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Ethics in research with children and teens: in search of virtuous standards and guidelines

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Abstract

During the course of human history, children and adolescents have often been the victims of science in clinical studies. When society was confronted with the horrors of the experiments conducted during World War II, it issued the Nuremberg Code, excluding minors from any such studies as they lack the competence to give autonomous consent. This permanent requirement of the code has resulted in therapeutic orphanhood for many aggravations of the health status of this population. Those who care for children and adolescents now face a dilemma: on one hand, they defend special protection for the group, but on the other, they work to not exclude them from the benefits that science and technology has to offer. Therefore an effort to balance these conflicting principles has emerged through the development of standards and guidelines for such special protection. The purpose of this article is to discuss those guidelines.
Keywords: Child-Adolescent. Research. Ethics. Guidelines as topic.

Resumo

Ética em pesquisa com crianças e adolescentes: à procura de normas e diretrizes virtuosas

Crianças e adolescentes foram vítimas da ciência em pesquisas clínicas, por grande período da história da humanidade. Quando a sociedade, diante dos horrores das pesquisas realizadas durante a Segunda Guerra Mundial, adotou o *Código de Nüremberg*, crianças e adolescentes foram excluídas das pesquisas por não terem competência para dar seu consentimento autônomo, exigência pétrea desse código, o que resultou em orfandade terapêutica para muitos agravos em sua saúde. Os que cuidam de crianças e adolescentes foram postos diante de um dilema: por um lado, defendiam a proteção especial para esse grupo; por outro, trabalhavam para não excluí-los dos potenciais benefícios oferecidos pelos avanços em ciência e tecnologia. Iniciou-se, então, um exercício para balancear os princípios em conflito, com a elaboração de normas e diretrizes de proteção especial. Discorrer sobre elas é o objetivo deste artigo.
Palavras-chave: Criança-Adolescente. Pesquisa. Ética. Guias como assunto.

Resumen

Ética en la investigación con niños y adolescentes: en busca de normas y directrices virtuosas

Niños y jóvenes fueron víctimas de la ciencia en investigaciones clínicas durante un largo período de la historia de la humanidad. Cuando la sociedad, ante los horrores de las investigaciones o estudios durante la Segunda Guerra Mundial, emitió El Código de Núremberg, los niños y adolescentes fueron excluidos de las investigaciones por no tener competencia para dar un consentimiento autónomo. Esta rígida exigencia de dicho Código, resultó en una orfandad terapéutica para muchas complicaciones en la salud de estos niños. Los que cuidan de los niños y adolescentes se vieron colocados ante un dilema: por un lado, defienden la protección especial para este grupo y, por el otro, trabajan para no excluirlos de los beneficios que la ciencia y la tecnología pueden ofrecer. Se inició, entonces, un ejercicio para equilibrar los principios en conflicto, con la elaboración de normas y directrices de protección especial. Discutir en torno a ellas es el objetivo principal de este artículo.
Palabras-clave: Niño-Adolescente. Investigación. Ética. Guías como asunto.

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Declara não haver conflito de interesse.

In recent decades, the advancement of biomedical research helped saving, prolonging and improving the lives of thousands of children and adolescents. The development of vaccines against polio, measles, mumps, Haemophilus, pneumococcus and several other diseases that affect children resulted in dramatic reduction in deaths and sequelae and discomforts resulting from these pathologies. At the same time, children and adolescents have also been favored for evidence of damages and ineffectiveness of other standard therapies considered, such as for example, the use of high doses of oxygen in premature infants with hyaline membrane.

Despite these advances, children have not benefited from advances in biomedical research in the same proportion as adults. Many medications with potential use in children and adolescents have not been tested in studies that involved them, and the drugs they are prescribed based on the judgment of physicians who, for lack of an alternative, extrapolate for children and adolescents the results obtained in studies with adults. Whereas children and adolescents are not mere miniature adults, because they physiologically differ from them in myriad ways, extrapolation based on adult dose and weight or age of the children and adolescents can be dangerous and lead to under- or overdosing or specific adverse effects, not evident in adults.

In addition, some conditions obviously only occur in children, such as prematurity. Similarly, certain genetic diseases such as phenylketonuria, if not treated on time, leave severe sequelae or lead to death. Other conditions, such as influenza, certain cancers and arthritis forms occur both in adults and in children and adolescents, but its physiopathology, severity, progression and response to treatment differ between the two groups.

