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Ανασκόπηση

Minors in clinical trials: balancing ethics, rights and medical innovation

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Abstract

This report explores the complex intersection of medical innovation, ethics and the rights of minors participating in clinical trials. While pediatric clinical research is fundamental for developing effective treatments, it also raises significant ethical concerns due to the vulnerability of this population, which stems from their reliance on parents and caregivers and their limited ability to fully comprehend the procedures involved.

The report addresses key issues such as the principle of informed consent and the requirement of assent, drawing from the legal framework governing this area. This includes instruments such as the UN Convention on the Rights of the Child and the EU Clinical Trials Regulation.

The guiding principle in all pediatric decisions is the child's best interest, which ultimately shapes ethical and legal parameters of clinical research. Risk/benefit assessments are crucial and must inform all stages of the clinical trial. Other essential safeguards include the right to withdraw from a trial and the right to be informed or not to be informed about one's medical condition. The report also examines situations of parental disagreement.

The ethical role of ethics committees is highlighted, particularly their responsibility to ensure the legitimacy of consent and prevent undue influence. The report stresses the need for these committees to include experts in pediatric ethics and child development.

Practical challenges are also explored, such as the difficulty of assessing risk, particularly with infants and children who cannot articulate discomfort. Innovative multimedia methods for explaining trials to children and parents are examined as ways to improve understanding and transparency. Special attention is given to modern controversial practices, including the use of healthy children as stem cell donors for their siblings and the use of hypothermia in cases of perinatal hypoxic ischemic encephalopathy.

The report concludes by arguing that excluding minors from clinical trials in the name of protection would unjustly deprive them of access to potentially life-improving treatments. Instead, clinical trials must be conducted not on children but with children, ensuring that respect of their rights, needs and demands is at the heart of every decision.

Keywords: Clinical trials, minors, informed consent, child's best interest, medical ethics.

Ανήλικοι σε κλινικές δοκιμές: εξισορρόπηση της ηθικής, των δικαιωμάτων και της ιατρικής καινοτομίας

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Περίληψη

Το άρθρο αυτό εξετάζει τη σύνθετη αλληλεπίδραση μεταξύ της ιατρικής καινοτομίας, της δεοντολογίας και των δικαιωμάτων των ανηλίκων που συμμετέχουν σε κλινικές δοκιμές. Αν και η παιδιατρική κλινική έρευνα είναι θεμελιώδης για την ανάπτυξη αποτελεσματικών θεραπειών, εγείρει επίσης σημαντικά δεοντολογικά ζητήματα λόγω της ευαλωτότητας αυτού του πληθυσμού, η οποία οφείλεται στην εξάρτηση των ανηλίκων από τους γονείς και φροντιστές τους και στην περιορισμένη ικανότητά τους να διαμορφώσουν και να εκφράσουν βούληση.

Το άρθρο εξετάζει βασικά ζητήματα, όπως η αρχή της ενήμερης συναίνεσης, με βάση το νομικό πλαίσιο που διέπει τον τομέα αυτόν, όπως η Σύμβαση των Ηνωμένων Εθνών για τα Δικαιώματα του Παιδιού και ο Κανονισμός της ΕΕ για τις Κλινικές Δοκιμές.

Η κατευθυντήρια αρχή σε όλες τις παιδιατρικές αποφάσεις είναι το συμφέρον του παιδιού, το οποίο τελικά διέπει τους ηθικούς και νομικούς όρους της κλινικής έρευνας. Οι αξιολογήσεις κινδύνου/οφέλους είναι ζωτικής σημασίας και πρέπει να αφορούν όλα τα στάδια της κλινικής δοκιμής. Άλλες βασικές εγγυήσεις περιλαμβάνουν το δικαίωμα απόσυρσης από μια δοκιμή και το δικαίωμα ενημέρωσης ή μη ενημέρωσης σχετικά με την ιατρική κατάσταση του ατόμου. Η μελέτη εξετάζει επίσης περιπτώσεις διαφωνίας των γονέων.

Τονίζεται ο ηθικός ρόλος των επιτροπών δεοντολογίας, ιδίως η ευθύνη τους να διασφαλίζουν τη νομιμότητα της συγκατάθεσης και να αποτρέπουν την άσκηση αθέμιτης επιρροής. Υπογραμμίζεται εξ άλλου η ανάγκη να περιλαμβάνουν αυτές οι επιτροπές εμπειρογνώμονες στον τομέα της παιδιατρικής δεοντολογίας και της ανάπτυξης του παιδιού.

