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The ethics of informed consent in novel treatment including a gender perspective

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[1] **R** = Report, **DEM** = Demonstrator, prototype, **DEC** = Websites, press & media actions, videos, **OTHER** = Software, technical diagram, etc

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V0.0	First drafting	15/10/2017	None: first draft	Prof. Laura Palazzani
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Table of Contents

1. Ethical and legal review of gender and age-related issues associated with the acquisition of informed consent: executive summary

1.1. Aims and scope

Informed consent for clinical research is both a communication process and a document to inform subjects about relevance, scope, risks and benefits of the involvement in research and to obtain consent to be involved in these studies. Relevant issues arise when the research involves particularly vulnerable subjects, such as minors or women in some circumstances (i.e. pregnancy or breastfeeding). Age and gender-related issues may become a huge challenge in terms of appropriateness, completeness and clarity of information and consent.

I-Consent project aims at developing guidelines on how to present informed consent in a comprehensive way, facilitating people's participation in research. Guidelines will be validated using different informed consent models related to vaccines and involving minors and pregnant women (Human Papilloma Virus, Respiratory Syncytial Virus). Hence the importance of an analysis of gender and age-related issues for the next steps of the project.

This report's aim is to examine the situation of the general ethical and legal framework (considering both hard law and soft law, see below) for women and minors taking part in clinical research and to verify how the European Directive 2001/20/EC has been transposed into national legislations of EU Member States with a focus on Austria, France, Germany, Italy, Spain and United Kingdom, as well as the impact of Regulation (EU) 1901/2006 and Regulation (EU) 536/2014 on national laws concerning gender and age-related issues in informed consent to clinical trials (for a brief explanation of the overlaps between the two, see par. 1.2.4). Informed consent to medical treatment is not considered in this report.

1.2 Methodology

1.2.1 Sources, databases and inclusion criteria

For further information see annex 1 – Research Protocol

Terminology

Concerning age-related issues in the acquisition of informed consent, the scope of the report is to examine the situation of the general ethical and legal framework for minors involved in clinical trials. Thus, the analysis addresses the topic exclusively with reference to paediatric clinical trials, not focusing on elderly people's issues, both from an ethical and from a legal point of view (see above 1.1: "Aims and scope").

This report uses the word "sex" to refer to the biological dimension (sexual difference between males and females) and "gender" for the psychological, social and cultural dimensions, which influence men and women's behaviours in their decision to participate in clinical research, requiring a differentiated approach in the

informed consent process. The two words are confused and often overlap in soft law. The evolution in the notion of gender beyond sexual binarism (the so-called gender or post-gender theories or ideologies) will not be taken into account in this document, as it does not pertain to the object of this review.

Hard Law: a systematic approach

The hard law analysis adopts a systematic approach in the review of measures. More specifically the legal review takes into account international law, European law and national laws.

First of all, referring to international legal framework, the analysis starts from Council of Europe's Convention on Human Rights and Biomedicine of 1997 and Additional Protocol concerning Biomedical Research, then continues with the analysis of European legal framework, both at the EU level and in six selected countries: Austria, France, Germany, Italy, Spain and United Kingdom. The research is conducted using the databases indicated in the review protocol and through the inclusion and exclusion criteria therein described.

Soft Law: a narrative approach

The analysis adopts a narrative approach in carrying out a soft law (ethical) review. Inclusion criteria comply with the ones listed in Task 1.3 research protocol: the analysis focuses on guidelines, recommendations and opinions issued by national, European and international bioethics/research ethics committees, scientific societies, European institutions and international organizations in six selected countries (Austria, France, Germany, Italy, Spain and United Kingdom). Documents were collected by visiting the websites of relevant institutions.

Research is not limited to the European context (national and international), but is also extended to USA, with reference to topics which are still not clearly defined (compensation, use of ICT, families coming from different cultural background) and thus needing further analysis. Beyond the scope of this report, Belgium and Canada were taken into account as illustrative cases, due to interesting developments with regard to gender considerations in the informed consent process.

Soft law/hard law distinction

In this report rules of conduct with no legal binding force are considered soft law (e.g. guidelines or codes of conduct). These rules are analysed together with institutional documents approved by national and international bioethics committees, which often contain non-binding opinions and recommendations.

As hard law all legal instruments of positive law (laws, regulations and authoritative decisions, thus case-law too) are considered. Indeed, in the section dealing with hard law analysis, reference is also made to the principle of informed consent in the Council of Europe's Convention on Human Rights and Biomedicine, which is enforceable and therefore binding only for States ratifying it. Among the binding documents analysed is the Directive. It is not directly applicable in the Member States, but requires transposition measures at national level. Unlike the Directive, the Regulation (EU) 536/2014 has binding legal force in all EU member states (the only exceptions are some specific areas where the Regulation allows national

legislation, such as participant consent requirements). However, Member States can adopt (France and Spain already have adopted) implementation measures in order to adapt their national legislation to the Clinical Trials Regulation.
The Regulation entered into force on 16th June 2014 but will not be applicable until six months after the EU portal and database have become fully functional. Clinical trials in the EU are currently governed by Directive 2001/20/EC and transposition measures at national level.
In this context, it is important to clarify that, unlike other Member States, France, Germany and Spain have already reformed domestic rules in the field of clinical trials, in order to implement Regulation (EU) 536/2014 in their legal systems.