A review of the Physician's Desk Reference of 1991 showed that 80% of the listed medications had inserts that did not make reference for use in children [1-3]. Based on 1991-1997 data involving new drugs, the Food and Drug Administration (FDA) found that 62% of them did not refer to their use in children [4]. In the year 1995, the American Academy of Pediatrics argued that this fact brings a dilemma for pediatricians, who often do not treat children and adolescents with potentially beneficial medications, or treat them with drugs based on adult studies or on specific empirical experiences [3]. These children may even benefit sometimes in the second case, but they are also affected because the drug dosage was ineffective or toxic. Even if they had some benefit, it is quite possible that they have not received optimal treatment because their physicians had no information about prescriptions validated for this age group.

Carvalho *et al.* [5] studied prescriptions for 51 patients who were checked into the Pediatric Intensive Care Unit (PICU) of Porto Alegre Clinical Hospital (*Hospital de Clínicas de Porto Alegre* - HCPA), between July and August 2002. A total of 747 prescription items were recorded, with a prevalence of 10.5% for not approved medicines and 49.5% for off-label medicines. The "not approved" concept considered drugs not approved for general users, not approved for children, contraindicated for children, manufactured at the hospital, modified at the hospital or without specific dosage for children.

The term "off-label" refers to drugs prescribed differently from the instructions in the insert with respect to age, dose, frequency, presentation, administration or indication for use in children. These authors reported that, from the results of the study published by Turner *et al.* [6] on adverse events caused by drugs in hospitalized pediatric patients, it is likely that certain drugs classified as "not approved" or "off-label" in their study could be the determinant agents of adverse reactions observed by them [5].

Carvalho *et al.* [7], reviewing 318 prescription items in 61 patients (mean of 5 items/patient), between July and August 2011, in a tertiary hospital in southern Brazil, found that only 13 patients were treated with appropriate medications (21%) and the use of unlicensed drugs had a prevalence of 7.5%, and 27.7% for off-label drugs. One patient received 10 unlicensed or off-label medications. The prevalence of off-label drugs was higher in premature infants and in severely ill patients.

The above examples refer to medicaments, but clinically important differences may extend to other areas. Radiation therapy, for example, is able to disrupt normal tissue development in children. Current studies have evidenced increased risk of both brain tumors and leukemia, assigned to the performance of computed tomography (CT) scans in children. It is estimated that the risk of death assigned to a single CT scan is 1 in 1,500 to one-year old patients and from 1 to 5,000 patients aged 10 years or older [8].

Institutions working to expand research involving children and adolescents face a dilemma: on one hand, they want children and adolescents to benefit from the dramatic and rapid progress of science in health care; on the other, they do not want to put them at risk for participating in such research, even though their involvement may be essential to advance their healthcare and their well-being.

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How did we get to this dilemma? How to balance the potentially conflicting goals? To answer the first question, we will start by the historical evolution of ethics in research involving human subjects. This may show one of the reasons, but not all, as we shall see.

Evolution

There is a long history of research on children... but a relatively short history of legal control of this activity [9].

The "martyrdom" – until 1947

According to Kipper and Goldim [10] in health research history there are many records of the use of children in different studies, with and without direct benefit to participants. Edward Jenner developed in 1796, the smallpox vaccine, using it on a 8-year old boy, James Phipps, and subsequently in his own son. In the year 1885, Louis Pasteur tested its rabies vaccine in a boy named Joseph Meister. Swedish researcher, Carl Janson, reported that, in the year 1891, his research on smallpox was being held in 14 orphaned children, although the ideal would be in calves. This choice was made because, according to him, calves were "too expensive" [10]. Such statements caused great indignation in many countries, leading to discussions about the relevance of these studies [10-11]. But ... in 1896, Albert Neisser publicly announced that he had immunized three girls and five prostitutes with blood plasma from syphilitic patients [10].

Lederer and Grodin [12] observed that physicians at that time often used their own children, employees' and slaves' children and institutionalized children as guinea pigs in the early experiments on infectious diseases and immunizations because children were more convenient and had not had contact with researched diseases [10]. For Sagan, quoted by the Advisory Committee on Human [13], even in the 1940s and 1950s, physicians were "kings"; they never had to ask permission for anything. They were in their office and no one questioned their authority [10].

