Contents of the Minor's Assent in Medical Research: Differences between the Scientific Literature and the Legal Requirements

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ABSTRACT: From an ethical and legal point of view, the assent of the minor to participate in a medical study is a subject of great importance. There is still a debate about the requirements to consider this assent valid and binding. This review analyses and compares the contents of the assent from the points of view of the legislation and the scientific literature.

KEYWORDS: Assent; bioethics; clinical research; hard law; informed consent

SUMMARY: 1. Introduction – 2. Objective – 3. Material and method – 4. Results and discussion – 5. Conclusion.

1. Introduction

Informed consent is one of the fundamental pillars of clinical research ethics, guaranteeing the autonomy of the potential participant in his/her decision to participate or not in an investigation. It consists in a communicative process and a document. The purpose of the informed consent is to protect the autonomy and voluntariness of the potential participant by informing him/her about all the relevant aspects of the study, before enrolment. The consent to participate can be revoked by the participant at any time.

International, European and National legal frameworks recognize both the importance of including children in clinical trials and the need to provide effective and specific protection for this vulnerable group. The best interest of the child is fundamental: this key principle, recognized by the United Na-

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This paper is an extension of the oral communication entitled "Contenidos del asentimiento del menor en investigación médica: diferencias entre la literatura científica y el requisito legal" presented on the V ANCEI Congress, held in Valencia on May 17th and 18th, 2018, and published in their book of papers in Spanish.

This essay is developed within the European project "Improving the guidelines for Informed Consent, including vulnerable populations, under a gender perspective" (i-CONSENT), funded by the European Union framework program H2020 (Grant Agreement n. 741856).

tions Convention on the Rights of the Child of November 20, 1989, has inspired the regulation of clinical trials involving minors at European and national levels.
The informed consent in studies with minors is made up of two parts: the minor's parents or legal guardians[1] have to accept the minor's participation in the study, through the parental informed consent; the child should agree to participate in the study, through the assent (if deemed able to do it). Therefore, the decision-making and legal responsibility of the minor's participation in the study is on the parents, but the minor's opinion is taken into account and, depending on the national legislation, he/she could be required to accept/refuse participation.
The hard law and the scientific literature deal with many aspects of assent, such as its possibility; the conditions to conduct a medical study with minors; the need of the parental consent; aspects about the child's age; the consideration of the minor as mature; his/her capacity to understand the information or the contents that the assent should include and how it should be presented.
This study analyses the contents of the assent with the perspective of the hard law and the scientific literature.

2. Objective

Analyse and compare the contents of the assent from the points of view of the legislation (hard law) and the scientific literature.

3. Material and method

Legal framework

The hard law analysis adopts a systematic approach in the review of measures, taking into account International, European and National laws.
The analysis begins from the Council of Europe's Convention on Human Rights and Biomedicine of 1997 and Additional Protocol concerning Biomedical Research, then continues with the analysis of the European legal framework, both at the EU level and in six countries: Austria, France, Germany, Italy, Spain and United Kingdom.
The search strategy contains documents from 2001. It includes general legal framework of mature minor's role on health care decision-making process; case law on D2001/20/CE or R 1901/2006 or R 536/2014 with regard to the informed consent process/assent of minors; case law with regard to the application of EU legislation in selected countries. Measures of transposition of the Directive were taken and implementing rules of European Regulations where implemented. The aim of the search was to identify and analyse the contents of the Informed consent/Assent by minors.
The databases used are Eurlex for the European Law and transposition measures in National regulation[2]; IURE for the European case Law; n-Lex for the national regulation on assent; Iurifast and Dec

[1] To facilitate the reading of the text, we will refer to the parents only from this moment, but it also includes the legal guardians of the minor.
[2] Search as described in http://eur-lex.europa.eu/collection/nlaw/mne.html?locale=en (CELEX number search).

ISSN 2284-4503

Nat for the member State case law which deal with the application of EU law; and the Common Portal of Case Law[3] for the national case law.
The search, screen and decision of including or not a result of finding has been done by pairs of reviewers by members of the LUMSA research unit involved in the i-CONSENT project.

