Ethical Issues Concerning the Informed Consent Process in Paediatric Clinical Trials: European Guidelines and Recommendations on Minor's Assent and Parental Permission

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ABSTRACT: Appreciation for minors' involvement in clinical trials and for children's autonomy is growing, but has to be combined with the parental and social duty to protect them. In recent years the ethical debate had shifted to specifically encouraging children's inclusion in trials, taking into account the benefit they can obtain, both direct and indirect. Nevertheless, there is a risk concerning the protection of children's rights and the proper acquisition of informed consent could become a legal and ethical issue. The article examines the ethical framework concerning informed consent in paediatric clinical trials at European level, with special reference to guidelines, recommendations and opinions issued by national, European and international bioethics/research ethics committees, scientific societies, European institutions and international organizations. The review aims at pointing out key issues regulated by common ethical standards and grey areas in which soft law regulation is still evolving. The focus is devoted to the topics of assent, parental permission and shared decision-making, analysed in the light of the general principle of child's best interest.

KEYWORDS: Informed consent; paediatric clinical trials; assent; parental permission; child's best interest

SUMMARY: 1. Introduction – 2. The inclusion of minors in clinical trials – 3. The balance between risks, burdens and benefits (direct and indirect) – 4. The role of parents – 5. Children and mature minors: different age, different issues – 6. Assent and parental permission – 7. Objection from the child – 8. Shared decision-making: from a legal point of view to an ethical perspective.

1. Introduction

Informed consent, parental permission and assent are both parts of a communication process and a legal requirement in paediatric clinical trials, but it is impossible to define a common international legal framework on these topics, because of the different national regulations. Nev-

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ertheless, from an ethical point of view we can delineate some common standards, concerning recruitment and decision-making, with special reference to the informed consent process. Yet, discrepancies appear also at ethical level about the weight of child's objection and the age thresholds.
This paper offers a narrative review of European and international rules of conduct with no legal binding force, such as guidelines, recommendations and opinions issued by European and international bioethics/research ethics committees, European institutions and international organizations and national bioethics committees in six selected countries (Austria, France, Germany, Italy, Spain and United Kingdom). Documents were collected by visiting the websites of relevant institutions.

2. The inclusion of minors in clinical trials

Children's vulnerability, due to incomplete physical and psychological development, is a preliminary question on every ethical discussion about paediatric clinical trials. Above all, there is a risk of harm because children are not able to protect themselves and this is highlighted by institutional documents. Beside the risk of health damage, there is a risk concerning protection of children's rights and proper acquisition of informed consent could become a legal and ethical issue. For these reasons, institutional documents highlight the importance of informed consent, risk assessment and inclusion criteria in clinical trials involving human subjects and these issues need to be developed carefully when dealing with minors, because they are not completely able to understand technical information and give consent freely[1].
In paediatric clinical trials the subject does not have full individual autonomy in the decision to be involved and a group of vulnerable people (minors and their families) needs to make decision in a context of uncertainty. Therefore, minors need appropriate support, not only from parents, but also from researchers and from the society as a whole. Specific protections are required and all institutional documents assume vulnerability as a major issue[2]. Vulnerability requires protection, but protection can restrict the right to participate in decision-making and to share benefits deriving from involvement in clinical trials. There is a tension between the need to avoid harm and the right to be informed and to be heard or to make choices.
In this regard, according to recent opinions issued by national and international institutions, children's participation in clinical trials is considered insufficient, in view of low involvement rates, so the balance has shifted to specifically encouraging children's inclusion in trials taking into account the benefit they can obtain, both direct and indirect[3]. Nuffield Council on Bioethics explicitly challenges the association between vulnerability and childhood, asking researchers to work in partnership with

[1] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17; European Medicines Agency (EMA), *Guideline for Good Clinical Practice*, 2016.
[2] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17.
[3] Working Party of research ethics committees in Germany, Ethische Aspekte der pädiatrischen Forschung, 2010; Austrian Bioethics Commission, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013; Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015.

