Ethical and normative aspects of a multicenter clinical study of pediatric oncology

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Abstract

The article aims to assess compliance with normative and ethical aspects of a multicenter clinical trial protocol in pediatric oncology. The analysis of the regulatory proceeding, as well as the process of obtaining the Consent of 180 patients from 16 institutions was undertaken through the medical records of patients. Ten of the sixteen centers submitted the Protocol to the Institutional Review Board. Regarding Informed Consent, 161 of 180 patients consented and signed by the researcher. The Coordination Study understands that there are some limitations related to these aspects, which was already expected because the study involved a significant number of institutions. For this reason, especially in multicenter projects, a more rigorous monitoring in terms of guidance and supervision of the regulatory proceeding as in the process of obtaining the Informed Consent, could prevent situations such as those encountered.

Key words: Ewing, Sarcoma. Informed consent. Ethics. Oncology service, hospital. Multicenter study.

Resumo

Aspectos éticos e normativos de um estudo clínico multicêntrico de oncologia pediátrica

O artigo objetiva avaliar o cumprimento dos aspectos éticos e normativos de um protocolo de experimentação clínica multicêntrico em oncologia pediátrica. A análise do trâmite regulatório, bem como do processo de obtenção do termo de consentimento de 180 pacientes de 16 instituições, foi empreendida por meio das fichas clínicas dos pacientes. Dez dos dezesseis centros submeteram o protocolo ao comitê de ética em pesquisa local. Em relação ao termo de consentimento livre e esclarecido, 161 dos 180 pacientes consentiram e assinaram o termo aplicado pelo pesquisador. A coordenação do estudo compreende que houve algumas limitações relacionadas com estes aspectos, o que já era previsto, pois o estudo envolveu significativo número de instituições. Por este motivo, especialmente em projetos multicêntricos, uma monitoria mais rigorosa, tanto em termos de orientação e fiscalização do trâmite regulatório como no processo de obtenção do TCLE, poderia prevenir situações como as encontradas.

Palavras-chave: Sarcoma de Ewing. Consentimento livre e esclarecido. Ética. Serviço hospitalar de oncologia. Estudo multicêntrico.

Resumen

Aspectos éticos y normativos de un ensayo clínico multicéntrico de oncología pediátrica

El artículo tiene como objetivo evaluar el cumplimiento de los aspectos normativos y éticos de un protocolo de ensayo clínico multicéntrico en oncología pediátrica. El análisis del proceso regulatorio, así como el proceso de obtener el consentimiento de 180 pacientes procedentes de 16 instituciones se llevó a cabo a través de las historias clínicas de los pacientes. Diez de los dieciséis centros presentado el Protocolo para la Ética en la búsqueda local. En cuanto a caducidad de Consentimiento, 161 de 180 pacientes consentido y firmado por el investigador. Coordinación del Estudio entiende que hay algunas limitaciones relacionadas con estos aspectos, que ya se esperaba debido a que el estudio incluyó un número significativo de instituciones. Por esta razón, especialmente en proyectos multicéntricos, un control más riguroso en términos de orientación y supervisión del procedimiento regulador como en el proceso de obtención de la IC, podría evitar situaciones como las que se encuentran.

Palabras-clave: Sarcoma de Ewing. Consentimiento informado. Ética. Servicio de oncología en hospital. Estudio multicéntrico.

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Research article

Recent epidemiological data show that the survival of patients with children and teenage cancer has improved significantly in the past 20 years [1,2]. Among the factors that have most contributed to improve the prognostic in this population are: the increase of specialized centers with intensive care and radiotherapy units; the availability of more accurate pathological and imaging exams, as well as more effective antibiotics; the development of new surgical techniques, and, most of all, the use of more effective and less toxic chemotherapy treatments identified in clinical studies [1].

