REVIEW ARTICLE

Ethical guidelines for human research on children and adolescents: A narrative review study

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The implementation of human research involving children and adolescents necessitates a nuanced understanding of the distinct ethical complexities and sensitivities that arise. This study aimed to conduct a comprehensive review of ethical guidelines for research with these populations by extensively examining existing standards and applied studies. The review revealed a myriad of challenges inherent in the involvement of children and adolescents as research subjects. The most important ethical challenges relate to the principles of bioethics and their compliance with human studies involving children/adolescents, informed consent, and risk assessment in studies on children/adolescents. To facilitate appropriate participation of youth in research endeavors, meticulous planning is required, in conjunction with a re-examination of the definitions of ethical principles in pediatric research, close monitoring of potential risks and benefits, and the utilization of a combination of innovative and traditional approaches to obtain informed consent that adheres to ethical standards. Performing research with children and adolescents requires special considerations to address the unique ethical issues that can emerge. By adhering to ethical guidelines tailored specifically to these vulnerable populations, researchers can help ensure that studies are conducted in an appropriate and responsible manner.

Key words: Adolescent, child, ethics, guidelines

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INTRODUCTION

Moral philosophy is divided into two categories: Theoretical ethics and practical ethics. The concept of practical ethics has the advantage of not losing sight of the work involved in caring for people and not lending itself to the interpretation of morality as an ideal but impractical concept, which advocates of the ethics of care often object to. Care is both a value and a practice.[1] Practical ethics includes different areas, such as medical ethics, family ethics, environmental ethics, engineering ethics, research ethics, professional ethics, education ethics, etc. However, ethics in research is one of the most modern branches of practical ethics. Ethics in research, an important issue of practical ethics, refers to the investigation of the possibility and conditions of observing ethical principles in theoretical and practical research. Ethics in human research goes beyond mere adherence to the rules of logic and correct deduction.[2]

Due to numerous factors, such as the vulnerability of children and adolescents, limited decision-making abilities, challenges in adhering to ethical principles, and obtaining informed consent, human research involving children and adolescents faces significant challenges.[3] The United Nations Convention on the Rights of the Child (UNCRC, 1989)[4] marked a significant milestone in children's rights. This agreement stipulated that children have independent human rights.[5] Consequently, children and adolescents are now recognized as autonomous beings who are experts in their own lives and capable of making decisions.[6] Considering children's and adolescents' opinions in the development of public policies has been advocated globally as an important strategy,[7] particularly in addressing current

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inequalities, emerging issues, and controversial matters affecting the present generation of youth and children.[8]

The recognition of children and adolescents as rights holders has significant implications for research. While the participation of children and adolescents in human research is not a new concept, the practice of participation has evolved considerably in recent decades.[9] The publication of UNCRC has accelerated a rights-based approach to child and adolescent studies. Previously, research was predominantly conducted on children and adolescents.[6] However, children and adolescents now have the right to express their opinions and viewpoints in research. They are active participants in studies, which poses additional ethical challenges, as researchers are responsible and committed to ensuring no harm is inflicted upon these vulnerable groups.[8,10]

Current debates surrounding the participation of children in human studies are quite complex, largely due to concerns about protecting them from harm and ensuring their well-being.[7] Research ethics committees often view the participation of children and adolescents in research not as equal participants, but rather as vulnerable subjects.[3] Consequently, they frequently evaluate studies primarily through the lens of ethical considerations related to scientific rigor and compliance with rules established to safeguard children and adolescents from harm. While this is necessary, it needs to be balanced with the concept of facilitating the full participation of children and adolescents in clinical studies.[10]

Researchers need to strike a balance between the inherent vulnerability of children and adolescents and the need to conduct research addressing their needs.[11] Over the past years, there has been a shift in the attitude toward the participation of children and adolescents in human research.[12]

While many frameworks have developed ethical principles for research involving children and adolescents, the challenges associated with their participation have not been adequately addressed in these frameworks. Expressing the ethical challenges faced by researchers can serve as an ethical strategy for others. Highlighting the ethical challenges in research with children and adolescents, and reviewing the published ethical guidelines, can raise both awareness and knowledge among researchers in this field.[9,13] It appears that reviewing and summarizing these standards and guidelines can provide valuable ethical guidance to researchers. Therefore, the present study aimed to review research on ethical guidelines for human research involving children and adolescents based on a literature review.