Despite much controversy and some attempts to establish standards and ethical guidelines for research with children and adolescents, such as the creation of the New York Society for the Prevention of Cruelty to Children (NYSPCC), by Henry Bergh in the year 1874, inspired by the American Society for the Prevention of Cruelty to Animals (ASPCA) in 1866 [10-14] the bill of law of US Senator Jacob H. Gallinger in 1900, which forbade scientific experiments in people under 20 years old [10-15], and the approval in Prussia of the first law to order research activities in humans in 1901, which also vetoed research with children [10-16]. However, no public action had the desired impact, and the adoption of ethical standards for voluntary consent would only have repercussions after World War II.

Therapeutic Orphans – 1947-1964

In the 20th century, in Nazi concentration camps, racial, political and military prisoners were placed at the disposal of medical doctors for any kind of experimentation. Right after World War II, at the Nuremberg trials, several medical doctors were considered war criminals. Those trials resulted, in 1947, in the document known as the *Nuremberg Code*, which established principles for conducting research in humans. Article I of the code defines the indispensable condition for its realization: *The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent* [17]. This was the beginning of the so-called "therapeutic orphans" because it excluded children and adolescents from participating in studies, given their legal incapacity to give consent.

Safeguards and incentive to the inclusion of children – from 1964 to present

From the *Nuremberg Code*, the idea of the right to autonomy emerges, which inspired the guidelines that followed. However, the enforceability of this document was not established and incorporated immediately, and the principles contained in it only became part of the researcher-participant relationships with the *Declaration of Helsinki*, drafted in 1964 – this opened the possibility of participation of minors in health research projects, provided that there was consent of their legal guardian and, more recently, consent of the child or adolescent, to the extent of their capacity [18].

However, notwithstanding this document, many abuses continued, and critics of studies with children gained new hopes in 1966, when Henry Beecher [19] published an article reviewing 22 ethically incorrect studies, four of which included children. In addition, in the 1970s, the public became aware of the Tuskegee Syphilis Study. The revelations of this study contributed to the development and approval of various official documents in the United States, such as the National Research Act (1974), the

creation of the Institutional Review Boards (IRBs); the Belmont Report (1978), marking the beginning of the bioethical principles; Research Involving Children (1983); and finally, the Children's Health Act (2000) [20], with additional protection for children participating in research.

Official Brazilian documents such as Resolution 1/1988 of the Conselho Nacional de Saúde (National Health Council – CNS) [21] provided that, when there is the ability to understand, the consent of subjects (under the age of 18) must be obtained, including the consent of their legal representative. Resolution 41/1995 of the Conselho Nacional dos Direitos da Criança e do Adolescente (National Council for the Rights of Children and Adolescents) [22] establishes the right of children and adolescents should not be subjected to clinical, diagnostic and therapeutic trials without the informed consent of their parents or guardians, and their own consent, provided that they are able to do so. The Resolution CNS 196/1996 [23] established that children and adolescents have the right to be *informed*, within the limits of their capacity – although they may not be able to take part in the informed consent process itself – and that the consent for their participation in studies should be given by their legal representatives.

Through CNS Resolution 251/1997 [24], children and adolescents were able to participate more actively in the informed consent process, to the extent of their capacity. Whereas Resolution CNS 466/2012 establishes that in research whose guests are children, *there should be a clear justification for their selection*, *specified in the protocol and approved by the REC and CONEP*, *as appropriate* [25]. In such cases, the clarification and informed consent steps should be followed through by the legal representatives invited to participate in the research, as long as their right to information is preserved, within the limits of their capacity.

International guidelines of the Council for International Organizations of Medical Sciences (CIOMS), of 1993, devote a specific item to research with children. Three items can be highlighted from Guideline 5: 1) *the parents or legal guardians must give their consent by proxy*; 2) *the consent of each child must be obtained to the extent of their capacity*; 3) *the child's refusal to participate in the research must always be respected unless according to the research protocol, the therapy that the child will receive has no medically acceptable alternative* [26].

In May 1996, a set of ethical and scientific standards and guidelines was published for designing, conducting, recording and disclosure of clinical studies, called "Good clinical practices" [27], followed, in March 2005, by the "Good Clinical Practices: Document of the Americas" [28]. These standards are the result of the globalization of clinical trials and aim to establish uniform standards to facilitate acceptance by regulatory authorities of the data obtained in clinical studies conducted in accordance with the ethical principles arising from the *Declaration of Helsinki* and consistent with good clinical practices and regulatory requirements. All multicentric trials, from the publication of these documents, should follow their rules and guidelines.