Εξετάζονται επί πλέον ορισμένες πρακτικές προκλήσεις, όπως η δυσκολία εκτίμησης του κινδύνου, ιδίως σε βρέφη και παιδιά που δεν μπορούν να εκφράσουν την δυσφορία τους. Παρουσιάζονται καινοτόμες μέθοδοι πολυμέσων για την εξήγηση των δοκιμών σε παιδιά και γονείς ως τρόποι βελτίωσης της κατανόησης και της διαφάνειας. Ιδιαίτερη προσοχή δίνεται σε σύγχρονες αμφιλεγόμενες πρακτικές, όπως η χρήση υγιών παιδιών ως δοτών βλαστικών κυττάρων για τα αδέλφια τους και η χρήση υποθερμίας σε περιπτώσεις περιγεννητικής υποξικής ισχαιμικής εγκεφαλοπάθειας.

Το άρθρο καταλήγει υποστηρίζοντας ότι ο αποκλεισμός των ανηλίκων από τις κλινικές δοκιμές με το πρόσχημα της προστασίας τους θα τους στερούσε άδικα την πρόσβαση σε θεραπείες που ενδέχεται να βελτιώσουν τη ζωή τους. Αντίθετα, οι κλινικές δοκιμές πρέπει να διεξάγονται όχι «σε» παιδιά αλλά «με» παιδιά, διασφαλίζοντας ότι ο σεβασμός των δικαιωμάτων, των αναγκών και των απαιτήσεών τους βρίσκεται στο επίκεντρο κάθε απόφασης.

Λέξεις κλειδιά: Κλινικές δοκιμές, ανήλικοι, ενήμερη συναίνεση, συμφέρον του παιδιού, ιατρική ηθική**.**

The World Health Organization (WHO) defines clinical trials as "*a type of research that studies new tests and treatments and evaluates their effects on human health outcomes*".[1] Everybody can take part in clinical trials, including minors.

Article 1 of the UN Convention on the Rights of a Child defines a minor as a person under 18.[2] However, the legal definition of a minor varies across States. As stated in Article 2, paragraph 2.18 of the EU Clinical Trials Regulation, a minor is "*a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent*".[3] Therefore, the notion is subject to national law.

Historically, children were excluded from trials, as they were considered a vulnerable population incapable of expressing their will. This opinion started to change during the AIDS epidemic of the 1980s, as "*the choice for children was either to include them in risky research or to allow them to die from AIDS*".[4]

Paragraph 3 of EU Regulation (EC) No 1901/2006 highlights the risks associated with the past dismissal and oversight of pediatric clinical trials, including issues such as adverse reactions, underdosing, and the lack of tailored formulations for pediatric medicines.[5]

Children's distinct and exclusive characteristics make them a different population, differentiating them from adults. Due to these substantial differences, clinical trials may provide different results depending on whether participants are minors or adults. Thus, including children in clinical trials can lead to important outcomes in addressing pediatric illnesses, which might not be achievable otherwise. Children often require specific medications instead of adjusted doses or modified versions of adult therapies.

Pediatric clinical trials are essential not only for developing cures for sick patients but also for preventing illnesses and improving overall child health.

However, involving minors in clinical trials raises important moral concerns. While pediatric clinical research is undeniably important for medical advancement, it is fundamental to balance these needs with the rights and demands of both patients and their parents.

1.1 The protection of children's rights

As a vulnerable population that may face difficulties in expressing their will, children are a central interest in numerous legislative frameworks.

The Convention on the Rights of the Child, signed by 196 countries, is one of the most

[1] World Health Organization: Definition of clinical trials, Accessed 5.11.2024.

[2] UN Convention on the Rights of the Child, 20 November 1989, General Assembly resolution 44/25, Article 1.

[3] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, Article 2.

[4] *Idem*, p. 364.

[5] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, Paragraph 3.

significant international agreements concerning the protection of minors' rights. Its 54 articles address various areas of childhood and recognize an extensive set of rights, including in the medical field.

Article 24 recognizes children the right to health and health services, establishing a duty for States Parties to ensure every child's right to the highest attainable standard of health, providing access to facilities for the treatment of illnesses and the rehabilitation of health. Clinical trials play a significant role in advancing medical knowledge, thereby contributing to the objective of pursuing "*full implementation of this right*".[6]

Another important principle is outlined in Article 3, as it states that the guiding criterion should always be the child's best interest.

