de Pesquisas Aggeu Magalhães/FIOCRUZ* (Register 01/09).

Results

A total of 98 Free Communications (FC) were approved for presentation at the congress. However, 5 were not presented and two authors could not be reached, which resulted in the assessment of 91 FC, with 76 (83.5%) being presented as Posters and 15 (16.5%) as Oral Communications. Only one summary was excluded from the analysis, as it did not contain enough information to assess the need for submission to a REC, thus totaling 90 FC.

There was an agreement between the two examiners regarding the need to submit the study to a REC in 100% of the cases. None of the authors refused to participate in the study.

Most (92.2% - 83/90) of the presented studies had been carried out in institutions from the state of Pernambuco, Brazil; 7.8% (7/90) had been carried out in other states of Brazil and 1.1% (1/90) in national institutions in cooperation with foreign institutions. The general characteristics of the FC and their respective authorships are summarized in Table 1. In addition to presenting their researches at the Congress, 50% of the interviewed authors disclosed the intention to submit their studies for publication in scientific journals.

The aspects related to the adequacy of the FC to Resolution 196/96 are highlighted in Table 2. As for the need to submit the projects to a REC, 65.5% of the interviewed authors stated that there was no such need, 18% were unaware of such need and 16.4% justified the non-submission by using other explanations, such as *"there was not enough time to submit the project to a REC"; "the coordinator of the REC participates in the research"; it is not our hospital's standard procedure"; these patients came from my private practice"* and *"I was aware of the need to do it, but I didn't"*.

The authors that used the FICF informed that one copy was given to the research subject and the other one was filed. The approval letter authorizing the research to be performed was obtained by 60% (54/90) of the authors of the FC presented at the congress, but in 27.8% (15/54) of the

Table 1 - General Characteristics of the Free Communications (FC) Presented at the XVIIII Congresso Pernambucano de Cardiologia. Porto de Galinhas, October 2008

Study design	N	%
Case report	41	45.6
Case series	34	37.8
Cross-sectional study	15	16.7
Source of data		
Database	5	5.5
Database + medical files	4	4.4
Medical files only	79	86.8
Medical files + blood collection	2	2.2
Sources of financial support		
Yes	4	4.4
No	86	95.6
Academic degree (highest degree) of the first author of the FC		
Doctor	7	7.8
Master	13	14.4
University professor	9	10.0
Physician (cardiologist, cardiovascular surgeon)	10	11.1
Medical resident	41	45.6
Medical student	8	8.9
Nurse	2	2.2

Table 2 - Adequacy of the Free Communications (FC) Presented at the XVIII Congresso Pernambucano de Cardiologia to Resolution 196/96 of CNS. Porto de Galinhas, October 2008

	N	%
Studies submitted to a REC	21	23.3
FICF among the FC submitted to a REC	14	66.7
FICF among the FC not submitted to a REC	6	8.7
Studies submitted to a REC among those whose authors intended to submit for publication in scientific journals	14	31.1
Authors that had never read Resolution 196/96 of CNS	72	80.0

REC - Research Ethics Committee; FICF - Free and Informed Consent Form.

cases, the authorization was granted by the direct supervisor and not by the Head of the Institution where the research was carried out. Of these, only 26.7% (4/15) of the studies were submitted to the assessment of a REC.

Among the interviewed authors, 46.7% (42/90) stated that they had employed a technique/diagnostic method or medications in their studies. However, only 1.1% of the authors reported an adverse effect as a consequence of the method or medication. Only one (1.1%) author stated that the research subject(s) was paid for expenses brought on by the research.

Table 3 shows the associations between the studies submitted to a REC and the independent variables related to the researches, the authors and the institutions where the studies were carried out. It was also observed that the authors who were aware of the Brazilian regulations on Research Ethics presented a higher level of academic formation (p = 0.003).

Table 3 - Free Communications Submitted to a REC and presented at the XVIII Congresso Pernambucano de Cardiologia, according to the variables related to the researches, authors and institutions where the studies were carried out. Porto de Galinhas, October 2008

		N	%	Value of p
Study design	Case report	1	2.4	< 0.001
	Case series	14	41.2	
	Cross-sectional study	6	40	
Use of techniques/ methods or medications	Yes	12	28.6	0.249
	No	9	18.4	
Studies carried out in teaching institutions	Yes	17	25	0.454
	No	4	17.4	
Studies that received financial support	Yes	2	50	< 0.001
	No	19	22.1	
Authorization	Yes	16	43.2	
	No	5	9.3	< 0.001
Academic degree of the first author	Doctor's Degree	2	28.6	0.111
	Master's Degree	6	42.9	
	Professor	3	50	
	M.D.	1	10	
	Medical Resident	7	17.1	
	Medical student	1	12.5	
	Nurse	1	50	
Authors that had read resolution 196/96	Yes	9	50	0.005
	No	12	16.7	

Discussion

Medical files were the most commonly used source of data. This information raises the issue of the concept of research adopted by Resolution 196/96, which states that the use of data from medical files constitutes research involving human beings.