Scientific Literature

Systematic search with PubMed[4] of experimental, observational and theoretical articles (case reports were excluded); published in English or Spanish; during the last 10 years; that include aspects about the information that is given or should be provided to the minor during the assent process in research.
Review of articles resulting from the search was done by pairs (by title and abstract), discrepancies were resolved by a third person. A critical reading and summary of the selected articles was made, with assignation of quality of the article, using the Osteba's Critical Appraisal Tools[5]. The review of the scientific literature was done by members of the FISABIO and UCV research units involved in the i-CONSENT project. The search in Pubmed was done on the 10th of July of 2017.

4. Results and discussion

Legal framework:

International and European legislation

The Convention on Human Rights and Biomedicine of 1997 (Oviedo Convention)[6] in its article 6, highlights the importance of the assent of the minor to any intervention in the health field, indicating that even the authorization should be given by the representative of the minor or an authority or a person or body provided for by law, the opinion of the minor will be taken into account, in proportion to his age and maturity. The EU Charter of Fundamental Rights[7] also expresses the importance of letting minors express themselves freely and taking their opinion into account in accordance with his/her age and maturity.
Regulation (EU) 536/2014[8] indicates the minimum contents of informed consent for clinical trials (article 29, section 2), and the requirements to obtain consent. According to it, informed consent must include: the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;

[3] http://network-presidents.eu/rpcsjue/ using Eurovoc Thesaurus (Edition 4.3)
[4]The search strategy used in Pubmed was: ((("Informed consent"[Mesh] OR "assent"[All Fields]) AND "Ethics"[Mesh] AND ("Research"[Mesh] OR "clinical research"[All Fields])) OR (("Informed Consent By Minors"[TW] OR "Consent Forms"[TW] OR "assent"[All Fields]) AND ("Ethical Theory"[TW] OR "Principle-Based Ethics"[TW] OR "Ethics,Research"[TW] OR "Research"[TW] OR "Clinical research"[All Fields]))) AND (English[lang] OR Spanish[lang]) AND ("infant"[TW] OR "child"[TW] OR "adolescent"[TW] OR "minors"[TW]) AND ("2007/07/14"[PDat]: "2017/07/10"[PDat]).
[5] http://www.lecturacritica.com (last visited 9 April 2019).
[6] ETS No.164, *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*, 1997.
[7] *Charter of Fundamental Rights of European Union*, 2000 (2000/C 364/01).
[8] 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, and repealing Directive 2001/20/EC.

the subject's rights and guarantees regarding their protection, in particular his/her right to refuse to participate and the right to withdraw from the clinical trial at any time without any resulting detriment and without having to provide any justification; the conditions under which the clinical trial is to be conducted, including the expected duration of the subject's participation in the clinical trial; the possible treatment alternatives, including follow-up measures, if the participation of the subject in the clinical trial is discontinued. The information must be comprehensive, concise, clear, relevant, and understandable to any person, provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned. The article also indicates that the information should be provided in an interview with a member of the investigation team. During the interview, special attention must be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. The article 2 of Regulation defines the minor as a "subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent".

Article 32 of that Regulation specifies that the legal guardian of the minor is the one who should authorise the participation of the minor, but also indicates that the minor must receive the information described in Article 29, adapted to his/her age and mental maturity, by researchers or members of the research team with training or experience in dealing with minors. Specific contents are not specified for assent in minors, considered the same as for informed consent. This article also indicates that the minor's involvement in the informed consent procedure shall be adapted to his/her age and mental maturity.

Article 93 of Regulation (EU) 536/2014[9], establishes the right to confidentiality in clinical trials. Regulation (EU) 2016/679[10], in its 8th article stipulates that the minor should be at least 16 years to give the consent to the processing of his or her personal data (national laws may provide a lower age, but not below 13 years old). If he/she is younger than the stipulated age, the authorization will be granted by the minor's legal guardians.

The informed consent is also necessary when biological samples or health data are collected and stored. Biobanking is an important issue to consider in relation to clinical trials. Privacy and data protection in biobanking is essential for securing acceptance of biobank research across Europe. The Article 22 of Council of Europe Convention on Human Rights and Biomedicine of 1997 establishes that "When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures". The European Union's existing regulatory framework in biomedical research, does not have a specific regulation for biobanks. Biobanks are governed under the general regulatory framework for biomedical research. Likewise, the Directive

[9] REGUL ATION (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, and repealing Directive 2001/20/EC, cit.

[10] REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

ISSN 2284-4503

2004/23/EC[11] on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissue and cells, does not cover research using human tissue (Recital 11 and Article 1).