METHODS

The present study was a narrative review conducted in 2023, involving a search of electronic databases, including PubMed, Google Scholar, and Science Direct. The search utilized keywords derived from MeSH, such as "rights," "challenges," "pediatric," "adolescence," "child," "ethic," and "human research." Articles published in English until June 2023 and classified as human research on children and adolescents in terms of ethics were included in the study.

The researchers initially retrieved 145 articles using relevant keywords, with two researchers independently conducting the searches to avoid bias. After removing duplicates and nonresearch articles such as letters to the editor and conference proceedings, the abstracts of the remaining articles were reviewed. Based on a predesigned checklist, articles containing no required information were excluded. The quality of the included articles was then evaluated by two researchers using a standard checklist, with articles scored from 0 to 44. The articles were categorized as high quality (score above 29.34), medium quality (14.67–29.34), or low quality (below 14.67). After reading the full texts and assessing for appropriate quality, 10 high-quality and 4 medium-quality studies remained. In total, 26 articles were thoroughly investigated, resulting in 14 relevant studies included in the final review.

RESULTS

The present study provided the results in several sections, including principles of bioethics and their compliance with human studies on children/adolescents, informed consent, and risk assessment. Table 1 presents a summary of the literature review.

The international principles of research ethics that researchers should attend to include both relational and procedural dimensions of research:

- Respect
- Benefit
- Justice.

In focusing on the above three principles, we acknowledge that existing ethical guidelines generally include these and/or related principles. The overarching ethics framework offered here takes these principles as a starting point, while remaining open to the possibility of adding and/or merging others based on the shared dialogue that is central to their interpretation and application.

Ethical principles in human research on children and adolescents

Biomedical ethics encompass respect for autonomy (independence), beneficence, nonmaleficence, and justice,[13]

Table 1: Summary of the literature review

Author, year, country (reference)	Type of study	Purpose of study	Results
Stalker *et al*., 2004, UK[14]	Descriptive	Explaining the ethical challenges of children in participating in research	To improve children's participation in research, unnecessarily complex access procedures should be eliminated. Children should be encouraged to decide whether or not to participate in research
Rojas *et al*., 2008, Boston[15]	Descriptive-analytical	Assess the effects of requiring parental consent upon study participation and self-reported substance-related problems among adolescents	Requiring parental consent in research may lead to significant self-selection bias toward a lower-risk sample
Embleton *et al*., 2015, Canada[16]	Descriptive	Describing the processes and results of compliance with ethical guidelines for vulnerable children and adolescents	The process of obtaining informed consent from vulnerable children and adolescents makes the researcher respect their independence and adhere to the principle of justice
Kelley *et al*., 2016, UK[17]	Qualitative	Describing ethical challenges in research on vulnerable and orphaned children	Ethical challenges in research on vulnerable children: Difficulty in identifying vulnerable and orphaned children, concerns about the meaningfulness of the guardian's consent, the difficulty in risk assessment, and responding to the needs of children
Lepola *et al*., 2016, Finland[18]	Descriptive-analytical	Analyzing the guidelines and requirements of 25 member countries of the European Union about obtaining informed consent from children to participate in clinical studies	The requirements for obtaining consent in different countries are heterogeneous "The informed consent toolkit" containing 27 items was provided for homogenizing
Ruiz-Casares and Thompson, 2016, Canada[19]	Quasi-experimental	Explaining children's understanding of informed consent, and the potential of visual methods of participation to improve the process of obtaining informed consent in research on children	The written informed consent forms cause fatigue, indifference, and/or anxiety in some children The process of obtaining informed consent using participatory visual methods for children is more accepted
Bennouna *et al*., 2017, USA[20]	Descriptive-analytical	Asking for the expert's opinions about protecting children in participating in studies in emergencies	According to the participants, capacity and contextual considerations are important factors affecting children's decision to participate in the study
Woodgate *et al*., 2017, Canada[21]	Analytical	Explores ethical challenges in qualitative research	Ethical considerations should be extended beyond the protocols of research ethics boards and "sustainable conscious presence" should be presented as a conceptual framework that guides practice for working with ethical challenges
Abrar and Sidik, 2019, Indonesia[3]	Descriptive	A critical evaluation of the ethical issues and research methods in pediatric research	The child-friendly methods to motivate the children to participate and give them the chance to express opinions and thoughts are ignored
Marsh *et al*., 2019, UK[22]	Qualitative	Describing children's and adult's perspectives about children's and adolescent's decisions to participate in health research	The common decision-making processes for older children and adolescents should be supported under the control of parents and understanding of risks
Arnott *et al*., 2020, UK[23]	Descriptive	Investigating three practical approaches to negotiate informed consent with children under 6 years of age	Innovative approaches to obtaining informed consent lead to their active participation in research Innovative methods should be in line with their maturity and abilities
Rogers *et al*., 2021, Canada[24]	Qualitative	Providing ethical guidelines for an interview conducted with children and adolescents in research	Elements of the proposed guidelines: Ethical commitment, obtaining agreement and informed consent, planning before the interview, creating trust, and involving children and adolescents in the research
Alves *et al*., 2022, Brazil[10]	Qualitative	Describing ethical barriers to the participation of children and adolescents in studies	The need to correct ethical regulations to facilitate the participation of children and adolescents in studies