Most studies presented at the congress had not been assessed by a REC before the data collection was initiated, as recommended by the Brazilian resolutions on Research Ethics. It is noteworthy the unawareness of the authors regarding the need to submit such research projects to the evaluation of a REC. These data are even more relevant when one verifies that most of the institutions related to the studies were teaching institutions. In this context, there seems to be still a perception of ethics in research on human beings similar to the one adopted in Resolution 01/88, where it was believed that the level of scientific production of certain research groups or institutions was synonym to ethical behavior by the latter[5]. Currently, very often due to the demand to publish, justified by the valorization of the amount of scientific studies published by the institutions[6], the possibility of an opposing relationship between ethics and the scientific production becomes even more threatening.

Francisconi et al[7] interviewed 37 authors of studies published in national congresses and verified that 73.0% of them submitted their researches to assessment, whereas only 24.0% of them were evaluated by a REC. The other assessments were carried out by Medical Ethics Commissions, Scientific Commissions and even colleagues or the Board of the Institution. Among the authors who belonged to institutions that had a REC, only 38.5% of them submitted their researches to this committee. Borracci et al[8] evaluated 100 authors of studies presented at the Argentinean Congress of Cardiology and verified that only 36.0% of them had submitted their studies to ethical review. Karunaratne et al[9] interviewed research subjects, researchers and members of REC in Australia to evaluate the communication deficiencies and research monitoring. They reported that 6.0% of the researchers believed that the FICF was not necessary, 44.0% of the research subjects were not informed on the existence of ethical committees and 12.0% of the researchers believed that the quality of research monitoring could be improved. Angell et al[10] reported a high rate of errors identified by the REC, which corroborates the importance of submitting a project to

the assessment of a REC before initiating the research.

Although the importance of the research protocol evaluation by the REC has been emphasized since the first version of the Declaration of Helsinki, McGuinness[11] observes that it should not been seen by the researchers as justification to decrease the researcher's responsibility when the projects are approved. Although the REC undertakes the responsibility when it approves a research project, the respect to the dignity of the research subject must be basically the responsibility of the researcher. For Amorim[12], the acceptance of the research-related risk depends on the individual submitted to it, whereas the researcher is entirely responsible for the assessment of the safety margin of the experiment. Lasagna et al[13] reported that 40.0% of the individuals who volunteer for experiments involving new drugs present social adjustment problems of which intensity is capable of interfering with the activities of daily living.

The methodology used in this study did not allows us to evaluate the actual submission of studies to REC, but some data point out to the possibility that the percentage of submission is even lower. The percentage of studies submitted to REC that used the FICF was low, even considering that most of the free communications presented at the congress were case reports and case series and that the contact with research subjects might not have been possible due to the difficulty in locating them, as a result of the deficiencies in the medical filing services of the hospitals. Another fact supporting this hypothesis is that some authors informed that they had submitted their studies to a REC that did not appear in the list of active RECs at the site of the National Commission of Ethics in Research (CONEP).

We observed a low percentage of authors that stated they had used a FICF, even though they had not submitted their research projects to a REC. The unawareness of the meaning of the term "FICF" associated to the possibility of confusion on the part of the authors with the agreement of the Head of the Institution where the research was carried out might justify this result. The recommendation in Resolution 196/96, that a copy of the FICF should remain with the researcher, while the other should stay with the research subject was followed by all authors that used the FICF in their studies.

Approximately 70.0% of the authors that intended to publish their researches in scientific journals had not submitted their projects to a REC. That reflects not only the lack of awareness regarding the resolutions that deal with ethics in research with human beings, but also, indirectly, the lack of requirement of documentation that verifies the assessment of the project by a REC as a pre-requisite for publication in some scientific journals. Francescutti[14] reported that 13.0% of the publications in England presented ethical problems and that this percentage has been increasing of late.

Severe violations to ethics in research and mainly to the subjects involved in the researches have been reported and are not limited to those described in the 70s by Beecher[15]. In India, a clinical trial with streptokinase was carried out, of which study protocol had not been submitted to the assessment of a REC; the research subjects were not informed that they were participating in a research and therefore, no FICF was obtained[16-18]. In a clinical trial with cariporide carried out in Argentina, it was verified that around 80 signatures in the FICF had been forged and that the ones who had indeed signed it were unaware of its content. Medical records were modified and disappeared[19].

Finlay et al[20] evaluated clinical research articles published in the 5 most renowned medical journals (BMJ, Lancet, Annals of Medicine, JAMA and New England Journal of Medicine) and concluded that, although infrequent, articles that did not explicitly mention previous approval by a REC or the use of the FICF were still being published by the scientific journals, without a forewarning to the reader on this deficiency at the editorial. The last version of the Declaration of Helsinki still recommends the refusal to publish articles that do not follow the principles established in this document[21].

A significant percentage of authors stated that they had used diagnostic techniques/methods or medications in their researches. However, the analysis of the abstracts and the study design suggested that the drug or the diagnostic method was not the study object. That fact might justify the low percentage of reported adverse effects and the lack statistically significant association between studies like these and their submission to a REC.