Considering that the incidence of children and teenage cancer is rare, an institution will seldom provide individual care for a sufficient amount of patients to conduct randomized clinical trial and obtain results scientifically valid within a reasonably short observation period. Therefore, the action of cooperative groups in pediatric oncology stimulating the inclusion of patients from different institutions in these studies, always respecting the concepts that outline clinical research, resulted in the identification of the treatments currently available.

The first international cooperative clinical studies in oncopediatry appeared in the 1970s, when researchers of many research centers recruited patients with the aim of applying and comparing different treatment regimens. The favorable results observed in these studies were incorporated to healthcare, improving significantly the cure rates within this population. However, despite the high survival rates among patients, cooperative groups still search more effective therapeutic schemes, always through clinical studies [3,4].

In Brazil, the *Sociedade Brasileira de Oncologia Pediátrica - SOBOPE* (Brazilian Society of Pediatric Oncology) recognizes the need of cooperative studies which take into account the national reality. Consequently, it has organized and encouraged the formation of cooperative groups to all types of tumors. These groups were created for the implementation of treatment and prospective research protocols, always considering the reality in each center, using resources available in the different institutions which assist children with cancer throughout the national territory.

The cooperative studies are very important in the scientific field and are characterized by being simultaneously executed in many research institutes, conducted by different researchers and supervised periodically by clinical research monitors. During monitoring visits, these professionals are responsible for verifying the information generated in each research center and confirming the data obtained. In addition, they evaluate if the clinical study is being conducted according to Good Clinical Practices [5] principles and in compliance with all applicable laws.

Ethical norms in research

Ethical and legal aspects in regard to the participation of patients in clinical studies are assured, firstly, by the approval of the clinical research by the Ethics Research Committee (ERC); secondly, by the process of obtaining written informed consent using Informed Consent Form (ICF), which details the nature of the study and describes the potential benefits, risks and damages to the patient that can happen during the conduction of the clinical study[6,7].

It was established, in the Declaration of Helsinki [8], the creation and implementation of ERC. In Brazil, Resolution 1/88, the first resolution of the *Conselho Nacional de Saúde-CNS* (National Health Council), established the need for ERC [9]. Afterwards, Resolution CNS 196/96 [10] strengthened issues involving research ethics and established that, in addition to ERC, it was also necessary the creation of the *Comissão Nacional de Ética em Pesquisa - Conep* (National Research Ethics Committee), establishing an integrated system of evaluation of research protocols. The Brazilian or international norms of research in health state that all projects with human beings must be submitted to analysis and approval of an ERC before its execution. The guideline VII.14.a of Resolution CNS 196/96 describes that *the ethics review of any proposal of research involving human beings must not be dissociated of its scientific analysis* [10]. In 1995, a survey performed by Francisconi *et al*, about Brazilian ERC (known as 'CEP' in Brazil), verified that among the 26 Brazilian hospitals evaluated, only 15 had local ERC. The authors lament about the inadequate way that clinical research was being performed in some institutions and emphasize the importance of knowing national and international legislations as well as the researchers´ attributions at ERC [11]. At the end of 2005, ten years after the survey performed by Francisconi *et al*, Conep registered 448 ERC in Brazil, among 650 requests [12].

Ethics norm requests that the participating patient provides his/her free informed consent, fundamental approach to ensure the right to autonomy and decision making in regard to his/her participation in the clinical study [10].

According to the definition established by Good Clinical Practice [5], informed consent *is the pro-*

cess by which a subject voluntarily confirms his or her willingness to participate in a particular research study, after having been informed of all aspects of the research study that are relevant to the subject's decision to participate. This consent is recorded in writing through Informed Consent Form which must be completed and signed [13]. In addition, Resolution CNS 196/96, in the introduction of guideline IV, affirms that *in order to respect human dignity, research must only be carried out after informed consent that had been freely given by the prospective research subjects, whether individuals or groups, who have expressed their agreement to participate in the research, on their own behalf and/or through their legal guardians* [10].

Information about the consent must be provided verbally and in writing, in comprehensive language. In addition, researchers must be available to clarify any doubts. The patient invited to participate in the study might need some time to talk with his/her family before taking the decision. In these cases, the researcher must respect the patient's request. The signature of ICF by the patient is the last stage of the process and defines the moment when the participant records his/her authorization to participate in the clinical study.