The objective of this report was to demonstrate that research involving children presented various approaches throughout its history. In the first period, there was total freedom, including the non-recognition of the respect for the dignity of children as people. In response to this, the laws that followed throughout the twentieth century banned the participation of children in research activities, which excluded many of the benefits provided by scientific advances. Currently, research with children and adolescents is being authorized, with restrictions, because it would be unfair not to allow their participation, by excluding them from its benefits.

Needs and challenges in clinical research on children and adolescents

Children and adolescents are therapeutic orphans for several reasons. However, the principle of fairness requires that individuals, groups or communities should not be unfairly included in research projects, but they should not be unfairly excluded from participating and enjoying the potential benefits of the research. Such exclusion is a failure to treat them fairly. Considerations about equity and fairness should define inclusion or exclusion criteria [29].

Clinical research with children and adolescents is more challenging than research with adults. Challenges include ethical and legal aspects, technical and economic aspects. However, despite all the difficulties, these studies are necessary and possible. Many of them have already been started, either in response to the demands from pediatricians or lawyers of family groups, or by initiatives of regulatory institutions or by law, a fact that is forcing the evolution of the current regulatory environment, in search of solutions to balance potentially conflicting objectives. Such initiatives are supported by Article 13 of the *Declaration of Helsinki – Groups that are underrepresented in medical research should be provided*

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appropriate access to participation in research [18] – and the principle of equity, which is an ethical, legal and moral imperative [30]. The challenges can be analyzed from different perspectives, as shown below.

Ethical and legal aspects

The ethical and legal aspects include the complexity of the process to obtain the consent of the parents and the child's consent, and the challenge for the participant to understand and conduct themselves according to the ethical guidelines and the special protection regulations. In addition, the lack of familiarity of companies with the clinical, ethical and regulatory needs of pediatric studies, as well as their concern for the legal consequences of adverse experiences in studies involving children.

Technical aspects

Pharmacotherapy of children and adults differ in several respects, which is why studies in children are needed to ensure their safety and effectiveness. They include: 1) appropriate formulations to their age, to allow an accurate, safe and palatable administration to a universe of children with wide variation in weight and developmental characteristics; 2) adjustment of medications to changes in body distribution and elimination, depending on the age and development (pharmacokinetics); 3) adaptation to changes related to age and development in response to medications (pharmacodynamics); 4) adequacy to variations related to age and development in adverse reactions to medications, both short and long term; 5) specific pediatric diseases and the need for development of specific medications [31].

In addition, the technical aspects cover needs such as: a relatively higher number of children with serious medical issues to justify the study; proper assessment of outcomes for different ages; adjustments in research procedures and environments, in order to accommodate different physical, cognitive and emotional development levels in children; reviewers and researchers specialized in different health areas of children and the range of the normal development of children, and qualified to perform the procedures appropriate to the age of participants; adequate infrastructure of the research center; special techniques for small volumes of data collection.

Economic aspects

The economic outlook encompasses the aspects reported below. Children raise less commercial interests than adults. In many cases, sponsors can never recover the sums invested in the development of medications, especially for rare diseases. Even when it comes to the most common diseases, the number of potential participants can be small, requiring studies in several centers, which would increase logistics and coordination costs. The costs increase because more time per patient is required. The growing number of prescriptions of many off-lable medications reduce the investment incentive of the industry. A pediatric study may last for a long time, prolonging the approval process. The research cost is excessive compared to the size of the potential market. There is no pressure or encouragement on the part of official bodies.

In the United States, research involving children should be in accordance with the policy and guidelines of the National Institutes of Health (NIH) [32], according to which children must be included in all studies conducted or funded by that organization, unless there are clear impeditive reasons for not doing so. Therefore, research proposals should describe plans for the inclusion of children or contain an acceptable justification for excluding them, according to the Code of Federal Regulations (CFR 45 part 46 subpart D) [33]. In the United Kingdom, the Royal College of Paediatrics and Child Health (RCPCH) [34] reviewed in the year 2000, its 1980 guidelines, and Canada did so in 2014, with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) [29]. These documents are the basis of our following reflections.