National legislation

The analysis of the national legislation shows that not all States considered have already implemented Regulation (EU) 536/20142 and that the age at which the minor is considered mature enough to understand the information and to consent to participate in a clinical trial varies, being a regulated aspect only at the national level (see table 1).

Table 1. Aspects about the age criteria; assent and dissent by country

	AGE CRITERIA	MINORS YOUNGER	MINORS OLDER	ASSENT	DISSENT	NATIONAL LEGISLATION
UNITED KINGDOM	16	Consent must be provided by parents or legal representative	They are considered as competent adults for decisions on clinical trial participation	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	Medicine for Human Use Regulation of 2004[12]
ITALY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by the researcher	D.lgs. 211/2003[13]
SPAIN	12	Consent must be provided by parents or	Children must give their consent in addition to the	Required for minor over 12 years old	The researcher must respect the minor's dissent	Royal Decree 1090/2015[14]

[11] DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[12] The Medicine for Human Use (Clinical Trials) Regulation n. 1031/2004.

[13] Decreto Legislativo 24 giugno 2003, n. 211. Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico.

[14] Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de tica de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

		legal representative	consent provided by parents or legal representative			
GERMANY	18	Consent must be provided by parents or legal representative	The consent of the child may be considered if, on a case-by-case basis, the maturity of the child is established	Required if the minor can understand the nature and implication of clinical trial (case by case approach)	The researcher must respect the minor's dissent if the minor can comprehend the nature and the implications of clinical trial (case by case approach)	Medicinal Product Act 2005[15]
FRANCE	18 or 16 in the case of emancipated minor, not living with parents and eventually having his/her own family	Consent must be provided by parents or legal representative	Emancipated minor is considered as a competent adult in decisions on clinical trial participation.	Not expressly required	The dissent of the child considered sufficiently mature must be taken into account	Public Health Code of 1953 (amended in 2004,2009 and 2016)[16]
AUSTRIA	18	Consent must be provided by parents or legal representative	The consent of the child must be considered in addition to the consent provided by parents or legal representative if he or she is 14 years old and sufficiently mature	Required if the minor is 14 years old and sufficient mature	The dissent of the child considered sufficiently mature must be taken into account	Austrian Medicinal Product Act 185/1983 (emended in 2004)[17]

Source: Compilation by the authors based on the above-mentioned legislation.

[15] Gesetz ber den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG) 2005.
[16] Code de la Santé Publique.
[17] Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).

Regarding the information provided to the minor or his/her legal representative, there is a broad uniformity (table 2), but neither the European legal framework nor the national standards considered take into account the literacy of the minor or his/her family.

Table 2. Information provided to the minor before the beginning of the clinical trial by country

Country	Information provided to the minor
UNITED KINGDOM	According to Medicine for Human Use Clinical Trials Regulations of 2004, the child must receive information according to their capacity of understanding from staff with experience with minors regarding the trial, its risks and its benefits. Paragraph 3 (1) of Part 1 of Schedule 1 establishes in a general way that the person involved in the research must have met with the researcher and been informed of the objectives, risk and inconveniences of the trial and the conditions under which it is to be conducted. The participant must also be aware that they will be involved in the research before starting the treatment. Further information on the content of the information is provided by the BMA guidelines, which are taken into account by the judge in any consequent judgment.
ITALY	Article 4 of Legislative Decree 211/2003 establishes that children must be informed by staff experienced in dealing with minors about the clinical trial, risks and benefits, in an appropriate manner to their capacity of understanding.
SPAIN	According to article 4 of Royal Decree 1090/2015, in the case of patients with special vulnerabilities, including minors, the person participating at the trial shall be informed about the access to the normal clinical practice for his/her pathology. Article 5 indicates that all clinical trial with minors must comply, in addition to the conditions established in Articles 3 and 4 of the Royal Decree, all those listed in Article 32 of Regulation (EU) No. 536/2014 of the European Parliament and the Council.
GERMANY	Chapter 6, Section 40 (4) of the Medicinal Product Act of 2005 indicates that "before the start of the clinical trial, the minor shall be informed, by an investigator who is experienced in dealing with minors who is a doctor or, in the case of a dental trial, a dentist or an adequately experienced member of the investigating team who is a doctor or, in the case of a dental trial, a dentist, about the trial, the risks and benefits, in so far as this is possible, taking into account the minor's age and mental maturity".
FRANCE	Article L- 1122-2 of the Public Health Code of 1953 indicates that non-emancipated minors that will participate in a research, should get infor-