Over the past years, several national and international studies have been published on the vocabulary and on the structure of the text of ICF used in researches. Many of these works indicated that the text is not understood well enough by the patients [14,15]. This is often caused by inadequate use of words and expressions in the term that sometimes is written in scientific jargon. Furthermore, most participants have little schooling, which makes it difficult to read fluently and to understand longer sentences, as well as words that are not in colloquial language [16].

One of these studies demonstrated that the use of audiovisual resources can make communication with patients easier: it was observed that patients who used this type of resource demonstrated better understanding on the topic when compared to patients who did not use it [6]. In regard to alternative ways to improve the participants' comprehension of the free and informed consent term, Abd-Elsayed *et al* recently described that consent terms highlighted or emphasized – for example, using different textures of paper or unusual shape – did not improve the comprehension of patients who participated in clinical studies [17].

The achievement of ICF in clinical studies conducted in pediatric oncology field demonstrates peculiar aspects in regard to the target population: children and teenagers. It is important to consider that in this age, the patients are emotionally more insecure and vulnerable to adversities, what is enhanced by impact of the cancer diagnosis. Due to the absence of legal rights for the child or teenager to give his/her own consent, the document is signed by the parents or legal representatives. However, in addition to their consent, it is necessary to obtain free informed consent of the own child, considering his/her ability of understanding. In Brazil, children and teenagers' participation in clinical studies is also regulated by Resolution CNS 196/96 [10].

Brazilian treatment protocol for Ewing's sarcoma

The Brazilian treatment protocol for patients who have Ewing's sarcoma family tumors was elaborated in 2004 based in the consensus among researchers of institutes dedicated to help children with cancer. This group understood that, considering that Brazilian patients with Ewing's sarcoma are generally diagnosed when the disease is in advanced stage compared to patients of North America or Europe, it would be necessary to elaborate and apply a treatment program adapted to the reality in Brazil and, later, to the one in Uruguay. Basically, the protocol recommended the treatment based on the group of risk, that is, the patients with more advanced disease, group called high-risk, received additional chemotherapy treatment when compared to patients in the low-risk group, who received conventional treatment.

The aim of this study was to evaluate the compliance of ethical and normative aspects of a multicenter clinical experimental protocol on pediatric oncology.

Materials and method

This is a retrospective cross-sectional study. The universe of research was composed of 180 patients with Ewing's sarcoma from 15 research centers in Brazil and one in Uruguay – totaling 16 participating centers. The coordination of the study is formed by Brazilian researchers and the team of monitors from the clinical research monitoring unit (*unidade de monitoração de estudos clínicos* - Umec) of the research center of one of the coordination members. Data were collected from information registered on medical records and files of patients, treated from 2004 to 2010.

The project Brazilian protocol for treatment of patients with Ewing's sarcoma family of tumors was elaborated by a group that includes pediatric oncologists, orthopedic surgeons, radiotherapists and pathologists aiming to evaluate if the therapeutic program proposed would be successful in regard to the tumor response and security profile. The design of the study consisted in classifying each patient in one of the two groups of risk – low risk or high risk –, considering the main clinical aspects that show prognostic influence.

The criteria used to characterize patients as high risk considered the presence of at least one of the following items: LDH serum level 2,5 times above the highest level; primary tumor in pelvic location; presence of metastasis; or unresectable tumor. The other patients were placed in low risk group. This clinical study recommended three clinical evaluations at different times. The first one, before the beginning of the treatment; the second one, after the phase called "induction" and the third one, after the end of the treatment. With such information, it would be possible to compare the exams in an evolutionary way. The tumor response obtained in this study was analyzed according to criteria recommended by Response Evaluation Criteria in Solid Tumours (Recist). The toxicity evaluation considered criteria of Common Toxicity Criteria version 3.0, commonly used to evaluate adverse events in patients treated with chemotherapy.