which should be considered in all ethical guidelines for research. Adherence to the principles of bioethics in studies involving children and adolescents presents challenges and problems that require researchers to pay special attention to this population. The ability and level of understanding, mental processing, and decision-making in children and adolescents differ according to their age, intelligence, and health. Moreover, cultural and social norms in different societies play a crucial role in parents' and guardians' decision-making.[25]

This section explains bioethical principles in research involving children and adolescents by describing the existing challenges. While there are many similar ethical challenges when conducting research with children and adolescents, some key differences exist. Obtaining informed

consent from parents is more critical when involving younger children in research compared to adolescents. Additionally, studies examining high-risk behaviors in adolescents pose greater ethical challenges than studies on younger populations. Despite overlaps in ethical issues, the age and maturity level of the involved youth must be considered, with extra care needed for protecting children and exploring sensitive topics with teenagers. However, overall, many of the core ethical considerations around consent, risk/benefit ratio, privacy, etc., apply across pediatric research.

Principle 1. Respect for independence

Respect for autonomy indicates the right to self-determination. It refers to providing individuals with sufficient information to make conscious, rational, and voluntary decisions about participating in studies.[26] In human research involving children/adolescents, where parents or guardians are the participants, adhering to this principle requires providing information about the research methods and consequences to both the children/adolescents and their parents.[25] In the process of obtaining informed consent, the children/adolescents and their parents need to be provided with appropriate and comprehensible information to participate in the study without any coercion. Parents or primary guardians must provide consent for their children's participation and bear the primary responsibility for granting permission, while the children/adolescents must also provide informed consent.[27,28]

Honesty is one of the essential values for researchers to adhere to the principle of respect for participants' autonomy. An important aspect of informed consent in this regard is providing accurate information to children/adolescents and parents about how the researcher will handle sensitive information extracted during the study, before obtaining informed consent.[26]

Honesty is one of the essential values for researchers to adhere to the principle of respect for participants' autonomy. An important aspect of informed consent in this regard is providing accurate information to children/adolescents and parents about how the researcher will handle sensitive information extracted during the study, before obtaining informed consent.[29] For example, an adolescent may choose not to participate in the study due to concerns about disclosing drug use to parents or guardians; therefore, before obtaining informed consent, it is necessary to explain how researchers would deal with such information.[30] Rojas *et al*. (2008) also demonstrated that in studies involving adolescents with high-risk behaviors, obtaining parental consent as the first step can potentially harm adolescent participants and introduce bias in the research.[15]