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children and parents, not to protect children "from" research[4]. This implies that minors have to be supported to participate and to make decisions and their autonomy has to be respected as much as their integrity, giving importance to their views, listening to them and allowing them to contribute to decision-making. Nuffield Council on Bioethics affirms that children's welfare is a basic aspect to take into account, but its definition should encompass the possibility to contribute to scientific knowledge that could be useful for all children in the future[5]. That does not imply a moral duty to consent for children and parents, but only another aspect to be taken into account in determining what is good for children.

Institutional documents ask to involve children in research, first of all, for scientific reasons[6]. It is important to involve in research people unable to consent, and also children, in order to enable them to access benefits for their own health, balanced with related risks. Yet, from an ethical point of view, their involvement in clinical research has not to be viewed as necessary evil[7]. The classic approach claimed that minors' involvement in clinical research would not be suggested if trials could be carried out with adult subjects. If deemed necessary, researchers would have to include, first of all, less vulnerable subjects[8]. In recent years, the ethical evaluation has shifted to encouraging minor's involvement, but concerning the order of involvement in research, it is yet preferable to conduct research on adults before children. The WHO Research Ethics Review Committee[9] states that, before seeking consent and assent to involve children in research, it must be demonstrated that comparable research cannot be done with adults to the same effect and scientific impact. Older children having more capacity to consent should be involved before younger children, unless there are thorough scientific reasons to involve them before[10].

3. The balance between risks, burdens and benefits (direct and indirect)

Since clinical trials involving minors have allowed a great increase in therapeutic and diagnostic opportunities, their exclusion is currently considered unjustified. Nevertheless, clinical trials are structurally uncertain, because they are built on a scientific hypothesis, which needs to be confirmed through investigation, thus risks for children have to be considered. The protection of children in this field is now conceived as risk and burden minimization, rather than as exclusion. Hence, researchers

[4] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.59.
[5] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.28.
[6] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 4.
[7] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.
[8] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 5.
[9] World Health Organization (WHO) Research Ethics Review Committee, *The Process of Seeking Informed Consent. Information for Researchers Concerning Informed Decision Making*, 2017.
[10] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.

have to minimize risks and burdens, balancing these factors with expected benefits for subjects involved and improvement of knowledge[11].

Risk assessment is a fundamental aspect of a research protocol. In paediatric clinical trials, it requires strict control. Major risks in clinical trials are related to the health of involved subjects and data reliability. Health-related risks depend on prior experiences with the intervention/product to be tested and its nature. If the risk is minimal, compared to normal clinical treatment, children can be involved taking into account all the benefits they can get. These benefits can be distinguished as direct and indirect: the direct benefit is the consequence of a treatment on the patient's condition in terms of health recovery; the indirect benefit enables general findings to be obtained for medicine about the condition of a certain group of persons, to which the patient belongs, or general information useful to society[12].

General knowledge produced through the investigation can be usefully applied to a group of patients to which the person involved belongs and this is really important in research involving children, because benefits can be related to groups of people in an age category and not only to groups of people suffering from the same illness. When the benefit is referred to society as a whole, the ethical assessment needs to be stricter and it is important to evaluate the risk factor: the risks must be minimized and no more than minimal[13].

In addition to risk, burden of research participation for minors has to be considered as an important factor, more than in clinical trials involving adults. It can concern anxieties, pain or interference in children's everyday lives, such as being separated from parents during the trial, frequent invasive procedures or burdensome side effects. Parents are usually more focused on risks for life and health of their children, but burdens can have harmful effects, which have to be taken into account. Burden perception is not objective and depends on individual feelings, but the burden minimization has to be pursued by researchers and to be taken into account by Research Ethics Committees. Overall pain is an important factor to consider in paediatric clinical trials, even though difficult to predict or assess, because it can affect the child's neurological, psychological and physical development[14].

Another important issue related to risks and benefits is the use of placebo in paediatric clinical trials. According to WMA[15], the use of placebo is justified only for scientific reasons and with the informed

[11] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the* paediatric *population*, 2000; World Health Organization (WHO), *Standards and operational guidance for ethics review of health-related research with human participants*, 2011; European Commission, *Report from the Commission to the European Parliament and the Council. Better Medicines for Children – From Concept to Reality*, 2013; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016.

[12] French National Consultative Ethics Committee for Health and Life Sciences, *Transposition en droit français de la directive européenne relative aux essais clinique des medicaments: un nouveau cadre éthique pour la recherché sur l'homme*, 2003, 3-5.