Once the treatment scheme was defined, the members-coordinators of the study wrote and sent the protocol to be approved by the ERC of *Hospital de Clínicas de Porto Alegre* (HCPA). After approval the pediatric oncology centers that would be invited to participate in the protocol were selected. The selection considered the centers whose clinical staff included one pediatric oncologist and one orthopedist who had experience with bone tumors, in addition to the availability of imaging exams like computed tomography and/or magnetic resonance and the chemotherapy drugs indicated by the study. It was also considered presence of the whole support team which covers healthcare to children and teenagers with cancer.

After the identification of centers in compliance with the criteria to participate in the study, the coordination sent formal invitation, by telephone and/or e-mail, to the respective researchers. Subsequently, a research monitor established contact with each potentially interested researcher and strengthened the information on the protocol, including aims, criteria of inclusion, design of the study, treatment and parameters of response evaluation criteria. This professional also explained how would be the regulatory procedures which consist of: submission of a project to ERC; the ethical procedures which include, especially, the application of ICF; the data recorded in medical reports; and the monitoring visit procedures along the study.

Centers which agreed to participate in the protocol received a visit of the monitoring team to clarify doubts of the researcher and his/her team, before including patients. In this meeting, the infrastructure of each research center, the capacity of each professional involved and the ability to recruit patients were also evaluated. Besides, the doubts regarding filling the medical reports were solved and information on the local ERC was collected. All collaborating centers participating in the study received, by electronic means, the written version of the protocol, of the ICF and of the medical reports to submit them to local ERCs for opinion.

The coordination established that only after the approval by the local ERC, the institution would be authorized to include patients in the study. Once the inclusion of patients started, research monitors conducted visits to the institutions analyzing medical reports, documents of the researcher's file, documents submitted to local ERC and source documents, as well as the medical records. All information and pending issues to be solved in the following visit were registered on medical reports´ copies of each patient – kept in the file of the coordinating center of the study.

With the clinical study in progress, an Uruguayan center was invited to participate in the study. The invitation considered its geographical proximity, the potential inclusion of significant number of patients, and affinity with the coordinating center, observed in previous experiences with other protocols. The fact that Spanish is the official language in Uruguay was not considered an obstacle to their participation in the protocol.

Results

Most of the 180 patients were male, with age group between 0 and 28 years old, white skin, with localized disease and belonging to high risk group, according to the protocol criteria. The general characteristics of patients are described in Table 1.

Table 1. Characteristics of patients and disease (N=180)

Characteristics	N (%)
Age of diagnosis in years	
Average	12
Variation	0,2 – 28,9
< 14 years old	108 (60)
≥ 14 years old	72 (40)
Gender	
Male	109 (60,5)
Female	71 (39,5)
Skin color	
White	148 (82,2)
Other	32 (17,8)
Histological analysis	
Ewing's sarcoma	86 (47,7)
Primitive neuroectodermal tumor	69 (38,3)
Askin's tumor	18 (10)
Other	7 (4)
Group of risk	
High	127 (70,5)
Low	53 (29,5)
Stage of the disease	
Localized	110 (61,2)
Metastatic	70 (38,8)

Submission of the Research protocol and ICF to ERC

Sixteen institutions have included patients in this clinical study. Ten (62,5%) centers submitted the research protocol and respective ICF to the local ERC, which approved them. The researchers responsible for these centers sent the letter of approval emitted by the local ERC via e-mail or fax to the unity of research of the coordinating center. Despite the recommendation of the coordinating center, five (31,2%) Brazilian research centers and the Uruguayan center (6,3%) did not submit the project to a local or regional ERC.

Signature of ICF

In the reviewing of the reports performed by research monitors, it was observed that 161 of 180 (89,4%) patients and/or their legal representatives consented and signed the ICF applied by the researcher responsible or people designated by him/her. Of these 161 cases, 123 (76,4%) signed specific ICF of the protocol previously approved by ERC and 38 (23,6%) consented the treatment upon signing appropriate ICF for each institution – of these 38 patients, 23 (60,5%) were under healthcare in the Uruguayan institution and 15 (39,5%) in Brazilian institutions.