The child's best interest is also the leading criterion used in the Charter of Fundamental Rights of the European Europe, Article 24, paragraph 2: "*In all actions relating to children, whether taken by public authorities or private institutions, the child's best interest must be a primary consideration*".[7]

2. The main sources of regulation

Clinical trials' main sources of regulation are the following:

- The EU Clinical Trials Regulation No. 536/2014
- The 69th World Health Assembly Resolution on promoting innovation and access to quality, safe, efficacious and affordable medicines for children[8]
- The Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine, also known as the 'Oviedo Convention'[9]
- The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research[10]
- The World Medical Association (WMA)'s Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Participants, adopted by the 18th WMA General Assembly, Helsinki, Finland in 1964 and lastly amended by the 75th WMA General Assembly, Helsinki, Finland in October 2024[11]

The EU Regulation No. 536/2014 aims to provide a harmonized statute regarding the medical field of clinical trials and to achieve a balance between two priorities: the protection of minors and the advancement of research, in order to discover new or improved treatments.

The EU relies on a system centered on the use of a single portal, called Clinical Trials

[6] UN Convention on the Rights of the Child, Article 24, paragraph 2.

[7] The Charter on Fundamental Rights of the European Union (2012/C 326/02).

[8] 69th World Health Assembly Resolution, 27 May 2016.

[9] The Oviedo Convention, 4 April 1997, European Treaty Series No. 164, Council of Europe.

[10] The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, 25 January 2005, Council of Europe Treaty Series No. 195, Council of Europe.

[11] World Medical Association: Declaration of Helsinki, Accessed 10.11.2024.

Information System (CTIS), which became the only EU portal available starting from 31 January 2023.

The 69th World Health Assembly Resolution emphasizes the necessity "*to strengthen research and development on appropriate medicines for diseases that affect children, to ensure that high-quality clinical trials for these medicines are conducted in an ethical manner and to collaborate in order to facilitate innovative research and development on, formulation of, and timely regulatory approval of, provision of adequate and prompt information on, and rational use of, medicines for children, including generic medicines*" (Paragraph 8).

Paragraph 9 highlights the urgency "*to facilitate clinical trials of medicines for children based on sound ethics, needs and principles of patient protection, and to promote clinical trial registration in any registry1 that provides data to the WHO International Clinical Trials Registry Platform and to make information on those trials publically available, including publication of summary and complete data of completed trials in accordance with national and regional legislative frameworks, as appropriate*".

The general goal is to support scientific advancement; consequently, the legal framework must adapt accordingly in all fields, including clinical trials, to improve children's health. As recommended by the Resolution, this development must "*incorporate consideration of the needs of children based on the national situation*".

The Resolution also underscores the importance of transparency throughout the process.

The Oviedo Convention is the only international legally binding instrument on the protection of human rights in the biomedical field. Its primary aim is to "*protect the dignity and identity of all human beings*", [12] particularly in the areas of biology and medicine.

The Convention sets out a series of principles and prohibitions, the most important being the principle of informed consent.

The Additional Protocol to the Convention on Human Rights and Biomedicine establishes a leading principle: the primacy of human beings. Article 3 states that "*The interests and welfare of the human being participating in research shall prevail over the sole interest of society or science*".

The Declaration of Helsinki lies on the key assumption that patients' health and well-being must always be the doctors' primary consideration (Article 3). This principle extends also to the research field: according to Article 4, "*It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research*".

Furthermore, the Declaration also sets the principle of compensation for participants: if the participants are harmed in the clinical trial process, they have the right to receive appropriate compensation (Article 15).

[12] Council of Europe, Human Rights and Biomedicine: Oviedo Convention and its Protocols, Accessed 10.11.2024.

Important guidelines are also provided by the World Health Organization (WHO) and the European Medicines Agency (EMA),[13] along with national institutions such as the National Health System UK (NHS).

In particular, the WHO deploys a particular software, called ICTRP (International Clinical Trials Registry Platform),[14] which serves as a portal that classifies pediatric clinical trials using a combination of filters and a unique algorithm. The first filter is age (0 – 18 years), whilst the second filter uses over 4000 key terms, such as "abandoned child", "acquired immunodeficiency syndrome" and "ADHD". The age filter is designed to be the most effective one: only when this filter fails does the second filter come into play.

3. Requirements for the conduction of clinical trials

According to Article 16 of the Oviedo Convention, one of the conditions under which research may be conducted is that "*the risks which may be incurred by that person are not disproportionate to the potential benefits of the research*". This establishes a risk/benefit proportionality criterion.

When a minor is involved, Article 17 of the Oviedo Convention permits research only if it has the potential to produce "*real and direct benefit to his or her health*", it cannot be conducted on another "population" (e.g. adults), it has been authorized in writing by the patient's legal representatives and the minor does not object.