[13] Austrian Bioethics Commission, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 40; Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 17.

[14] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 12.

[15] World Medical Association (WMA), *Declaration of Helsinki* (as amended), 2013, art. 33.

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consent of the patient, but should be restricted in paediatric clinical trials, because randomization and procedure's risks are not easily understood by parents and children. Placebo should not be used if effective treatments are available.

Exploitation of people unable to consent is unacceptable and a mandatory ethical review by ethics committees is an essential requirement[16]. Research integrity also needs to be considered, to guarantee compliance with ethical principles and professional standards[17]. Research ethics committees have an important role in protocols review and their focus is on the "ethical acceptability" of the research[18]. Dealing with paediatric trials, research ethics committees need to have specialist expertise on children healthcare to assess adequately risks and burdens of the envisaged procedures. The scrutiny process involves both scientific and ethical aspects, thus an adequate ethical and peer review is required. Failure to follow ethical guidelines implies that Ethics Committees or competent authorities do not give permission to proceed.

4. The role of parents

The role of parents is very important, both from a legal and an ethical point of view. It cannot be interpreted only as a right to decide or a duty to protect, but also as assistance and support to children's evolving autonomy. Parental decisions should evaluate the "child's best interest", a complex concept determined on a case-by-case basis, considering individual needs and rights. Indeed, since clinical trials are not only focused on the participant's interests, Nuffield Council on Bioethics[19] affirms that parental consent to research "should be based on their confidence that participation in the proposed research is compatible with their child's immediate and longer term interests". This is a proposal to avoid that the minor's "best interest", fundamental in clinical practice, overrides other ethical values and becomes the only issue to consider in decision-making.

Parents need to be supported in decision-making, overall if decision has to be taken in difficult situations and trials imply burdens or risks. In cases of serious illness or when parents begin to deal with a child's illness, distress could compromise the parental capacity of judgement. Parents could need to consult their child's physician about the chance to participate in a clinical trial. If the investigator is also the physician, particular attention needs to be paid to undue influence and conflict of interests: willingness to participate in a clinical trial cannot be influenced by the concern to be undermined in normal access to care. If the researcher is also a clinician in charge of providing care to the minor involved in a clinical trial, commitment to investigate cannot override the duty to care and the interest in the success of research cannot compromise the patient's interest to be properly treated[20].

[16] Council of Europe, Committee on Bioethics (DH-BIO), *Guide for Research Ethics Committee Members*, 2012, 40.
[17] European Group on Ethics in Science and New Technologies (EGE), *Statement on the formulation of a code of conduct for research integrity for projects funded by the European Commission*, 2015.
[18] World Health Organization (WHO), *Standards and operational guidance for ethics review of health-related research with human participants*, 2011, 12.
[19] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, paragraph 4.33.
[20] Nuffield Council on Bioethics, *Children and clinical* research*: ethical issues*, 2015, xxxiii.

If parental permission is impossible to obtain and the study is emergency research, investigators can ask an approval to the ethics review committee and must inform and involve parents as soon as possible, but if the minor is able to understand and decide, his/her decision should be respected[21].

5. Children and mature minors: different age, different issues

To be minor is a legal status and the age of adulthood is conventionally fixed by the law. To be a child or young is an existential condition and there are great differences between infants, children and young people. Minors' continuous development is actually an ethical issue: "What is more difficult and especially deserves 'ethical weighing' is research on children as children continually develop their ability to give consent as they grow older"[22].

All the institutional documents affirm that as age advances, maturity and capacity to understand become more relevant, as well as the importance of individual autonomy. Considering the ethical value of the minor's will, some documents propose an age-based classification. ICH distinguishes newborns (0 to 27 days); infants and toddlers (28 days to 23 months); children (2 to 11 years); and adolescents (12 to 18 years). In the same document ICH states that "any classification of the paediatric population into age categories is to some extent arbitrary", but however useful to think about the study design[23].