	mation provided in Article L. 1122-1 adapted to their ability to understand. The article L. 1122-1 indicates that the information has to include: the objective, methodology and duration of research; the expected benefits and foreseeable risks, even if the trial ends earlier than expected; possible medical alternatives; the medical care provided at the end of the trial if such assistance is required; the opinion of the committee referred to in Article L- 1123-1 and the authorization of the competent authority referred to in Article L-1123-12; if necessary, prohibition of simultaneously participating in another search; information about how personal data will be handled; information about the right to receive health data held by the investigator; information about the right to refuse to participate in research or to withdraw consent without incurring any harm.
AUSTRIA	According to §42 of Austrian Medicinal Product Act 185/1983, prior to commencing the clinical trial, the minor must receive and understand appropriate information about the nature, significance, scope and risks of the clinical trial. The minor always has to be informed by an investigator who is experienced in dealing with minors, who must take into account the stage of maturity of the child.

Source: Compilation by the authors based on the above-mentioned legislation.

About confidentiality and privacy, domestic laws do not provide specific norms on the condition of minors who exercise these rights through their legal representatives. Following the analysis of applicable European legislation, it is clear that even in the field of scientific research, the specific consent of the person is necessary for the use of their personal data. In the case of clinical trials involving minors, the ability to provide informed consent must be examined also for consent to the handling of data.

It has been observed that, in spite of the fact that, in many aspects, there is uniformity between the different national legislations and with respect to European legislation, in others, there are still discrepancies. Some of these differences are in relevant issues such as the child's participation in the decision-making process.

What does the scientific literature tell us?

The scientific literature presents the assent as a process that respects and promotes autonomy in the child's development, to express his/her opinion and decide on the health or illness processes that affect him/her. The empowerment and the development of their moral capacity for the autonomous exercise of future decisions are pursued[18,19].

[18] B.J. Pinto Bustamante, R. Gulfo Díaz, *Asentimiento y consentimiento informado en pediatría: aspectos bioéticos y jurídicos en el contexto colombiano*, in *Revista Colombiana de Bioética Universidad El Bosque*, 8(1), 2013, p. 154.

[19] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* in *Adolescent medicine: state of the art reviews,* 22(2), 2011, p. 198.

ISSN 2284-4503

Although much has been written about assent, there is still no agreement in several aspects about this topic, such as the quantity and quality of the information that must be provided to the child or the information that they really want and need to know, among others.
In the literature review carried out, 306 results were obtained from the search strategy, but only 10 articles (1 experimental, 6 observational and 3 theoretical) analysed aspects about the information that is provided or should be provided to the minor during the process of informed consent or assent. Of these, 3 were considered to have high quality by the reviewers, 2 medium quality, 4 low quality and 1 was not classifiable due to the lack of data after critical reading, as shown in table 3.

Table 3: Studies on the information of the assent, according to the quality of the evidence

First Author, Year	Quality of evidence[20]	Type of study	Nº subjects
Unguru, 2010[21]	High	Observational study	37 interviews with children (7 – 19 years)
Tait, 2018[22]	High	Experimental study	55 minors/55 parents (minors: 8-12 years; 13-17 years)
Lee, 2013[23]	High	Observational study	123 minors (12 - 17 years)
Dove, 2013[24]	Medium	Observational study	43 paediatric consent forms
Tait, 2017[25]	Medium	Observational study	20 expert stakeholders
Roth-Cline, 2013[26]	Low	Theoretical study	Not applicable
Twycross, 2008[27]	Low	Theoretical study	Not applicable

[20] Considered by the reviewers using Osteba's Critical Appraisal Tools.
[21] Y. Unguru, A.M. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent,* in *Pediatrics*. 125(4), 2010, pp. 876-883.
[22] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?,* in *Academic pediatrics*, 18(4), 2017, pp. 370-375.
[23] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad et al., *Comprehension of a simplified assent form in a vaccine trial for adolescents*, in *J Med Ethics*, 39(6), 2013, pp. 410-412.
[24] E.S. Dove, D. Avard, L. Black, B.M. Knoppers, *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, in *BMC Medical Ethics*, 14(5), 2013, pp. 1-10.
[25] A.R. Tait, M.E. Geisser, *Development of a consensus operational definition of child assent for research*, in *BMC Medical Ethics,* 18(41), 2017, pp. 1-8.
[26] M. Roth-Cline, R.M. Nelson, *Parental permission and child assent in research on children,* in *The Yale journal of biology and medicine,* 86(3), 2013, pp. 291-301.
[27] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, in *Paediatric nursing*, 20(6), 2008, pp. 14-18.