If the research does not meet the condition of direct benefit, it may still be exceptionally authorized if the study can contribute to "*the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition*" and if it involves "*only minimal risk and minimal burden for the individual concerned*".

Thus, for research involving minors, the Oviedo Convention emphasizes that it must be aimed primarily at the patient's well-being. Exceptions are made only for studies that are critical for providing considerable findings for science, provided they impose no more than minimal risk and burden. For example, drawing a blood sample is a classic case of a minimal-risk procedure.

Regarding whether it is always necessary to separate children and adult participants in clinical trials, Article 17 of the Oviedo Convention states that pediatric clinical trials can be undertaken if they are the sole means of obtaining crucial information about certain diseases that cannot otherwise be achieved. In these situations, it is required to separate children and adults to account for the specific ways that diseases affect each group.

Article 17 of the Additional Protocol defines the criteria for "*minimal risk and minimal burden*".

Minimal risk entails that, given the nature and the scale of the intervention, the effects of the study are, if anything, forecasted to cause only a "*slight and temporary negative impact*

[13] European Medicines Agency, Accessed 10.11.2024.

[14] World Health Organization: International Clinical Trials Registry Platform (ICTRP), Accessed 10.11.2024.

on the health of the person concerned". Minimal burden refers to the study producing only a "*temporary and very slight*" discomfort for the patient.

According to the Explanatory Report, "*the notions of risk and burden include not only physical risks and burdens but also social or psychological risks to the participant*".[15]

The term *benefit* encompasses a variety of considerations. First, the beneficial scope of the research may not only involve curing the disease, but also lessening the pain caused by the disease itself and providing relief to the patient. Additionally, benefits may not be limited to the direct advantages for the research participant. In some cases, there may be no cure for the disease, or the participants may not be ill in the first place. Instead, the benefit may extend to the scientific community or other patients. This means that a minor could participate in a clinical trial aimed at finding a cure for their disease, even if the minor themselves would not directly benefit from their participation.

However, an important question arises: where do the limits of benefit lie? Can benefit be justified in light of the principle of human dignity, set forth by the Oviedo Convention itself? Does this approach risk using the patient as an instrument for general research purposes?

Although Article 16 of the Helsinki Declaration states that "*Medical research involving human participants may only be conducted if the importance of the objective outweighs the risks and burdens to the research participants*" (Article 16), if the term benefit is interpreted too broadly, there is a risk of undermining the protections guaranteed by Article 3 of the Oviedo Convention. In fact, Article 3, in stressing the primacy of individuals over the interest of society or science, is an important safeguard against the exploitation of patients in clinical trials. The Article recalls that the rights, dignity, and well-being of individual participants must remain the ultimate guiding criteria of medical research ethics.

Thus, researchers must not prioritize medical advancement at the expense of participants' physical or emotional well-being, regardless of the width of the potential benefit involved.

To further safeguard against this, minors have the right to raise concerns. If they object, the research must be interrupted in accordance with the principles of autonomy and dignity ("*The wish of the person concerned prevails and is always decisive*").[16] Moreover, the study must meet scientific, ethical and legal standards and be authorized by the qualified institution.

Throughout the process, the patient's dignity must always be respected and it must serve as a guide when deciding how to carry out the research.

[15] Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, p. 5.

[16] Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, p. 16.

The Additional Protocol specifies and reinforces the general rules outlined in the Convention, as research may only be undertaken if:

- "*there is no alternative of comparable effectiveness*" (Article 5)
- it does not "*involve risks and burdens to the human being disproportionate to its potential benefits*" (Article 6)
- it "*has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aims of research, and multidisciplinary review of its ethical acceptability*" (Article 7)

Furthermore, Article 9 of Additional Protocol states that every research project must be ethically justified and approved by an independent ethics committee. The committee's primary aim is to protect "*the dignity, rights, safety and well-being of research participants*".[17] In particular, it must assess whether participation in the research is motivated by financial interests or any other undue influence (Article 12).

Every State employs a different system, so the notion of an 'ethics committee' is broad, encompassing any body "*authorised to review biomedical research involving interventions on human beings*"[18]. For example, Brazil relies on a system that revolves around the supervision of the National Research Ethics Board – Comissao Nacional de Etica em Pesquisa (CONEP).[19] Moreover, there is a strong support around physicians and researchers for the creation of a Latin American pediatric research network to better manage multicenter clinical trials.[20]

An interesting case is Germany, where, following the implementation of the EU Clinical Trials Regulation and the German Medicinal Products Act,[21] the authorization of any clinical trial is issued by the competent national competent authority, taking into account the ethics committee's favourable opinion on the matter.[22] Thus, in the German context, there is a strict cooperation between these two bodies.