Current regulatory context: the pursuit of virtue

The general principles of the current regulatory scenario may become more understandable by presenting, in a summarized form, its main arguments drawn from Field and Behrman [31]:

- A robust protection system of participants in general research projects should serve as a basis for the specific case of the protection of children and adolescents participating in research projects, considering the vulnerabilities inherent to their immaturity, they need additional protection to that offered to capable adults. This principle underlies all others;
- The research design should address the physical, cognitive, emotional and social development of children and adolescents, and the protection offered to research participants must be appropriate to their developmental stage;

- Special emphasis should be given to protection against damages caused by standard medical procedures and treatments based on research with adults and not validated for these age groups. However, unless impossible and unreasonable, research with animals or adults should precede studies with children to minimize the risks;
- Well designed and implemented research is essential to improve the health of future children - and future adults. Therefore, they should be encouraged and sponsored, and additional resources and attention must be offered to the pursuit of ethical and legal standards for the protection of participants;
- The protection system of children and adolescents in research projects, as a provider of this protection, should not prevent, without reasonable justification, studies that can benefit them. Children and adolescents are not miniature adults. They have a number of additional specific interests, and no subgroup should be unduly harmed for participating or being excluded from studies;
- The effective implementation of protection policies for children and adolescents requires appropriate expertise in the health of these age groups, at all research design, review and conduct stages. This expertise includes knowledge of child and adolescent psychology and development, as well as awareness of the scientific, psychosocial and ethical needs of these age groups and their own challenges in clinical care and research;
- Research with children should only occur if these studies can not be conducted in capable adults;
- All those parties responsible for research involving children and adolescents must know not only the ethical issues relevant to conduct such studies, but also the special protection to be offered, and they should be advised by professionals with expertise in the care of people in these age groups. In some cases, ethical standards will prevent research, which would initially be desirable;
- The degree of research benefits should be compared with the risk of damages, as well as discomfort or pain – the risk-benefit ratio;
- Research involving children and that do not bring direct benefits (non-therapeutic) are not necessarily incorrect or illegal from an ethical point of view;
- The free informed consent must be obtained from the participant or their legal representative, and the consent or not of the child will only occur if they are able to understand so.

Risks

Categorizing, assessing and weighing the risks of a proposed study with children and adolescents are among the most challenging and subjective tasks for those reviewing research protocols. Field and Behrman define minimal risk as *the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations and tests*[31]. Undoubtedly, this standard will result in different studies regarding the interpretation, which will depend on the respective places of these studies and their ethics committees. In regard to all the documents analyzed herein, the idea that minimal risk can be greater than those to which children are already subjected in their daily life is vehemently rejected.

Regarding risks, five categories of projects are established in which the participation of children can be approved:

- Research that does not involve greater risk than the minimum for the child;
- Research involving greater risk than the minimum, in which a) the risk is justified by the possible benefits provided to participants and b) the risk-benefit ratio is at least as favorable as that presented by existing alternative approaches;
- Research with risks greater than the minimum and no prediction of benefits to participants, but in which a) the risk only represents a small increase over minimal risk, b) experiences comparable to those experiences inherent to medical, dental, physiological, social or educational conditions are involved; and c) the result is able to generate generalizable knowledge crucially important to the knowledge of the child disorder or condition;
- Studies normally not approved, but in which the ethics committee at local and / or national level, determines that opportunities are presented to understand, prevent and alleviate a serious problem affecting the health or well-being of children, and should be conducted according to the ethical principles;

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- Research involving high risk, approved only when the procedure is necessary to treatment, such as biopsies, blood samples.

The US law allows the approval of research involving a small increase above the minimal risk and without any direct benefit to the participant when they display a "disorder" or "condition". These terms should be interpreted as referring to a physical, psychological, social or neurodevelopmental characteristic that a group of clinical and scientific evidence established as harmful to health and well-being of the child or with the potential risk of progression to a health problem in the future.

It is recommended that the evaluation of potential damage or discomfort resulting from the inclusion of children in research, researchers and reviewers should: 1) interpret minimal risk based on common average experiences of the daily lives of normal healthy children; 2) pay attention to the equivalence between potential damage and discomforts in research and the common damage and discomforts to the average normal and healthy children in their daily life or during experiments or tests in routine physical or psychological tests; 3) consider the risks of damages or discomfort according to the ages of the children who will be included in the research; 4) obtain, in addition to the probability, length and magnitude of the potential harm or discomfort to determine the level of risks.

Zago [35] argues that, for healthy children and adolescents, the possibility of legal permission to participate in research projects is not anticipated in Brazil, given the clear legal determination that the health, well-being, development and safety of children and teenagers are protections integrating the core of fundamental human rights, whose respect is promptly and expeditiously required.