Baker, 2013[28]	Low	Observational study	20 minors/ 57 parents
John, 2008[29]	Low	Observational study	73 children (6-8 years old)
Giesbertz, 2016[30]	Not classifiable	Theoretical study	Not applicable

Source: self-made

Tait and Geisser[31] did a Delphi study with a panel of expert stakeholders to provide consensus about the definition of child assent for research study. They highlight the importance of providing information appropriate to the child's age, taking into account their cognitive and emotional aspects, such as it can be read in the final definition of assent proposed in the study:

"Children who lack the legal authority to provide informed consent per state laws should provide their assent to participate in a research study unless they either lack the cognitive ability, their clinical condition precludes their ability to communicate a choice, or the research holds out the prospect of direct benefit that is only available in the context of the research. Assent is an interactive process between a researcher and child participant involving disclosure of cognitively and emotionally appropriate information regarding, at minimum, why the child is being asked to participate, a description of the procedures and how the child might experience them, and an understanding that participation in the study is voluntary. Children should understand that they can decline participation or withdraw from the study at any time. Assent requires that the child explicitly affirms his or her agreement to participate in a manner that reflects their age-appropriate understanding and that is free of undue influence or coercion. In the absence of an explicit agreement, mere failure of the child to object cannot be construed as assent"[32].

Analysing the information that the assent should include, they consider essential to inform about the reasons why he/she has been chosen to participate; the procedures and how he/she will experience them; the indirect benefits if there is no expectation of personal benefit; and about the voluntariness and the right to revoke at any time. Understanding this basic information is paramount and the child should be aware of how it will affect his/her personal situation. The freedom of the child to decide about his/her participation in the study without any undue influence or coercion was also pointed out. It is interesting to highlight that during the Delphi process the experts suggested to change "must provide assent" with "should provide assent", making it a recommendation more than an obligation.

[28] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et Al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* in *Cancer*, 119(23), 2013, pp. 4154-4161.

[29] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, in *Archives of disease in childhood*, 93(5), 2008, pp. 379-383.

[30] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord, *Personalized assent for pediatric biobanks*, in *BMC Medical Ethics*, 17(59), 2016, pp. 1-7.

[31] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 1-8.

[32] A.R. Tait, M.E. Geisser. *Development of a consensus operational definition of child assent for research*, cit., p. 4.

Previously, Roth-Cline and Nelson[33] had already sought evidence regarding the information that the assent must contain. In their review of the literature, they found that there is considerable disagreement about important aspects of the assent, such as: "the age at which investigators should solicit assent from children; how to resolve disputes between children and their parents; who should be involved in the assent process; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need; the necessity and methods for assessing both children's understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model"[34].

They noted that the regulations do not specify the information necessary for the assent, but identify factors to take into account when assessing the minors' capacity, such as the age, maturity and psychological state.

They point out that the minor should understand at least why he/she has been asked to participate and the procedures to be carried out, and must agree to participate, whether parents are provided with more detailed information (such as risks, benefits or alternatives), reinforcing the importance of parental permission during the process. They concluded that the amount of information a child should understand should vary with his/her age and maturity, and argue that the model of assent in adolescents should be different from that of younger children; even so, they cannot affirm with scientific evidence the sections of information that must be included in each assent.

Including the same contents in the informed consent and the assent, as stipulated in the regulation, can also be criticized if we take into account the words of Unguru: when he talks about consent for clinical treatment, he notes that informed consent and assent are not the same and that they are based on different terms, informed consent is based on competence, while assent is based on capacity[35]. This difference may also be valid for clinical research where assent or consent requires a more nuanced and refined decisional capacity than in clinical treatment[36].