EMA makes no distinction between minors and children, using these terms as synonyms[24]. Nevertheless, the document deals with the issue of consent and its value according to age groups and the subject's level of maturity: for children from birth to 3 years, it is impossible to obtain a valid assent; from 3 to 6 years, there is no specific indication, whereas for children of school age (from 6 years) information and obtaining of assent is recommended; children from the age of 9 are considered able to better understand the information; adolescents are more independent and need respect for their autonomy, not only protection: "Assent from an adolescent who is a minor should be sought, and, where possible respected"[25]. Researchers must however assess that adolescents have understood the information provided.

If research implies minimal risks and minimal burden for minors involved, Austrian Bioethics Commission[26] asks for parental permission only for children up to the age of 14.

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[21] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, paragraph 6.35; ITALIAN COMMITTEE FOR BIOETHICS, *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situation*, 2012.

[22] AUSTRIAN BIOETHICS COMMISSION, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 44;

[23] INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 7.

[24] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 7.

[25] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 12.

[26] AUSTRIAN BIOETHICS COMMISSION, *Research on persons without the capacity to consent-with special consideration of the concept of risk*, 2013, 46.

Dealing with the broad concept of "childhood", Nuffield Council on Bioethics[27] distinguishes three different situations without fixing rigid age thresholds instead:

1. Case One: children who are not able at this time to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are so unwell or are unconscious.
2. Case Two: children who are able at this time to form views and express wishes, but who are clearly not yet able to make their own independent decisions about research involvement.
3. Case Three: children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be minors in their domestic legal system.

All children will be included in case one at the beginning of life. When a child can be included in Case Three, his/her assent has a particular weight, comparable to an actual informed consent.

According to CIOMS "As adolescents near the age of majority, their agreement to participate in research may be ethically (though not legally) equivalent to consent. In this situation, parental consent is ethically best considered as 'co-consent' but legally, the adolescent's agreement remains assent. If child or adolescent participants reach the legal age of majority according to applicable law and become capable of independent informed consent during the research, their written informed consent to continued participation must be sought and their decision respected"[28].

In long-term trials, investigators should periodically check minor's maturity and capacity to consent and seek their assent or informed consent, if deemed appropriate, or once the subject reaches the legal age to consent[29].

6. Assent and parental permission

To be legally and ethically justified, clinical trials need to be freely accepted by the subjects involved, on the basis of adequate information about relevance, purpose, risks and burdens of the envisaged procedures. Subjects must have a clear idea that they are going to be involved in research and not in normal clinical care, even though some benefits are expected[30].

In paediatric clinical research, the informed consent process requires parental permission and child's assent. According to WHO Research Ethics Review Committee[31] obtaining informed consent in paediatric clinical trials should follow some essential rules:

[27] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, paragraph 4.5.

[28] COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.

[29] EUROPEAN MEDICINES AGENCY (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 10; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Addendum to E 11: *Clinical investigation of medicinal products in the paediatric population* (Step 1 version), 2016.

[30] COUNCIL OF EUROPE, COMMITTEE ON BIOETHICS (DH-BIO), *Guide for Research Ethics Committee Members*, 2012; WORLD MEDICAL ASSOCIATION (WMA), *Declaration of Ottawa on Child Health* (as amended), 2009; UNESCO INTERNATIONAL BIOETHICS COMMITTEE, *Report On Consent*, 2008.

[31] WORLD HEALTH ORGANIZATION (WHO) RESEARCH ETHICS REVIEW COMMITTEE, *The Process of Seeking Informed Consent. Information for Researchers Concerning Informed Decision Making*, 2017.

- According to the Convention on the Rights of the Child, "child" means "every human being below the age of eighteen years unless under the law applicable to the child, majority is attained earlier".
- Once it has been determined that the research should be permissible, researchers must obtain parental/guardian consent on an informed consent form for all children.
- Children sufficiently able to understand the proposed research should have the opportunity to be informed about the research, to have their questions and concerns addressed and to express their agreement or lack of agreement to participate.
- While the age at which this informed assent should be taken varies, researchers should consider asking for assent from children over the age of seven years with assent taken from all children over the age of twelve years.
- Children express their agreement to participate on an informed assent form written in age appropriate language. This form is in addition to, and does not replace, parental consent on an informed consent form.
- Assent which is denied by a child should be taken very seriously.