Free Informed Consent

For Goldim, the most widely accepted definition of informed consent refers to the *process in which a person receives a detailed explanation of the procedure, understands the information, acts voluntarily, is able to act and finally agrees or not with the participation* [36]. According to Article 12 of the *Convention on the Rights of the Child*, adopted by the UN, *States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child. For this purpose, the child shall in particular be provided the opportunity to be heard* [37].

Lundy [38] considers that the focus of Article 12 is to ensure children the enjoyment of their rights and that the research community must demonstrate in practice the active commitment to include children in research, not as an adult option, but as a legal imperative, because it is a right of children. The concept of parental and child consent was developed, in legal texts as standard for ethically correct research involving children. However, no one replaces the person, which adds responsibilities to all the parties involved in the research project, extended to society and the State.

Foreman, quoted by Goldim [36] proposed in 1999 the "family rule", which recommends the active participation of both the child and their families in obtaining the informed consent. The good balance between the participation of the child or adolescent, together with their legal guardians, even though the latter may be under severe stress and pressed for time, it seems to be the best strategy to safeguard the moral and legal characteristics required for the ethical adequacy of informed consent to these age groups.

Active participation in the informed consent process has been one of the most difficult and controversial ethical matters applied to research with children and adolescents. It requires technique and art ... and not to mention, patience. The important thing is to recognize that children and adolescents have dignity, regardless of age, degree of capacity or autonomy. To ensure that the child's participation in the research is voluntary, Zigaud *et al.* [39] describe the approach strategies based on the needs in the development process and individual characteristics of children.

The involvement of children in discussions and decisions about their inclusion in the research project implies respecting their emerging maturity, preparing them for participation in research, giving them the opportunity to express their agreement and objections and possibly to infer what displeases them. Moreover, and most importantly, it requires tailoring the process to the biopsychosocial developmental stage of children, which will morally validate their participation.

Payment to research participants

Resolution CNS 466/2012 [25] sets forth two forms of payment to research participants: 1)

indemnity, *i.e.*, material coverage for the damage caused by the research to the participant, and 2) refund, *i.e.*, material compensation related only to the participant's expenses and their companions when necessary. The ethical standards of participation in the study require that acceptance to be a participant should be freely given, that is, the person can not be coerced or unduly influenced by psychological, financial or other pressures.

In this article, however, people who participate in the experiments are called "participants", because we recognize that their role in the research went from being a passive subject to an active agent, which results in questions about the right to compensation [25].

Roles and responsibilities

Our focus here will be on those parties conducting, reviewing, regulating, encouraging and funding research, although we agree that the central role of parents should be recognized and respected. In order to promote and further the initial process of parental permission for the participation of children in research, researchers, comitê de ética em pesquisa (research ethics committees – CEP) and research institutions can support them in fulfilling their responsibilities, thus helping them feel that they did the best for their children.

Researchers

To preserve public trust in research, the scientific community must go beyond a culture of compliance – it must strive for a culture of conscience – one in which we do the right thing not because we are required to, but because it is the right thing to do [40].

The researcher has the final responsibility to ensure the safety, rights and welfare of study participants. To varying degrees, the research institution, the sponsor and the parties responsible for controlling the study should understand that the success of the researcher to meet their responsibilities significantly depends on the administrative, financial, educational and infrastructure support.

According to Beecher, *in addition to the knowledge and compliance with the standards and guidelines by research participants, the more reliable safeguard is provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator* [41]. According to Pellegrino [42], Beecher's statement serves to define the character traits of a morally responsible researcher. The specific responsibilities of the researcher in conducting studies with children and adolescents consist of:

- Acquiring and maintaining specific training, credentials and skills to carry out or oversee all necessary clinical procedures and research;
- Acquiring and maintaining appropriate knowledge and training to meet all the regulatory and ethical prerequisites;
- Ensuring that the safe process of parental permission and child or adolescent consent is in accordance with regulatory and ethical standards and that these standards are effective and active throughout the research;
- Communicating with children and adolescents who participate in the research according to their development – and also guiding their parents – about what can be expected during the course of research.