In regard to the date of signature of ICF, 141 (87,6%) patients and/or legal representatives signed the ICF after receiving information on the clinical study proposed. However, the date of signature of ICF of 20 patients (12,4%) is subsequent to the beginning of the treatment.

Monitoring visits did not found any type of ICF, either specific of protocol or institutional, in the medical records of 19 (10,5%) patients. These patients were distributed in seven different institutions. The results exposed above in regard to ICF are summarized in Tables 2 and 3.

Table 2. Signature of Informed Consent Form (N=180)

	N (%)
ICF of protocol	123 (76,4%)
Institutional ICF	38 (23,6%)
Uruguay	23 (60,5%)
Brazil	15 (39,5%)
Did not sign ICF	**19 (10,5%)**

Table 3. Time of signature of Informed Consent Form (N=161)

Signature	N (%)
Before the beginning of treatment	141 (87,6%)
After the beginning of treatment	20 (12,4%)

Discussion

The survival indexes of patients with children and teenage cancer have increased significantly in the last years, result of the set of actions which includes basic healthcare improvement, availability of more accurate laboratory and imaging exams, and use of more efficient treatments identified by multicenter clinical studies. Children and teenage cancer is considered rare condition; therefore, only with the conduction of studies involving many institutions, it is possible to obtain significant amount of patients to meet the aims in reasonably short period of observation.

Nowadays, both cooperative clinical studies and studies coordinated and sponsored by the pharmaceutical industry must obey the same ethical, scientific and quality standards. The studies which involve registration of new drugs must be submitted to monitoring, auditory and inspections by third parties. In clinical studies which involve only assistance issues inherent to daily clinical patients healthcare, the medical officer must obey Good Clinical Practice precepts, behavior that must be followed independently if the patient is included or not in any study protocol.

There are many cooperative studies that add important knowledge on safety and effectiveness of one or more approved drugs. In some countries, like the United States of America, these studies demonstrate continuous monitoring by professionals of the coordinating center itself, as observed by many authors who express concern on data quality [18-22]. Some descriptive studies demonstrated the importance of specific training to research teams that conduct clinical studies in oncology field [19,20].

The monitoring visits influence effectively the quality of conduction of these studies and have as allies, the knowledge and experience of the researchers [20]. Knatterud *et al* created a guide to standardize the quality control of multicentric studies, including recommendation of appropriate actions to the issues that happen more frequently during a clinical study [21].

It is important to emphasize that in addition to the concern on reliability of data collected in the clinical study, other aspect equally important, which also requires special attention, is the adequacy of the study to ethical, legal and scientific recommendations of the current legislation. Such aspects have been focus of attention of cooperative studies in pediatric oncology field, not only in those developed in Brazil, but also in institutions worldwide.

In regard to ethical and legal aspects discussed in this article, any clinical research involving human beings must follow international and national norms and guidelines. After planning and designing the research, the research protocol and ICF must be evaluated and approved by ERC and, in some cases it is necessary evaluation by Conep.

In the clinical study, the coordinating center submitted the research protocol and respective ICF to local ERC. After approval, the copy of the protocol and ICF were sent to all institutions interested in participating in the study, so they could submit it to their ERC. This documentation was sent via e-mail or post, including letter of approval of ERC and HCPA attached. The candidate centers were informed that if there was any doubt on regulatory context, research monitors would be available for clarifications. In addition, the coordination of the clinical study insistently recommended candidate institutions to send their research protocol and ICF to be approved by local ERC.