3.1 Informed consent

Informed consent is universally acknowledged as a necessary requirement for medical procedures, including clinical trials. Consent needs to be present from the beginning throughout the whole process.

Since children are minors, parents are legally required to provide consent for their participation in clinical trials. However, this alone is not sufficient: the child must also be given a clear explanation of the procedure they

[17] The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Article 9 paragraph 2.

[18] Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, p. 8.

[19] Arenas-López S, Fajardo C, Valls i Soler A, García-Corzo JR, Lima-Rogel MV, Calle G, Leite R, Lobos E, Hume-Wright Q, MacLeod S., Pediatric clinical trials in Latin America and Guyana: present views of local practitioners and ways to embrace the future, Paediatr Drugs. 2011 Aug 1;13(4):257-65, p. 259.

[20] *Ibidem.*

[21] Medicinal Products Act, Arzneimittelgesetz – AMG, Section 40.

will undergo and provide their assent to it. Thus, even though minors are not legally able to consent, they must not be excluded from the process.

The Oviedo Convention provides one of the most comprehensive frameworks on the matter.

Article 5 establishes that "*An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time*". The term '*intervention'* encompasses a wide range of medical procedures, including research.

Article 2, paragraph 2.21 of the EU Clinical Trials Regulation defines informed consent as "*a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trials that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subject, an authorisation or agreement from their legally designated representative to include them in the clinical trial*".

The general framework for consent is subject to derogations when it involves individuals unable to give consent, including minors. In these cases, Article 6 of the Oviedo Convention specifies that "*Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit. Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity*". Thus, while parents' or caregivers' consent is essential, the patient's opinion must also be considered.

Regarding this matter, the '*Informed Consent and Assent Tool Kit*' provided by the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)[23] employs a list of countries, categorizing them based on whether consent is required from one or both parents. For instance, Hungary, Ireland and Spain require the consent of only one parent, whereas Italy, Germany, France and Portugal require the consent of both.

It is useful to define the elements that form the basis of informed consent.

The minor's legal representatives "*shall be given adequate information in a comprehensible form*", which covers "*the purpose, the overall plan and the possible risks and benefits of the research project, and include the opinion of the ethics committee*".[24]

The same information must also be provided to the minor, "*unless this person is not in a state to receive the information*" (for instance, if they are in a comatose state).[25]

It is interesting to note that the criteria for determining whether a person is unable to consent vary across Europe: some countries require an empirical verification in each specific case, whereas others apply a system of legal incapacitation, "*whereby a person may be declared incapable of consenting to one or*

[23] Lepola P, Needham A, Mendum J, *et al*, Informed consent for paediatric clinical trials in Europe, Archives of Disease in Childhood 2016;101:1017-1025.

[24] Additional Protocol to the Oviedo Convention, Article 16 paragraph 1.

[25] Additional Protocol to the Oviedo Convention, Article 15 paragraph 1.

several types of act"[26]. Each State determines its approach according to its own legislation.

3.2 Withdrawal of consent

According to Article 6 of the Oviedo Convention, the person representing the minor can withdraw their authorization at any time, provided it is done "*in the best interests of the person concerned*". The best interest of the patient should always serve as the guiding criteria in decision-making.

This principle has important implications when it comes to the withdrawal of consent. While a person who is able to consent may decide to withdraw it at any time – even against medical advice and despite potential negative consequences –, the same rule does not apply with minors: here, withdrawal of consent is permissible only if it aligns with the patient's best interest.

3.3. Consent in emergency situations

The Oviedo Convention clarifies the legal framework in emergency situations in Article 8: "*When because of an emergency situation the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned*". In emergencies, doctors do not need to wait for the patient's parents' authorization. However, this applies only to situations that cannot be postponed.

3.4 Assent

Consent differs from assent.

While the Oviedo Convention does not define assent, the EU Clinical Trial Regulation provides clarity. According to Article 29, paragraph 8, "*in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial*".

At a national level, countries like Germany require that if a minor has the 'capacity to understand', their assent must be obtained to participate in the research.[27]

An interesting example is the concept of 'Gillick competence', a common law standard used to assess whether a minor is able to provide consent to a medical procedure. Minors are 'Gillick competent' if they reach "*an age and maturity to judge what the treatment entails and assess its benefits and disadvantages*".[28]

Subcategories that divide minors in different age groups are very common. For example, the document "*Ethical considerations for clinical trials on medicinal products conducted with minors*",[29] provides specific guidance regarding assent: newborns and infants are entirely unable to provide

[26] Explanatory Report to the Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, p. 7.