CEP and research institutions

These institutions shall:

- Educate CEP members and, where necessary, pediatric consultants on the ethical, legal and scientific standards for approving research with children and adolescents and conduct their proper interpretation;
- Educate researchers who conduct studies with children and adolescents about their specific ethical, legal and scientific responsibilities;
- Apply ethical and regulatory standards for initial and ongoing review and approval of research protocols, including careful risk assessment and categorization;
- Provide people with appropriate expertise in healthcare and research with children to evaluate the protocols and make sure the people who will conduct the study also rely on this expertise;
- Provide research materials and resources with children, including information on ethics in these studies on websites and educational programs;
- Carry out assessments to guide improvements in CEP performance to evaluate and monitor research involving children;
- Develop specific guidelines and policies for important topics, with additional guidance to CEP members and researchers.

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Regulatory bodies

In countries where there are special protection rules and guidelines for research with children and adolescents, regulatory bodies have become more engaged in monitoring the application of these policies, providing comprehensible, consistent documents and periodically reviewed on the interpretation and application of these policies. Countries that do not possess them, should provide them urgently, as in the Brazilian standards, free informed consent on behalf of those responsible parties and the possible participant's consent is not enough. Several special protection items are missing, rendering it nearly impossible to protect the confidentiality of children and adolescents.

Federal agencies responsible for the health of the population and the development of technologies to protect them should strive to develop standards specifically aimed at protecting the vulnerable, in addition to financing and encouraging specific research with these groups – the therapeutic orphans.

Furthermore, it is important to have a sufficient number of properly trained researchers to design and conduct valid and ethically correct studies. This role could be shared among higher education institutions, especially in medical residency programs in pediatrics, in which basic clinical research concepts could develop the critical thinking necessary to raise awareness of physicians to current problems. As an example of what happens in the United States, the partnership between the Sociedade Brasileira de Pediatria (Brazilian Society of Pediatrics – SBP) and the Agência Nacional de Vigilância Sanitária (Brazilian Health Surveillance Agency – Anvisa) can be productive, whether in the reality check on the use of drugs in Brazilian children and adolescents, or the development of strategies to minimize known problems. Thus, the SBP would not only play the uncomfortable role of critic to the use of off-label or not approved drugs for children, but would also play the role of protagonist in the health and well-being of this population.

The movement toward the performance of multinational research that reflects issues such as the difficulty in recruiting participants, the research cost and the accuracy of current rules for their implementation, should be well received in Brazil.

Article 35 of the *Declaration of Helsinki* recommends that all clinical trials be registered in a public database before starting the recruitment of the first participant, and article 36[18] provides that researchers, authors, sponsors, reviewers and publishers have ethical obligations as to the publication and dissemination of results. Nevertheless, Shamliyan and Kane[43] mention that a lot of studies with children are not completed (28%), only 29% of completed studies are published and that the results are not available in more than half of them. Recording and notification of the results should be mandatory for all research involving children.

Final considerations

The contexts in which the hierarchy of bioethical principles of beneficence, non-maleficence, fairness and respect for humans are rare and permeates all decisions in clinical research involving children and adolescents. As a start, it presents the dilemma of how to benefit them with advances in science and technology, but at the same time protect them in their vulnerability. In parallel, other questions arise: how to avoid risks and damages resulting from the use of or ineffective drug dosage validated for adults? How to get morally valid consent of human beings whose autonomy is in development, avoiding their unfair exclusion as participants in clinical research?

The special protection of the vulnerable group consisting of children and adolescents is needed to prevent abuses that occurred in the past (and that still happen in many clinical trials). However, this protection can result in therapeutic orphans for many health issues of this population, as they are either often treated in a dangerous or ineffective way with procedures based on data obtained for adults, or they are excluded from the treatment. The institutions concerned with this dilemma, have managed to develop acceptable regulatory frameworks to balance the conflicting interests, supported by a robust regulatory system to protect the human beings involved in clinical research.

In addition to the required specialization of sponsors, researchers, CEP, research institutions and regulatory bodies in the protection and care of this vulnerable group, incentive and/or financing by public bodies are required for research with children and adolescents in view of the ethical and regulatory requirements, the technical difficulties and the lack of economic interest of the industry. Participation in multicentric studies is one of the suggested ways.

Educational institutions have the role of training professionals to meet these challenges. Class institutions such as the SBP, in addition to the role of children's advocate, they fulfill the task of being the

protagonist of a better future for them. It must be recognized that, because of the huge lack of available data, there is a gap between what was done, what is done and what must be done in terms of medications for children and adolescents. The matter of greatest concern is that, apparently, the smaller and sicker the child is, the greater is their therapeutic orphanhood.

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