Five Brazilian research centers did not send the project to be approved by local ERC. The justification for not doing this procedure is not recorded

in monitoring reports. The reasons why some data were incomplete and difficult to be rescued by the currently operating team were: a) in 2004, when the protocol was established, many researchers were still not familiar with the clinical research context; b) it is a treatment protocol which recommended use of chemotherapy scheme very similar to assisted treatment; c) in some collaborating institutes there were changes in the team involved with the project; d) it is also possible that these centers were not used to send projects to approval by the local ERC, and e) monitors did not know or were not used to keep up with such requirement.

In 2004, the Uruguayan research center did not submit the project to ethics committee because the legislation of that country did nor demand the approval of projects of this nature by an ERC. However, in 2008, the Decree-Law 379/08 of the Executive Power of Ministry of Health of Uruguay – very similar to Resolution CNS 196/96 – came into force. The items 26 and 28 of Chapter VI of this decree specify, respectively, that *all research must be submitted to approval of Ethics Research Committee and, if there is impossibility of forming an Ethics Research Committee, the institution must have its project approved by another institution which has Ethics Research Committee, observing the parameters of the National Ethics Research Committee* [23]. Therefore, as the planning and the regulatory context of the study began in 2004 and this regulation went into effect in 2008, the Uruguayan research center applied the protocol without submitting it to Ethics Research Committee. It is also emphasized that, in the decree mentioned, there was not any mention to the submission of projects in progress, which started before 2008. Curiously, the Uruguayan institution contributed satisfactorily, having applied its institutional ICF to all participating patients and showed the lowest amount of pendency during all period of study, besides having included significant number of patients.

The process of collecting ICF defines that the patient or his/her legal representative are informed about the risks, discomforts or benefits that the clinical study can provide, aiming, this way, to preserve the autonomy principle in regard to his/her participation. In Brazil, the application of ICF in clinical research is based on Resolution CNS 196/96, in addition to international norms and guidelines. Each research center must elaborate its own ICF for daily activities. However, in national or international multicentric clinical studies, it must be adopted a unique model for all participating institutions, avoiding contradictions in the process of elaboration of the document. In clinical research, only the ICF specifically drafted to the project (and subsequently approved by ERC) has regulatory value.

Based on Resolution CNS 196/96, the ICF of the project was elaborated by the researcher responsible for the clinical study, meeting all legal requirements. In this clinical study, all research centers were oriented to use the same ICF of the project. Thirty-eight participating patients signed the consent by institutional ICF, emphasizing that the same is only valid for routine assistance activities. However, in a clinical study, if the researcher chooses institutional ICF, it must include specific information in regard to the research to be developed, version that must be submitted to the approval of ERC. The use of institutional ICF for application of chemotherapy was considered protocol deviation and this irregular behavior was recorded in the monitoring reports of the centers.

The item "c" of guideline IV.2 of Resolution CNS 196/96 affirms that ICF must *be signed or identified through dactyloscopic identification system, by every subject of the research or by their legal representatives.* It is important to emphasize that the signature is very important, but fundamental is the process of obtaining consent which, must be preceded by the needs of information supply. It is obligatory that the responsible researcher or his/her team is not only sure that all participating patients in the research had signed specific research ICF but also understood its content thoroughly. In this clinical study, it was verified that 19 patients or their legal representatives, treated in seven different institutions, did not sign ICF. Such attitude is violation of protocol and the situation of these patients should be evaluated individually so the exact reason of absence of ICF is understood.

However, as it was mentioned previously, the reason why these patients did not sign the consent was not recorded in medical records or monitoring reports. It is likely that this failure is due to the fact that ICF presentation is not routine activity in these centers. As these patients received treatment according to the protocol, the coordination of the study, in this case, considered this sample and did not exclude the ones of the analysis of the results because data collected in these patients could contribute for further clinical findings. It is nevertheless observed that it is still necessary to strengthen knowledge and to improve the researchers' practices regarding aspects related to the process of obtaining informed consent in studies involving human beings [23].