[27] Buchner B, Hart D. Research with minors in Germany, Eur J Health Law. 2008 Jul;15(2):127-34, p. 130.

[28] Cave E. Seen but not heard? Children in clinical trials. Med Law Rev. 2010 Winter;18(1):1-27, p. 5.

[29] Ethical Considerations for clinical trials on medicinal products conducted with minors, 2017, p. 13.

assent; pre-schoolers (2-5 years of age), although often not able to express an opinion, should still be given information appropriate to their age and maturity; school-aged children (6-9 years of age) are generally capable of providing assent and should therefore be informed and asked for it; finally, adolescents should always be informed and asked to provide their agreement.

However, when deciding whether a minor can provide assent, it is important not to focus only on their age. Researchers should also consider "*factors such as developmental stage, intellectual capacities (e.g. children with special needs and/or learning difficulties), and life/disease experience*".[30]

Although assent may be perceived as a 'light' requirement compared to consent, this should not be the case. As the Nuffield Council on Bioethics states, "*where children and young people have sufficient maturity and understanding to make their own decision but are not yet treated as fully 'adult' by the law of their country*",[31] their assent should still be obtained. When this is not possible because they do not have the necessary capacity or maturity, they should nonetheless be involved in the decision-making process. As the Council emphasizes, "*it is the process of involvement that is ethically significant*".[32]

Therefore, assent is a distinct and necessary requirement alongside informed consent. It stresses the fact that children are not instruments or test subjects, but rather active participants who must engage with the procedure. Assent has legal value and depends on the child's level of maturity.

3.5 When the child does not agree

Both the EU Clinical Trials Regulation and the Oviedo Convention emphasize that the minor's wishes must be considered, in line with the principle of respect for human dignity.

Article 32, paragraph 1.c of the EU Regulation states that "*the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator*". This provision refers to the concept of dissent.

Dissent does not always need to be explicit: if a State Member requires the child's assent as a condition for participation, the absence of assent corresponds to dissent.

In a hypothetical scenario where a child disagrees with their parents about participating in a clinical trial, researchers are ethically and legally obliged to immediately cease the trial in accordance with the child's will.

3.6 Right to be informed and not to be informed

According to Article 10, paragraph 2 of the Oviedo Convention, "*Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed*". Certain restrictions may apply in exceptional cases.

The Convention states that all patients have a right to be informed about their health; however, a different situation may arise when the patient is a minor. Children may not be able to comprehend the meaning of the words, especially if they are in the preschool-age area.

Data shows that in some cases it is difficult not only for minors but also for parents to accurately understand the information provided about the project. To address this issue, some scholars have introduced a new method worth examining. Approved by the

[30] *Idem*, p. 12.
[31] Nuffield Council on Bioethics (UK), Children and clinical research: ethical issues, March 2015, p. 148.
[32] *Idem*, p. 175.

University of Michigan's Institutional Review Board,[33] it focuses on using multimedia programs instead of traditional paper documents. In the study, both parents and minors were randomly assigned information either on paper or through an iPad program. The programs used 2 and 3-D images along with a voice-over that narrated the text displayed on the screen. The study demonstrated that minors who received information through the multimedia service had a significantly better understanding of the clinical trial compared to their peers who used traditional paper documents.

Interactive media is especially useful for conveying information to both parents and minors in the most effective and accessible way. Both visual and auditory elements are engaging for children and should therefore be implemented more widely.

The Convention also recognizes the patient's right 'not to know': sometimes it may be justifiable that children are kept hidden from this kind of information to protect their feelings. However, this right is controversial because it is not directly exercised by the minor. Instead, it is the parents or legal representative who decide to apply this form of protection, often without the child's say. It is a form of guardianship imposed without considering whether minors actually want to be kept hidden from receiving information about their health. Overall, the right not to know frictions with the principle of human dignity and respect for the person.

4. The role of parents and caregivers

After acknowledging the legal obligation for parents or caregivers to provide informed consent, it is important to emphasize the implications of their role.

According to the Nuffield Council of Bioethics,[34] when deciding whether to agree to their child's participation in a clinical trial, parents should evaluate three key ethical considerations.

First, they should have respect for their child as an individual; this means treating their child as a participant and not just a means to discover new scientific knowledge, considering their personal preferences and opinions, regardless of their age and maturity. Children should not be forced to do something they do not want to.