Honesty is a critical value for researchers to uphold the principle of respect for participants' autonomy. To be honest, the researcher is committed to maintaining confidentiality throughout all stages of the research. Full and straightforward communication with the child/adolescent and parents or primary guardians about the conditions of confidentiality can contribute to resolving potential problems and challenges in the future.[31] For example, parents may want to know about their child's condition, or researchers may become aware of child/adolescent abuse by parents or guardians. Children and adolescents need to be informed of the limitations of confidentiality before participating in the study, and typically, the researcher is committed to not disclosing the results to parents or guardians without prior consent. However, there may be some information that cannot be kept confidential. Therefore, the limitations of maintaining confidentiality in research should be considered when designing all stages of the study and at the time of obtaining informed consent by the researchers.[32] In some cases, researchers are allowed to disclose information when facing specific conditions that threaten a child's/adolescent's life, such as suicidal tendencies.[17]

Principle 2. Beneficence

Beneficence refers to promoting the well-being of others. This principle is rooted in beneficence and is a moral commitment to act for the benefit of others, help them achieve their interests, and prevent or eliminate potential harm.[26] In pediatric and adolescent research, it is crucial to avoid the vulnerability of young children who may not be able to provide consent to participate in the study.[33] A key aspect in this field is "risk assessment;" therefore, when designing a study, researchers should evaluate the level of risk and any potential benefits for the participants. In adult studies, if the participants willingly agree to a treatment that benefits humanity, the researcher can proceed with the research by accepting a small level of harm; however, this is not acceptable in pediatric and adolescent research due to their inability to fully understand the risks.[17]

Principle 3. Nonmaleficence

The principles of beneficence and nonmaleficence require researchers to avoid harming or injuring participants, either through action or inaction. While the primary objectives of any study are to collect and analyze data, as well as produce evidence, these goals should never take precedence over the rights and well-being of individual participants. Nonmaleficence necessitates examining the characteristics, competence, and skills of researchers to ensure the safety of all participants. It also requires the use of tools to assure privacy, safety, and prevention of any negative effects on the participants.[13]

Harm can often be invisible and elusive, complicated by differing perceptions and estimations among researchers, participants, and caregivers, as well as differences between short-term and long-term outcomes. While the need for ethical controls in medical research is evident due to the potential for serious and immediate harm, many social researchers perceive their work as largely benign or harmless. However, social researchers can intrude into people's lives and cause significant distress and embarrassment during the research process.[34]

In addition to practical considerations, the issue of beneficence and the elimination of harm in research involving children also has philosophical aspects. Since the results of clinical human research cannot be fully predicted and controlled, and such activities are conducted with the hope of achieving more effective treatment methods, unexpected and undesirable consequences may arise.[35] Therefore, research involving children is avoided as much as possible,[36] leading to a potential neglect of important research questions or very limited research involving this age group. Consequently, it is impossible to refrain from conducting research on children and adolescents solely based on the principles of beneficence and nonmaleficence. In this regard, a constant evaluation of risks and benefits before starting a study is recommended to avoid potential harm.[35]

Principle 4. Justice

An ethic of justice focuses on questions of fairness, equality, individual rights, abstract principles, and their consistent application.[37] Justice, synonymous with fairness, refers to the ideal distribution of risks and benefits throughout a population when conducting research. The selection of subjects should be fair, and vulnerable individuals should not be exploited for the benefit of the general public. According to the principle of justice in human studies, the burden and consequences of research should not be disproportionately borne by any group within society.[33]

In human research involving children and adolescents, the principle of justice requires researchers to avoid targeting specific populations of children or adolescents who lack the social position or power to refuse participation, such as those with mental disorders in care centers. Inclusion or exclusion of subjects in studies must be based on valid scientific questions, not discriminatory factors or the ease of enrollment.[33,36] Factors affecting the fair distribution of participation in studies include demographic differences (e.g., ethnicity, wealth, language), mental conditions, and coercion (based on financial incentives). The use of financial incentives in research involving children and adolescents is particularly concerning, as it may unduly influence or pressure them to participate in studies.[7,33]

Informed consent in human research on children and adolescents

Informed consent is a central topic in contemporary biomedical ethics. However, attempts to establish defensible and feasible standards for obtaining consent have led to persistent challenges.[38,39] According to Manson and O'Neill, first published in 2007, consent requires distinctive communicative transactions, by which other obligations, prohibitions, and rights can be waived or set aside in controlled and specific ways.[38]