Indeed, minors have no legal capacity to give informed consent to be involved, but they are not completely unable to understand and they gradually mature and develop their capacity to make autonomous decisions. Nonetheless, their participation in decision-making is pivotal to ensure respect for their dignity, even though they are not entitled to give an actual informed consent. Hence, they can be involved in decision-making process giving an "assent" to research, but this term has different meanings[32], depending on the context and on the minor's age. Its purpose is to facilitate a context in which minors can cope with distress, be involved in decisions, be heard and considered about their wishes and concerns. According to EMA "assent should be understood … as the expression of the minor's will to participate in a clinical trial"[33].

Ethical guidelines often require documentation of assent and in some cases place great value upon it: "The processes for informing the child and seeking assent should be clearly defined in advance of the research and documented for each child"[34]. Through the assent engagement of minors can be assured in the research discussion and in decision-making, depending on their individual capabilities. Familiar context and personal circumstances should also be taken into account. In cases of chronic disease, minors can have more experience and capacity than the parents to understand risks, burdens and benefits of a clinical trial.

Nuffield Council on Bioethics distinguishes three different situations (see above) to highlight that in some cases children are unable to participate in decision-making, but in other cases they can be involved to contribute with their view, or even decide independently. In Case One, assent has no value, but in Case Two it should be balanced with parents' views to determine risks, benefits and burdens, taking into account the child's maturity and capacity to understand. In Case Three, young children

[32] Spanish Bioethics Committee, *Informe del Comité de Bioética de España sobre el proyecto de Real Decreto de ensayos clínicos*, 2013, 15-16.

[33] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 8.

[34] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 11.

can potentially make decisions for themselves, even if parents still have moral and legal duties to protect them.

As the minor is not entitled to provide a full legally binding informed consent, an authorization has to be provided by parents, after adequate information. Parents need time and detailed information to decide, because they bear responsibilities for their children and not only for themselves. They might need to talk with their child on their own, after being informed, and researchers should not take part in the decision-making. Family members must be free from undue pressure and be informed of the possibility to revoke informed consent without any prejudice for their children's care.

Parental permission and assent should be obtained at the same time. Informed consent should be obtained from the subject involved once he/she reaches the age of consent, because parental permission and assent have not the same value as the consent given by an adult. Children who are wards need an advocate's assistance. The Italian *Codice dei diritti del minore alla salutee ai servizi sanitari*[35] provides that the minor has the right to consent or disagree and personally sign the informed consent together with the legal representative.

Research protocols can also be designed for emergency situations, involving patients unable to consent (e.g. sepsis, head trauma or stroke). In such circumstances, researchers must try to talk with a legal representative to obtain consent as soon as possible, but if a substitute is impossible to contact, the research can be carried out only if an ethics committee has previously given the authorization to proceed without consent. This authorization has to be obtained when the research protocol is approved, because it concerns circumstances in which a decision must be taken quickly. In evaluating the protocol, an ethics committee must assess a sound scientific background and likelihood of benefit for the subject. Risks associated to the trials have to be reasonable and previously expressed wishes concerning involvement can be taken into account[36]. Italian Committee for Bioethics recommends the constitution of *ad hoc* independent ethics committees for clinical trials in emergency situations[37].

7. Objection from the child

According to EMA "Strong and definitive objections from the child should be respected"[38] and especially when no direct benefit is prospected by researchers. Some exceptions are proposed by ICH, exclusively in view of potential benefits: "Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pae-

[35] Istituto Nazionale per i Diritti dei Minori (INDiMi), *Codice dei diritti del minore alla salute e ai servizi sanitari*, 2012, art. 14.

[36] Council for International Organizations of Medical Sciences (Cioms), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 16.

[37] Italian Committee for Bioethics, *Clinical trials in adult or minor patients who are unable to give informed consent in emergency situation*, 2012.