But one thing is what the legislation, experts in pediatric bioethics and researchers decide, and another one is the information that children consider relevant for themselves. A study conducted by Tait et al.[37] with 55 parent-child dyads compares the information priorities on research among adolescents (13-17 years) and younger children (8-12) and what the parents consider important to their child. They conclude that for minors and parents (what they believe is important for their children) all the contents are important, but they differ in some aspects. The main interests for the children focus on the procedures of the study, confidentiality and the direct and indirect benefits. There are statistically significant differences in the interests depending on the age of the minor. Adolescents prioritise more the information about voluntarism, direct benefits and procedures, than the younger minors. Comparing the importance given by minors to the information and parent's perceptions of what is relevant for their children statistically significant differences are found in the greater im-

[33] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., pp. 291-301.
[34] M. Roth-Cline, R.M. Nelson. *Parental permission and child assent in research on children,* cit., p. 296.
[35] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 198.
[36] Y. Unguru, *Making sense of adolescent decision-making: challenge and reality,* cit., p. 200.
[37] A.R. Tait, M.E. Geisser, L. Ray, R.J. Hutchinson, T. Voepel-Lewis, *Disclosing Study Information to Children and Adolescents: Is What They Want, What Their Parents Think They Want?*, cit., pp. 370-375.

portance that children attach to confidentiality and the lesser importance given to the purpose of the study and the direct benefits.

Parent's perceptions about the child's information priorities also vary depending on the age and gender of the child. They consider that girls will be in general more interested in all the information than boys, except in the case of the information about alternatives that parents consider less important for girls under 13 years than for boys of the same age group. Other statistically significant differences by gender are the priorities of information about the procedures (higher in girls than boys in both age groups) and about the purpose of the study, the direct benefits, the voluntarism and the right to withdraw in any moment (higher in adolescent girls). There are also statistically significant differences in parents' perceptions depending on the child's age, considering that adolescent girls give more importance to information about the purpose of the study and the alternatives than younger girls; and that adolescent boys care more about risks and confidentiality than younger boys. The study also shows that children and adolescents make decisions with parents and investigators, and that they perceive a beneficial effect of shared decision-making.

Unguru, Sill and Kamani[38] also studied the children's preferences about information related to research. They found that most children consider important to know why research is done before being asked to enrol in it, and some consider that it would be useful to be able to talk to other children with experience participating in research to help them understand what participation in a study entails. Another important factor that appears in this study is that some minors enrol or remain in studies because they feel pressured by their parents or physicians. More than one third of the children did not feel free to dissent and half of the children believed that they had little, very little or no role in deciding to enrol or not in the study. By asking minors how they can be more involved, they point out several things that the physician can do, such as talking directly to them and not only to their parents; ask them about their concerns; speak in an understandable language for them or do not treat them as children just because of their age.

As for the involvement of the children in the decision-making, in a study conducted by John et al.[39], in 2008, with young healthy children (6-8 years) who had participated in a study on a vaccine, most parents and several children considered that the parents should be the ones making the decision about the children's participation in the study. It was concluded that the majority of children between 6-8 years do not have the ability to understand the factors surrounding a clinical study, with marked individual differences. They highlighted that these important individual differences in understanding among children of this range of age, makes inappropriate to provide them with all the information about the study, and consider very important the role of the parents directing how capable the child is to understand this information and guiding the meeting of the child with the healthcare professionals. The authors indicate that these results cannot be extrapolated for older children.

[38] Y. Unguru, AM. Sill, N. Kamani, *The experiences of children enrolled in pediatric oncology research: implications for assent*, cit., pp. 876-883.

[39] T. John, T. Hope, J. Savulescu, A. Stein, A.J. Pollard, *Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research?*, cit., pp. 379-383.

ISSN 2284-4503

Regarding the amount of information, Baker[40] in a qualitative study using coded interviews carried out in 2013, tried to identify how to improve the quality of the Informed Consent Process received from parents and adolescent and young adult patients (aged 14-21 years) in a Phase I pediatric oncology trial. From the interviews carried out with 20 children between 14 - 21 years old and 57 parents, it was extracted that the most frequent suggestions were related to the information given during the assent process. More information was demanded about the risks, benefits, purpose of the study, scientific grounds that justify their participation and objectives and logistical issues specific to Phase I trials. The respondents expressed their willingness to have a process based on honest communication, without technicalities, adapted to the needs of children and their families. They also suggested that the written information included in the informed consent could be sent in advance, that other formats be used in addition to the written one and that they be provided with a summary sheet with the key aspects, which should be kept in mind during the study development. They also appreciate having more time to make the decision; that the physician explains the study several times, ensures their understanding, has a follow-up meeting to allow the family to discuss their options and guides them in the decision about participating.