Informed consent in research involving children and adolescents is one of the most challenging issues. According to the informed consent provisions, "subjects should have the opportunity to choose what happens to them. This is achieved when adequate standards for informed consent are met." The standards for informed consent are as follows:

1. Potential participants should be provided with information that allows them to make an informed decision about whether to participate in the study
2. The information provided should be comprehensible to the individuals
3. Participants should understand that their participation in the study is completely voluntary, and they are free to withdraw from the study at any time.[40]

Obtaining informed consent in research involving children and adolescents is generally divided into three groups: Young children who cannot properly give informed consent (infants to children up to 6 year old), children (7–12 years), and adolescents (13–19 years). For children under the age of seven, researchers can provide a simple oral explanation about the purpose and methods of the research. It is important to document this conversation in the parental consent form. The scope and context of the information provided to children and adolescents vary depending on their level of maturity, health conditions, and specific complexity.[33]

According to the Declaration of Helsinki, "if the subject lacks legal capacity, informed consent must be obtained from their legal guardian under the nationally approved law. When physical or mental incompetence makes it impossible to obtain informed consent or when the subject is a young child, obtaining consent from the responsible relatives under the nationally approved law replaces the subject's consent. If the young child can give informed consent, their consent must be obtained in addition to the consent of their legal guardian." Therefore, researchers must cooperate with the child's guardian to observe the standards of informed consent as much as possible.[41]

Informed consent is a legal document, and the participant's age must be considered. Ethical documents and requirements

generally consider participants over the age of 16 as having individual competence, sufficient knowledge to understand the information, and sufficient authority to make wise decisions in their best interests to provide written informed consent.[28,33,42] However, it is often assumed that "children are not sufficiently competent to provide informed consent, and a 'competent adult' is required to provide consent for the child."[25] This issue has been a major challenge in numerous studies involving children.

Obtaining honest and complete informed consent is a necessary part of upholding the principle of respecting the autonomy of children, adolescents, and their parents in research. Before obtaining informed consent, it is necessary to identify the confidentiality parameters and explain them clearly to the participants. Additionally, the general framework of information that cannot be considered confidential should be identified, anticipated, and provided to the participants.[28]

Procedures should be in place to evaluate and respond to challenging situations that may arise during the consent process. Informed consent should be obtained freely, without coercion, threat, or undue influence, from children who have the cognitive capacity to consciously decide.[43] Given the differences in requirements and core principles for obtaining informed consent to participate in research involving children and adolescents, researchers must consider various factors, including the study setting, participants' developmental stage, health condition, decision-making capacity, and their guardians' decision-making capacity, as well as the cultural, social, and legal environments of the country where the research is being conducted.[27,43]

Respecting the developing autonomy of children requires adopting consent procedures that are consistent with the cognitive levels of children and adolescents. These procedures should encourage participants to make informed decisions about participating in or withdrawing from the study, as well as providing or refusing to provide information.[32]

Bennouna *et al*. found that decision-making capacity and contextual considerations are the most important factors influencing children's decisions to participate in a study.[20] Furthermore, in the common decision-making framework for participation in studies, children's and adolescents' ability to understand information about the disease and treatment is crucial.

Ruhe *et al*. identified three issues that contribute to insufficient knowledge about decision-making capacity in children and adolescents and emphasized the need for researchers and physicians to consider the development of children and adolescents when designing informed consent concepts to facilitate their decision-making ability. These factors included: (1) ambiguity in concepts and lack of clear terminology in describing purposes, (2) lack of valid tools to reliably assess decision-making capacity in children and adolescents, and (3) the need to include a developmental framework for understanding decision-making capacity in children and adolescents.[44]

Obtaining informed consent from certain groups of children and adolescents, such as vulnerable populations or those with severe mental disorders, presents unique challenges. Two primary challenges regarding children and adolescents with mental disorders are: (1) standard methods for assessing study criteria like pain and pain sensitivity are often nonverbal, which can be problematic for those unable to understand the instructions due to their disorder; and (2) children and adolescents with severe mental disabilities cannot provide informed consent to participate in research themselves, and their unwillingness may not always be recognized.[45] As a result, they are sometimes included in studies without consent. Researchers must consider ethical guidelines for mentally disabled individuals and adopt innovative approaches to involve them by providing information and obtaining informed consent from their guardians.[46]