[38] European Medicines Agency (Ema), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 13.

diatric patient would be jeopardized by his/her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study"[39].
In dealing with children's "deliberate objection", CIOMS equally highlights the importance of child's wishes in decision-making, but asks to consider expected benefits. A deliberate objection should be respected "even if the parents have given permission, unless the child or adolescent needs treatment that is not available outside the context of research, the research intervention has a clear prospect of clinical benefit, and the treating physician and the legally authorized representative consider the research intervention to be the best available medical option for the given child or adolescent. In such cases, particularly if the child is very young or immature, a parent or guardian may override the child`s objections"[40].
Conversely, child's objection has more value than parental permission when research has no direct benefit for the subjects involved. Silence or absence of objection cannot be considered as assent[41].
Consent can be withdrawn at any time, also during a procedure, unless when there is a serious danger for the subject's health. Withdrawal of consent does not provoke the end of relationships between the researchers and the subjects involved[42].
If assent and parental permission are impossible to obtain, the consent can be waived, but this waiver needs to be approved by an independent research ethics committee. CIOMS[43] requires some conditions to approve a consent waiver:

- the research would not be feasible or practicable to carry out without the waiver;
- the research has important social value; and
- the research poses no more than minimal risks to participants.

8. Shared decision-making: from a legal point of view to an ethical perspective

Professionals interacting with children and families need to have both technical and non-technical skills to communicate adequately. The role of ethics review committees is also important in improving children's participation in clinical trials: the action of these bodies could be not only protective, but also facilitative, as highlighted by Nuffield Council on Bioethics[44] that emphasizes the ethical value of paediatric research.
Nevertheless, to be ethically justified, clinical research involving minors must consider the concepts of "minimal risk" and "best interest" of the child, because the risks must be minimized and no more than minimal. Usually "minimal risk" means that the probability and magnitude of harm or discom-

[39] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E 11: *Clinical investigation of medicinal products in the paediatric population*, 2000, 11.
[40] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Commentary on Guideline 17.
[41] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Addendum to E 11: *Clinical investigation of medicinal products in the paediatric population* (Step 1 version), 2016, 5.
[42] European Medicines Agency (EMA), *Ethical considerations for clinical trials on medicinal products conducted with paediatric population*, 2008, 11.
[43] Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Health-related Research Involving Humans*, 2016, Guideline 10.
[44] Nuffield Council on Bioethics, *Children and clinical research: ethical issues*, 2015, xxv.

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fort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological activity. The "best interest" approach generally promotes an effort to be more objective in balancing risks and benefits, weighing them in the specific situation regardless of individual wishes. In the case of clinical research, however, the concept is too generic, since the balance between risks and benefits is undefined and it is hard to define the child's best interest in a situation of clinical uncertainty.

Therefore, in the research setting a certain emphasis on autonomy seems to be justified because of the consequent risks and subjects may be granted a higher level of autonomy than in clinical practice, where it is instead appropriate to give greater weight to the best interest of the minor. Yet, to prevent a conflict of autonomies between children and parents, the Nuffield Council on Bioethics recommends to adopt the "Shared decision-making" approach, emphasizing the importance of a partnership between researchers, families and children, to avoid the idea of informed consent as a parental permission cancelling or reducing professional responsibilities and the importance of minors' involvement. Parental permission should not be considered as conclusive as an informed consent given about an adult's own participation in clinical trials and the assent is not an independent event. Since the individual autonomies could collide, it is important to seek protection for the family as a whole. Hence the ethical importance of shared decision-making, to adopt a global perspective about families and their autonomy. The researcher's role is crucial to facilitate shared decision-making, notably when conflicts arise between family members about the children's involvement in research. They should assess when family members do not communicate well and give parents and children enough time to ask questions and think about the alternatives. That is why it would be important for researchers to have communication skills and knowledge about children's psychology and family counselling.

If disagreement between family members is impossible to solve, it is difficult to choose who to listen to. In these cases, it is not clear if the child's objection to research is binding. If shared decision-making should be assumed as a major value, disagreement would become a barrier to the informed consent acquisition. In this case, Nuffield Council on Bioethics[45] (2015, paragraph 6.24-6.25) recognizes determinative value to dissent, both expressed by parents or by children. By affirming that, Nuffield Council of Bioethics shifts from a formal concept of informed consent, as legal requirement, to an ethical approach to the process, seen as an instrument to facilitate an agreement between different persons to share goals and benefits. This different point of view deserves consideration as a way to prevent conflicts and assure a proper involvement of minors and their families in clinical trials.

[45] NUFFIELD COUNCIL ON BIOETHICS, *Children and clinical research: ethical issues*, 2015, 6.24-6.25.