Approximately 60.0% of the authors stated that they had the authorization from the Head of the Institution where the research was carried out; however, throughout the interview, 27.7% reported that, in fact, this authorization was obtained from the Heads of the Departments, such as the Emergency Department, Infirmary and Coronary Unit - and not from the Head of the Institution. It is noteworthy the fact that the Head of the Institution is co-responsible for the research, as well as the REC that evaluated the project, according to what Resolution 196/96 states[1]. The statistically significant association between studies that received the approval of the Head of the Institution and the submission to a REC reflects simply the fulfillment of the instructions established in Resolution 196/96 by the authors that submitted their researches to a REC, as obtaining the approval from the institution is one of the requirements of the REC. However, it is noteworthy the importance of the role of the Heads of the Institutions in stimulating and requesting that researches being carried out their institutions be evaluated by a REC.

A significant percentage of the researches presented at the congress were carried out in public health institutions, where the lower economic-social classes seek medical treatment. The low socioeconomic status and level of schooling of these research subjects make them fit into a concept of extrinsic vulnerability, as mentioned by Rogers and Ballantyne[22]. In our outpatient clinic practice, we have observed that many of these subjects report difficulties to return to the outpatient clinic for follow-up due to lack of financial means to pay for transportation to the hospital. This context contrasts with the fact that only 1% of the authors reported that the subjects were paid for the expenses brought on by the research, such as the costs of transportation to the healthcare service. On the other side of this question is the low percentage of researches supported by Scientific Development Agencies, which contributes to justify these results.

The great majority of the authors has never read Resolution 196/96 and its amendments and the researches submitted to the assessment of a REC were more often submitted by authors that had already read such resolution. These data corroborate the importance of knowledge in practical practice, which can also be demonstrated by the significantly higher proportion of authors with a higher level of technical formation among those who had already read the resolutions on ethics in research with human beings.

In contrast to these data, we verified the lack of a statistically significant association between researches from teaching institutions and submission to a REC. The lack of specific disciplines in the curriculums of the universities or openings throughout the medical formation aimed at discussing ethical problems regarding research with human beings can, in part, justify these results.

Most of the first authors of the studies presented at the congress were medical residents. This information, associated with the lack of specific basic knowledge in research methodology and the short time available during the medical residency period to perform studies with a more complex methodology can justify the statistically significant influence of the study design on the research submission to a REC.

No cohort studies or clinical trials were presented. The cross-sectional studies were more frequently submitted to the evaluation of a REC. Furthermore, many studies presented in congresses are carried out based on the analysis of data that have been collected due to the interest aroused regarding study submission when the deadline for submission is near. Therefore, some studies are sent without a clear design and methodology and without having been submitted to a REC.

It is worth mentioning that, according to Resolution 196/96, case reports and case series, as long as they involve human beings in any way, must be, for that reason, evaluated by a REC[1]. Some authors defend that observational epidemiological researches, based on pre-existing data, obtained through the retrospective review of medical files are exempt from ethical review[8]. This reasoning represents a return to Resolution 01/88, admitting that scientific integrity is a synonym of ethical integrity. The fact that the data were recorded in databases or medical files and were not collected prospectively does not prevent ethical transgressions, as their inappropriate use can put human dignity and rights at risk. In cases where it is not possible to obtain the research subject's authorization through the FICF, due to the fact that these data have already been collected, Resolution 196/96 states that it is necessary to obtain the authorization of the person in charge of these data (Hospital Director, Head of the Service, etc) and justify to the REC why it is not possible to obtain the FICF.

Willison et al[23] evaluated the diversity of conducts by the REC when approving protocols of which source of data consisted of medical files. They interviewed REC coordinators related to Schools of Medicine in Canada and reported that 47.0% of them require individual consent from the research subject. It is not the researchers' responsibility to decide to submit their researches to the evaluation of a REC, when the study involves collection of data from medical files or databases, due to the clear conflicts of interest that are involved in such decision.

The results presented herein are subject to an information bias on the part of the interviewees. With the objective of minimizing such bias, the data were collected exclusively from the first authors or those who presented the FC. We tried to minimize possible memory biases, in cases where the collection was not possible during the congress, by contacting the authors as soon as possible, up to three weeks after the congress.

Regarding the ethics in research and, consequently, the protection to research subjects, Brazil has a prominent position in Latin America, due to the fact that the country has well-defined regulations that deal with this question and that are contemplated in Resolution 196/96 and its amendments. However, the results of the present study have shown that most researches presented at the *XVIII Congresso Pernambucano de Cardiologia* did not follow Resolution 196/96, suggesting that the knowledge diffusion and update, as well as incentive and monitoring of the use of this knowledge must be improved. As most researches presented at the congress had been carried out in institutions in the same state, educational actions aimed at professionals from research institutions, universities and teaching hospitals, as well as at the potential research subjects treated at those institutions, must be planned and more easily achieved.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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