The most significant challenge with vulnerable children and adolescents is the potential disregard for the principle of justice when obtaining informed consent. In this context, Embleton *et al*. investigated the application of ethical principles in the participation of vulnerable street children and adolescents. They expressed concerns about the abuse of this group being included in studies without informed consent and emphasized the principle of justice, which gives them the right to decline participation in research.[16]

Lepola *et al*. analyzed the principles and guidelines of informed consent for children's participation in clinical research across the 25 member countries of the European Union. They found heterogeneous requirements for research ethics principles, which varied depending on cultural conditions, customs, and social norms.[18] This highlights the importance of considering societal and cultural norms when obtaining informed consent from children participating in studies. Huang *et al*. also emphasized the role and significance of acknowledging cultural differences when obtaining informed consent from children and adolescents in research.[31] Furthermore, Bennouna *et al*. underscored the impact of cultural and social factors on the participation of children and adolescents in human research.[20]

Primary caregivers and guardians of children/adolescents play a crucial role in the process of obtaining informed

consent. To facilitate the participation of children and adolescents in research, researchers should collaborate with the "primary caregivers," including parents, school staff, and caregivers at care centers.[47] However, this process can be complex depending on the situation. For instance, research involving children in care centers or those with mental health issues can be particularly intricate when it comes to access and obtaining informed consent, as the number of caregivers involved in these cases is typically higher than normal.[48,49]

The process of obtaining informed consent from children and adolescents should be approached differently than adults. Written informed consent forms for children and adolescents should be concise, study-specific, with subheadings or numbered paragraphs, age-appropriate language, a simple and easy-to-read format, and limited to one page if possible.[33] A study by Ruiz-Casares and Thompson revealed that completing written informed consent forms can cause fatigue, indifference, and/or anxiety in children, which can be a significant barrier in the informed consent process.[19] In this regard, several recent studies have suggested using innovative and child-friendly methods, such as visual aids, animation, plays, and simulations to explain the study's purpose and foster better cooperation from children and adolescents in research, leading to positive results.[19,50,51] Ruiz-Casares and Thompson demonstrated that visual methods led to increased cooperation from children in the informed consent process, and children's understanding and representation of complex ethical concepts can provide useful insights to improve the process.[19] Arnott *et al*. showed that using innovative methods to obtain informed consent creates a cooperative environment for children, leading to active participation in research projects.[23] However, it should be noted that although several studies have emphasized the effectiveness of innovative and child-friendly approaches, Abrar and Sidik conducted many studies on children and found that researchers have not widely adopted child-friendly methods to increase children's participation in research.[3]

It's crucial to note that the use of innovative approaches in obtaining informed consent from children and adolescents requires adherence to certain ethical principles. These approaches should align with the maturity and abilities of children and adolescents. Regardless of the innovative method employed, it is the researchers' responsibility to ensure that consent is continuously negotiated with children and adolescents throughout the project through reflective questioning.[23] Additionally, proper communication of information to guardians and children/adolescents about the potential risks and benefits, which are at the core of informed consent and serve as a protective factor for both patients and physicians, is another essential requirement when obtaining informed consent from children and adolescents participating in the study.[28]

Evaluating risks of human research on children and adolescents

When designing research involving children and adolescents, researchers are required to carefully assess the risks before obtaining informed consent and initiating the study. Risk assessment in this field can be performed in various ways. Kelley *et al*. investigated the ethical challenges in research involving vulnerable children by drawing upon the experiences of researchers working with children and adolescents. They found that assessing research risks for some children and adolescents was not straightforward, and it was difficult for researchers to identify vulnerable children, necessitating an integrated procedural approach.[17] Podany classified risk-causing research studies on children and adolescents to facilitate risk assessment. These risks were categorized at different levels based on the risk-to-benefit ratio that directly affects the children/adolescents, with higher risk-to-benefit ratios requiring more support in research involving children/adolescents. High-risk studies and research situations were classified into five categories:

1. Studies with minimal risks, such as venipuncture and chest X-rays
2. Studies with situations higher than minimal risk; however, a direct benefit to the child/adolescent is expected, e.g., shortening the treatment period compared to conventional methods
3. Studies with situations higher than minimal risk, in which no direct benefits to the child/adolescent are expected, e.g., urinary catheterization, skin or bone marrow biopsy
4. Conducting a study in situations where the action cannot be confirmed or implemented, nor can the results of previous studies be confirmed. Carrying out research in this regard is considered a new opportunity to understand, prevent, or reduce a serious problem
5. Situations where it is not possible to obtain consent or agreement and indeed involve situations that lead to the identification of patient's information at the time of publication of the study.