Second, they should recognize their child's developing capacity of making decisions, meaning helping them throughout their life to understand themselves and the proper way to make conscious decisions. Through their parents' help, children should be able to have the means to understand the risks of the procedure and refuse to participate.

Finally, they should always bear in mind their child's welfare. The concept of best interest, as outlined in many pieces of legislation seen before, is not always helpful due to its vagueness: sometimes it is not clear if it is in the best interest of the child

[33] Tait AR, Voepel-Lewis T, Levine R., Using digital multimedia to improve parents' and children's understanding of clinical trials, Arch Dis Child. 2015 Jun;100(6):589-93.

[34]Nuffield Council on Bioethics (UK), Children and clinical research: ethical issues, March 2015, p. 102.

participating or not in the clinical trials, since they are innovative procedures which do not often guarantee results. Parents should be concerned about the possible pain and discomfort their child may feel during the whole process, as well as long-term effects, while also considering the possible benefits.

4.1 Disagreement between parents

Although there is no specific legal provision addressing the hypothesis of parental disagreements in the context of clinical trials, the UK Research and Innovation (UKRI) provides a useful guideline. According to UKRI, while consent from just one parent or caregiver is sufficient for the clinical trial to be authorized, "*it is good practice to involve both parents and, if there is disagreement, then it is advisable to exclude the child from the research (unless it provides access to treatment that is otherwise unavailable)*".[35]

The UK National Health System (NHS) provides additional clarity. It states that "*By law, healthcare professionals only need one person with parental responsibility to give consent for them to provide treatment*", but "*In cases where one parent disagrees with the treatment, doctors are often unwilling to go against their wishes and will try to gain agreement. If agreement about a particular treatment or what's in the child's best interests cannot be reached, the courts can make a decision*".[36]

In conclusion, when one parent or legal representative does not agree to their child participating in the clinical trial, researchers should attempt a negotiation by discussing with the dissenting party. However, if the trial presents significant potential benefits for the child, an intervention of the court may be necessary.

5. Ethical questions about participation in clinical trials

Since clinical trials are highly innovative and rely on voluntary participation, often without any guarantee of results and, in some cases, even with the risk of potential harm, they raise significant moral and ethical concerns, especially when minors are involved.

Regarding this matter, the EU document "*Ethical considerations for clinical trials on medicinal products conducted with minors*" (2017) outlines four key principles that should guide the conduct of clinical trials: beneficence, non-maleficence, respect for persons and justice.[37] The first one refers to "*the ethical obligation to secure/promote well-being*", whereas non-maleficence entails the "*obligation to avoid harm*". Respect for persons means the obligation to "*treat individuals as autonomous agents and protect those with diminished autonomy*", such as children. Finally, justice is the "*fair distribution of risk, burden and benefits of research*".

Another key principle is proportionality: risks associated with clinical trials are ethically justifiable only if there is a 'proportionate

[35] UKRI: Involving Children in Research, p. 7.
[36] National Health System, Accessed 10.11.2024.
[37] Ethical Considerations for clinical trials on medicinal products conducted with minors, 2017, p. 5.

counterpart', mainly a direct benefit for the participant.[38]

In the current debate, there are two types of clinical trials that are particularly controversial.[39]

The first one concerns the use of healthy children as stem cells donors for their siblings. Bone marrow donations are a common practice, but they still carry potential risks for the donor, making it difficult to categorize them as 'minimal risk' procedures.

The second controversy concerns the use of hypothermia to treat infant perinatal hypoxic ischemic encephalopathy. This is a controversial procedure debated among scholars: some view it as very promising, while others remain skeptical. The use of hypothermia particularly highlights the challenging balance that researchers and ethics committees face when deciding if there is sufficient evidence to confidently assert that an innovative treatment is both better than the standard one and safe for minors.

Both procedures require a thorough evaluation of risks and benefits, as well as a highly specific process of informed consent.

The central problem is balancing two competing needs: on one hand protecting children from the risks associated with clinical trials and, on the other hand, ensuring they have access to potentially life-changing scientific research.

However, measuring risks in clinical trials is not easy. First, there is no precise mathematical formula capable of fully assessing them. Secondly, a universal definition of risk or discomfort does not exist because minors respond differently to medical procedures as they may have different pain tolerances. For instance, clinical trials involving newborns are particularly challenging to assess from an ethical perspective: as a matter of fact, newborns tend to cry during any kind of medical procedure, as crying at that age is often a response to unknown stimuli. Therefore, should crying be interpreted as a form of dissent or are researchers ethically justified to proceed?