The guideline IV.4 'a' of Resolution CNS 196/96 advocates in regard to the restriction of freedom and clarification necessary to adequate consent of the participating patient in research, in situation of substantial decrease in his/her consent abilities. The resolution indicates that in these *cases, the requirements of free informed consent must be met by the legal representatives of the participants, keeping the guest's right of information, in the limit of his/her ability* [10]. Whenever it is conducted researches with children and teenagers, these ones must actively participate in the process of obtaining consent. In this case, two types of consent will be elaborated for the clinical research: one consent term for the underage patient (being invited to participate in the research) and one consent term for the legal representative (being informed that the underage patient is being invited to participate in the research and requesting his/her authorization).

So, it is mandatory that every patient involved in clinical studies in pediatric oncology field also participate in the consent process through signature of the authorization term, as long as he/she knows how to write his/her own name. In the clinical study protocol, there was not any authorization term for children and teenagers.

As ICF was stored in the corresponding research center, it was not recorded in the coordinating center if ICF was signed by the parents or by the patient. As it was mentioned before, the most adequate procedure would be including an authorization term for the underage patient, in addition to the ICF for his/her legal representative. It was also observed that 20 patients signed the ICF after the beginning of chemotherapy drugs administration. However, all of them, before starting the treatment as stated in medical records, received from the responsible researcher, verbal explanation on the disease and treatment proposed by Brazilian protocol.

Finally, the deviations and violations described in this article were handed to the coordination of the study and the monitoring team. We can conclude that the non-compliances found can be due, especially, to the change of members in the research centers' team, to the lack of regulatory and normative knowledge and to insufficient attention and communication between the research monitor and the assistance team. It was observed that most monitoring reports were written objectively, but only some pending issues were described in more detailed way. This is an important aspect that can interfere in data analysis, since the abundance of information contributes to more adequate clinical research interpretation, besides allowing identifying changes and acting immediately with corrective actions. For this reason, especially in multicentric projects, more rigorous monitoring, in terms of orientation and supervision within the regulatory context, such as in the process of obtaining ICF and authorization term, could prevent situations like the ones found here.

Final considerations

In the last years, clinical studies have been extremely important in the identification of new drugs and therapeutic schemes in pediatric oncology field. With the increase in amount of clinical studies in this field, it is fundamental that researchers are more and more familiar with ethical, legal and regulatory aspects of clinical research for the studies to ensure dignity and respect to the participating patients.

The coordination of the study understands that there were some problems regarding these aspects, what was already expected, as the research involved significant amount of institutions of many places in Brazil and abroad, each of them with peculiar characteristics in healthcare routines. Another important issue is that, at that time, many institutions were still not familiar with the regulatory aspects of research involving human beings.

Despite being a therapeutic research aimed to evaluate if the program proposed would be successful in relation to the tumor response and security profile, it is fundamental to reaffirm that the treatment proposed in the research protocol is the same standard treatment provided in all institutions which participated in the study. Therefore, if this clinical study was not performed, patients with Ewing's sarcoma treated in these institutions would receive the same treatment scheme proposed, but they would not be benefited by data quality control. However, we consider that, even with some ethical and regulatory irregularities identified in this article, the conduction of a clinical study in this field must consider the potential benefits to patients, especially in cases which therapeutics are already proven in terms of security, efficiency and effectiveness, as it happened in this study.

Under such circumstances, it is important to consider the benefit/risk ratio as ethical parameter of evaluation of the study, which, in this case, proved to be favorable, as being the standard therapeutics, the study does not imply additional risk and

brings the benefits of data quality control and methodic monitoring of chemotherapy drugs effects by the monitoring team.

We know that it is obligatory having approval of the research project by CEP/Conep and process of obtaining the ICF. Such requirements have been discussed in many medical congresses and also meetings on clinical research in Brazil and worldwide. The compliance with ethical, regulatory and technical norms is fundamental for a clinical experiment to be well conducted, because they lead to diffusion of knowledge and scientific experimentation to the professionals involved and society. In addition, such compliance increases the security and protection level of participating patients, increases the qualification level of participating institutions and stimulates the adhesion of patients to the research protocol proposed.

Finally, the authors recognize and thank the effort and participation of each research center.

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