In the first and second categories showing low risk, it is suggested to obtain consent from the child/adolescent and one parent to conduct the study. In the third category, consent from the child/adolescent and both parents should be obtained. In the fourth category, in addition to the consent of the child/adolescent and both parents, the consent of the ethics committee should also be obtained. However, in the fifth category, it is not ethically possible to conduct the study since the risk-to-benefit ratio is high.[33]

DISCUSSION

Clinical research involving children and adolescents faces numerous challenges, ethical issues, and difficulties. Various ethical recommendations and requirements have been presented in different countries in the form of ethical guidelines, which are mostly heterogeneous with key differences in some areas. This heterogeneity and variation have prompted researchers to review the bioethical challenges and situations, leading to the development of key ethical guidelines to facilitate research on children and adolescents. The United Nations Children's Fund and the Information Commissioner's Office state that it is good practice to invite the views of children and young people to help researchers identify risks, design safeguards, and develop their understanding to inform future research.[52] The present study aimed to review ethical guidelines for clinical research on children and adolescents based on existing ethical guidelines and applied research.

Applying biomedical ethics to human research involves considering and reconciling the conflicts between principles and multiple stakeholder interests. In human and clinical studies, researchers, managers, parents, children, and adolescents may have concerns about conflicts of interest, and the interpretation and implementation of ethical principles require negotiations that should be comprehensively considered for the research to proceed ethically.[32] Research with children and adolescents can reveal sensitive information about practices that affect their mental and physical health, such as sexual activity, smoking, drug use, alcohol consumption, self-injurious behaviors, and suicide.[53] The operational application of these principles in pediatric and adolescent studies includes planning how to use the information provided by the study participants and deciding whether to disclose such information.[30] Different perspectives of adolescent participants, parents, and researchers, as well as the conflicting goals of protecting participants and conducting clinical research without interfering with the natural process of events and the unique circumstances that each situation creates, lead to challenges in designing research methods in the field of children and adolescents.[47] Adolescents need information before making a decision, and one of the most important areas is sexual behavior. Drago *et al*.'s study showed that only 0.5% of teenagers have knowledge about sexually transmitted diseases, and 54% of them have no knowledge about Pap smear tests.[54] Rahnavard *et al*. showed that 70% of teenagers have low awareness of ecstasy pills.[55]

Children and adolescents can be actively involved in studies as valuable data resources. Their active participation in data collection relies on researchers observing ethical standards and principles, as children's and adolescents' participation may raise concerns for ethics committee members and researchers due to their vulnerability.[56,57] Moreover, facilitating the participation of children and adolescents in human research requires both the correction and revision of ethical regulations. This necessitates a paradigm shift to balance the concepts of protecting children and adolescents against harm and respecting their autonomy.[10] Although there are many statements about respecting the rights of children and adolescents in human research for autonomy and their ability to take care of themselves, there are also many ethical challenges in obtaining informed consent from children and adolescents and adhering to the four ethical principles by researchers. Obtaining informed consent in clinical research on children and adolescents is a sensitive issue because consent must be obtained from both the child/adolescent and parents, and sometimes, according to the risk assessment, researchers are required to obtain an agreement from central and supervisory bioethics committees.[15] Proper communication of information to guardians and children/adolescents, especially about potential risks and benefits, is at the heart of informed consent. Since many adults do not have sufficient health knowledge, it is important to ensure that caregivers receive relevant information about the research their children are being asked to participate in.[28] Research information should be provided in a language, style, and format that is accessible to the specific group of children from whom assent or consent is sought. This may include written or printed materials, spoken words, different art forms such as drawings and objects, or any other media of the child's choice.[34,53]