The difficulty of assessing risks is further complicated by the common mistake made by researchers to treat participants the same: in particular, if we consider participants as a homogeneous group, we risk not considering individual health backgrounds. Therefore, researchers must consider "*the heterogeneity of the pediatric population and the large diversity of research projects*".[40]

Moreover, the debate also revolves around the concept of assent, in particular what it entails and when a child is capable of providing it. How can we ensure that children fully understand the procedures involved and how can we guarantee that their voices are heard and their opinions respected? Not all minors are capable of expressing their opinion: babies cannot speak and some children may be permanently or temporarily unable to do so

[38] Bos W, Tromp K, Tibboel D, Pinxten W. Ethical aspects of clinical research with minors, Eur J Pediatr. 2013 Jul;172(7):859-66, p. 863.

[39] Laventhal N, Tarini BA, Lantos J. Ethical issues in neonatal and pediatric clinical trials. Pediatr Clin North Am. 2012 Oct;59(5):1205-20.

[40]Bos W, Tromp K, Tibboel D, Pinxten W. Ethical aspects of clinical research with minors, Eur J Pediatr. 2013 Jul;172(7):859-66, p. 865.

due to disabilities or conditions, such as being in a coma.

Additionally, to express an informed opinion, it is essential that the child's maturity is properly evaluated to determine whether they are capable of forming a mature will. However, a potential conflict of interests may arise, as maturity is assessed by the clinical trial investigators themselves, who often have a personal interest in recruiting volunteers. Considering this, it might be more appropriate for an independent agent or specialized body, such as the ethics committee, to be responsible for assessing the maturity of participants. For instance, the EU Regulation No 1901/2006[41] suggested the establishment of an ad hoc scientific body within the European Medicines Agency known as the Paediatric Committee (PDCO), whose main role is "*to assess the content of paediatric investigation plans (PIPs)*".[42]

For all these reasons, there need to be higher protection thresholds to allow pediatric clinical trials.

Furthermore, it is crucial that ethics committees are formed by members with appropriate pediatric expertise. This does not simply mean "*having professionally worked with children'*, but also entails possessing the proper '*education, training and experience on various aspects of ethics, child development and psychosocial aspects*".[43] All members must have comprehensive knowledge of childhood, even if in practice it is extremely challenging to find individuals who meet all the required criteria.

Additionally, pediatric clinical trials require a continuous follow-up process, which is commonly longer than adult research in order to monitor the long-term effects.

To minimize pain and distress during clinical trials, strict guidelines must be followed: "*physical pain and distress intensity must be assessed and regularly monitored, and treated according to guidelines, particularly in neonates and children who cannot express it verbally*".[44] Doctors should prioritize less painful and invasive procedures, and analgesia or sedation should be used when necessary.

Emotional distress should also be addressed by ensuring that children are constantly reassured in a nurturing environment and, if possible, not separated from their families.

In my opinion, it would be unfair to exclude children from access to clinical trials in the name of a so-called protection purpose. Exclusion would mean denying them the possibility to improve their quality of life.

It is also true that, although it cannot be denied that clinical trials are a fundamental milestone in the scientific scene due to their potential value in research, this function needs to be balanced with the protection of minors,

[41] EU Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, Paragraph 8.

[42] EMA: Paediatric Committee (PDCO), Accessed 22.11.2024.

[43] Ethical considerations for clinical trials on medicinal products conducted with minors, 2017, p. 14.

[44] Ethical considerations for clinical trials on medicinal products conducted with minors, 2017, p. 16.

who are a vulnerable population that in most cases face difficulties in expressing their will.

On one hand, the Declaration of Helsinki states that "*The primary purpose of medical research involving human participants is to generate knowledge to understand the causes, development and effects of disease, improve preventive, diagnostic and therapeutic interventions and ultimately to advance individual and public health*" (Article 7), but it is also inarguable that the leading criteria should always be the right to life, health, dignity, integrity and the respect for person. In fact, as the Declaration itself states, "*These purposes can never take precedence over the rights and interest of individual research participants*" (Article 7).

In conclusion, the real challenge in the clinical trials area is to assess the risk/benefit threshold, parental informed consent and child assent. Clinical research must "*be with children and young people, not on them*";[45] this means that clinical trials should not use children as a mere means to the superior end of reaching scientific advancement, but respect their person and their opinions, remembering that, although vulnerable, they are still human beings who deserve to be recognized and heard.

[45] Nuffield Council on Bioethics (UK), Children and clinical research: ethical issues, March 2015, p. 172.

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