This personalization of the agreement tailored to the needs of the child has also been proposed by Giesbertz et al.[41] in a theoretical study in which they tried to answer the question about how the content and the process of assent should be personalized to the child in the specific case of biobanks. Although the lack of data of this publication makes its quality unclassifiable, the article states that for the information to be personalized, it must begin with concrete information (that is easier to understand) and continue providing more information at the child's request, according to his/her desires and capacities. It is recommended not to use only the classic written format, but also different techniques and technical innovations and styles. Information technologies can play an important role to facilitate continuous communication.

In an analysis of the thematic content of paediatric informed consent models by Dove et al.[42], performed with Canadian consent forms, they observed a lot of variability between consent forms and that many of them presented important information gaps. For example, some consent forms did not include aspects such as the child's ability to dissent, the possibility to withdraw, details about the transfer and data sharing or the scope of parental right to access information concerning their child. The majority did not consider cumulative or non-physical risks. Some forms presented a lack of specificity about the role of the minor in the decision-making or the procedures to resolve conflicts in the decision-making between parents and minors.

Looking into the importance of understanding, Lee et al.[43] evaluated in 2013 the comprehension of a modified document in text format with supporting images for a clinical trial of Hepatitis B vaccine.

[40] J.N. Baker, A.C. Leek, H.S. Salas, D. Drotar, R. Noll, S.R. Rheingold, et al., *Suggestions From Adolescents, Young Adults, and Parents for Improving Informed Consent in Phase 1 Pediatric Oncology Trials,* cit., pp. 4154-4161.

[41] N.A. Giesbertz, K. Melham, J. Kaye, J.J. Van Delden, A.L. Bredenoord. *Personalized assent for pediatric biobanks*, cit., pp. 1-7.

[42] E.S. Dove, D. Avard, L. Black, B.M. Knoppers. *Emerging issues in paediatric health research consent forms in Canada: working towards best practices*, cit., pp. 1-10.

[43] S. Lee, B.G. Kapogiannis, P.M. Flynn, B.J. Rudy, J. Bethel, S. Ahmad, et al. *Comprehension of a simplified assent form in a vaccine trial for adolescents*, cit., pp. 410-412.

They found that only 56% of the children answered correctly all the questions (six). The issues better understood in the assent were those related to randomization and the possibility of withdrawing from the study; the worst-understood issue was the blinding of the choice of vaccine. They suggested that the inclusion of a quiz in the process of assent could have a positive impact to assess the understanding of the information and ensure the complete comprehension of the study.

Twycross, Gibson and Coad[44] tried to establish a formula so that the information provided to the minors involved in research is appropriate. Through meetings with experts conducted during the Research Society's International Nursing Research Conference, a consensus was reached regarding the information that needs to be provided to the minor and the format that the information should have. The National Research Ethics Services (NRES) consider that the following information needs to be provided[45]:

- "What is meant by research (or a project).
- That they are being invited to take part in research.
- Who else will be taking part (and how many).
- That agreement to take part in the study is voluntary (even if their parent/carer has agreed). They can still say no at any time.
- What the research is about.
- What the researcher will do.
- What they have to do.
- How long it will take.
- Any benefits or anything good that will come from the research; if there are none, say so.
- If there is a reward then you should say.
- That the information they provide is private, unless the child discloses that he or she or someone else is at risk of harm.
- A contact person for further information."

The recommendations about the format are[46]:

- "The information should be kept to a manageable length, in keeping with age and development.
- The sheet should be no more than one double-sided A4 page (excessively detailed information sheets can overwhelm participants).
- The leaflets should be designed so that they can be read to the child but are interactive enough for them to engage in the process.
- The language used needs to be appropriate to the age and developmental stage of the child.
- Pictures can be used to increase engagement but ensure they are appropriate to the child's development, prior learning and setting.

[44] A. Twycross, F. Gibson, J. Coad. *Guidance on seeking agreement to participate in research from young children*, cit., pp. 14-18.
[45] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 18.
[46] A. Twycross, F. Gibson, J. Coad, *Guidance on seeking agreement to participate in research from young children*, cit., p. 16.