Researchers need to adopt a coherent approach that includes identifying aspects of research that may lead to a lack of confidentiality in children's/adolescents' and parents' information. This requires a precise examination of the study course and planning to fulfill the promises made to the participants.[32] In this regard, researchers should make efforts to obtain parents' consent, establish a moral relationship with parents and children/adolescents, and seek creative and emotionally adaptive ways to obtain their consent. Informed consent should be continuously considered throughout the research, and the researcher should repeatedly negotiate with children and adolescents during the research process because this process is different from that for adults, and children may not have the abstract ability to make comprehensive decisions about all stages.[23,58] The use of innovative approaches to obtain informed consent from children and adolescents during the research is of great importance; thus, most studies have emphasized the important role of approaches and innovations in improving the process of obtaining informed consent. To obtain informed consent, most studies have suggested combining traditional and innovative methods

and paying attention to a reflective approach during the research.[59]

Moreover, there are significant differences across different contexts and cultures. Different contexts can affect the participation of adolescents. The study by Akbar Haghdoost *et al*. showed that in street interviews, respondents reveal more sensitive information than in telephone and home interviews. Therefore, interview methods influence the responses to sensitive and nonsensitive questions.[60] Chu *et al*. (2024) also confirmed these findings and demonstrated that high-risk behaviors in adolescents are related to culture, so family culture and school friendships in different nationalities affect the occurrence of high-risk behaviors differently.[61] Research interventions involving children and adolescents must align with the family culture. Assessments related to ethnic identity, racial socialization, and conscious parenting practices should be conducted before intervention.[62]

The present study aimed to investigate the four bioethical principles of beneficence, nonmaleficence, autonomy, and justice, and their consistency with human studies involving children and adolescents, based on a literature review. Additionally, it discussed the significant challenges faced by researchers in pediatric and adolescent studies and provided evidence-based guidelines. Furthermore, the study examined the ethical challenges of informed consent and the principles of evaluating risks in research involving children and adolescents, with the goal of increasing benefits and reducing potential harms, presented in the form of applied guidelines. The study's most notable strength was the adaptation and application of bioethical principles in analyzing the results of existing studies. However, a key limitation was the heterogeneity of ethical guidelines and suggestions concerning ethical challenges in research involving children and adolescents in previous studies, which led to limitations in drawing conclusions on some cases, including risk evaluation and respect for individual autonomy.

In summary, clinical research involving children and adolescents is crucial for advancing our understanding and ensuring optimal care for these populations; however, ethical challenges and adherence to bioethical principles may pose limitations to conducting such research. The most significant ethical gaps identified in child and adolescent research were related to insufficient oversight and monitoring of studies, lack of cultural compatibility between the studies and the cultural context in which they were conducted, and inadequate provision of information prior to conducting studies (particularly in the area of high-risk behaviors), which hindered accurate assessment of the risks and benefits of the research.

CONCLUSION

While clinical research on children and adolescents is essential for improving their healthcare, it is paramount to address the ethical challenges and ensure adherence to bioethical principles throughout the research process. Establishing robust oversight mechanisms, promoting cultural sensitivity, and providing comprehensive information to participants and their families are critical steps to bridge the identified ethical gaps. Additionally, ongoing efforts should be made to strike an appropriate balance between maximizing potential benefits and minimizing risks, guided by the principles of beneficence, nonmaleficence, autonomy, and justice. Furthermore, it is crucial to foster a collaborative approach involving researchers, ethicists, policymakers, and community stakeholders to develop comprehensive ethical guidelines tailored to the unique needs and vulnerabilities of children and adolescents. These guidelines should address issues such as informed consent, privacy and confidentiality, compensation, and posttrial access to interventions, among others.

By prioritizing ethical considerations and implementing robust safeguards, clinical research involving children and adolescents can be conducted in a responsible and ethical manner, ultimately contributing to the advancement of knowledge and the improvement of healthcare outcomes for these vulnerable populations.

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Authors' contributions

GA and MV carried out the conception and design of the study; SG-H, MV, and SJN drafted the article or revised it critically for important intellectual content; SG-H and GA finalized approval of the version to be submitted. All authors have read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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