- Do not just increase the size of the typeface of an information leaflet originally designed for older children.
- Information leaflets should be printed on the headed paper of the hospital/ institution where the research is being carried out. Plain paper is not acceptable even for young children.
- Information leaflets need to include the information required for informed consent, as set out by NRES. This might mean being creative in the way you phrase the question or provide the information or else the young child might not fully understand."

Many of these recommendations allude to aspects of legibility, both linguistic (grammatical and lexical) and typographic (graphic characters), which will allow the child to read and understand it more easily.

In the same study, Twycross et al. explored other interesting aspects such as the age at which minors can give a "so-called informed agreement" to participate in a research study or how to verify that the minor has understood the information. Concerning the age, they indicated that if the information is presented in an appropriate way, children from 18 months or 2 years old could already give informed agreement to participate in the study. They recommended to verify the understanding of the minor by asking him/her to repeat back to the researcher what the project is about and what their participation will involve, or include a written or picture-based list of questions to be answered at the end of the information sheet.

5. Conclusion

Even if the importance of minors' participation in clinical research is highlighted in the legal and scientific documents, there is a lack of high quality studies conducted in Europe on this topic that make it difficult to draw conclusions. The topic of the contents of the assent has not been explored at depth, probably because the legal texts establish the contents and they are the same as for the informed consent in adults. The focus has been usually put on the adaptation of the content to the age and maturity of the minor, the understanding of the document, the profile of the person who should give this information and the importance devoted to the minor's opinion.

Analysing the European legal framework, the specific issue of informed consent in the context of clinical trials involving minors allows us to identify some key points: a) the rule takes into account the proxy consent that must be provided by parents or other legal representatives; b) Regulation No. 536/2014 (Article 32, Clinical trials on minors) requires the child to receive the information referred to in Article 29(2) in a manner appropriate to their capacity of understanding, provided by staff with experience with minors; c) the explicit dissent to start or continue research participation at any time expressed by a minor who is capable of forming an opinion and assessing the information relevant to participation in the clinical trial must be considered by the investigator.

Comparing the legislation with the scientific literature, it has been seen that there are differences in the information that the assent should include from the point of view of the legislators, researchers, parents, and minors (being also different the priorities for adolescents and younger children). There is also a current debate about the convenience of giving the minor all the information (adapted to his/her age and maturity) or giving only some contents to them (also according to his/her age and

maturity and taking into account that all the information is given to parents in their consent). Even so, there are some contents that are identified most of the times as essential in the assent, such as why they have been asked to participate, the study procedures, the voluntariness of participation or the option to leave the study at any time. There is no agreement on the age at which the child's opinion should be taken into account, nor about the role that parents should play during the information phase and the child's decision-making process.

There are differences about the information that the investigators and the parents consider relevant for the minors and that the minors consider relevant for themselves. This should be taken into account when investigators or parents inform minors, as probably they will give the information that they consider relevant to minors and not what minors consider relevant for themselves. The information that the parents deem important for minors is different according to gender and age, so the impact of gender on the information process should also be taken into account when parents inform minors or help them during the decision-making process.

More studies about the interests and needs of the minors are needed to adapt better the contents and the process of assent to them instead of considering that adults and minor have the same needs of information.

In addition to what is said (content and quantity), it is relevant how it is said (method/format used, information order, legibility), who says it (skills of the person reporting), how many times it says it (continuity and adaptation of the information throughout the study) and what the child wants to know or cares about.

It is also essential to ensure an adequate understanding of the information. Additional actions such as personalising the process, talking directly to minors and soliciting their concerns, asking minors to repeat back the information provided, including a quiz in the process of assent or giving him/her the possibility of talking with other minors with previous experience participating in clinical trials may have a positive impact in the process and contribute to ensuring the comprehension of the information and involving minors in the decision-making.

The role of the minor in the decision-making also needs to be better set. The legal documents give importance to the minor's opinion through the assent (depending on their age and maturity), but the scientific literature suggests their lack of influence in the decision-making. Moreover, the scientific literature shows the lack of efforts or mechanisms to ensure that the opinion/wish of the minor to participate in research is taken into account, neither to facilitate the understanding of the information by the minor and their parents. Legal documents have a key role in the consideration and importance given to both aspects, in setting out standards and requirements.

ISSN 2284-4503