1.2.2 Internal procedure of revision

Pairs of reviewers independently performed the search following the inclusion and exclusion criteria. Notably, L. Nepi and F. Cavalcanti analysed age-related issues, while L. Persampieri and V. Ferro explored gender issues. L. Palazzani, F. Macioce and A. Rinella proceeded to screen the proposed results and findings, and decide whether the studies found were relevant and met the inclusion criteria. In a subsequent phase, independent and external reviewers (prof. L. d'Avack, dr. C. Petrini, prof. E. Rigo) have been asked to read a first draft of the report, so as to highlight shortcomings, errors, lack of information, and to propose other or different data and resources. Finding results have been reported in the final draft by the members of the Lumsa research unit.

1.2.3 Questionnaires

A short questionnaire on gender and age-related peculiarities in informed consent to clinical trials within national legislations has been prepared by Prof. Palazzani and Dr. Persampieri and circulated to contact experts in this field. Such a questionnaire was meant to identify the legal review process and collect up-to-date data relevant for the work-package objectives.

1.3 Main findings

1.3.1 Age-related issues: soft law

All institutions considered approved guidelines and recommendations about the topic of informed consent in paediatric clinical trials. The review has pointed out some issues with common ethical standards and grey areas in which soft law regulation is still evolving.
Appreciation for minors' involvement in clinical trials and for children's autonomy is evident, but has to be combined with parental and social moral duty to protect them. Some document states that conducting research on children should only take place if the study cannot be done on adults. Recently the balance had shifted to

specifically encouraging children's inclusion in trials taking into account the benefit they can obtain, both direct and indirect (see Nuffield Council on Bioethics).
Discrepancies are on the risk/benefit balance and the importance of child's objection. Minors' assent seems to be mandatory to carry out clinical trials, but guidelines do not agree about the age to provide a valid assent. The assent's importance grows in relation to minor's age and risk associated with clinical trials, but in soft law documents there are differences concerning age limits, age ranges and circumstances to consider (e.g. direct benefit for involved subjects).
Other discrepancies concern the interpretation and use of terms "parental permission" and "informed consent": these are not synonyms and sometimes documents highlight the ethical difference between a parental permission given in the child's best interest and an informed consent given by an adult in his or her own interest. Nevertheless, there are not unequivocal interpretations of these terms. No indication is provided about the case of disagreement between parents and the mature minor's opinion is often considered binding, but parental authority does not lose effectiveness in legal terms.
It also seems that ethical documents represent informed consent as a process, but rarely provide in depth examination of consent or assent procedures in paediatric clinical trials, nor recommendations about the way to assess the comprehension of information. Furthermore, the impact of ICT on informed consent process and the importance of cultural mediation is not always taken into account.
With reference to compensation and undue inducement to be involved in research, is not easy to fix acceptability thresholds clearly distinguishing licit and illicit benefit. Good ethical criteria seem to be that compensation cannot be related to the level of risk undertaken and cannot be presented as a benefit related to the involvement in the study.

1.3.2 Age-related issues: hard law

International, European and national legal frameworks recognize both the importance of including minors 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 UN Convention on the Rights of the Child of 20 November 1989, has inspired the regulation of clinical trials involving minors at a European and a national level.
The need to ensure specific protection for minors involved in clinical research emerges from the analysis of both the European and national legal frameworks. In particular, the European regulation of clinical trials involving minors and related domestic laws, establish additional conditions for this kind of experimentation beyond those set forth for clinical trials involving adult subjects.
The Convention on Human Rights and Biomedicine of 1997, the Additional Protocol concerning Biomedical Research of 2005, EU Directive 2001/20/CE and the Regulation (EU) 536/2014 establish that clinical trials involving minors may be undertaken only if they can produce direct benefits to participants. Exceptionally, and under the protective conditions prescribed by law, research is also permitted for indirect benefits, provided that the risks and burdens are minimal.

Domestic laws gave particular attention to these principles and to the balance between risks and benefits. Informed consent is a fundamental prerequisite for the participation of any person in scientific research.
Nevertheless, important legal issues are at stake:
1) most minors are not capable of granting legally valid consent;
2) in some legal systems, the age at which a person is considered able to give a valid consent is not necessarily the same as the age of legal majority;
3) the capacity to understand information is often not fully developed in minors; consequently, for valid informed consent, it is generally necessary to involve an adult subject acting as a surrogate in decision making;
4) the involvement of an adult proxy raises the issue of the assent of the minor, necessary to ensure respect for children's fundamental rights, despite the fact that children are not entitled to provide full and informed consent;
5) the capacity to understand information and to provide autonomous consent raises the issue of the value of the explicit dissent of the minor.
All these issues are taken into account in the laws of the six Member States analysed. While there is uniformity in the identification of the necessary conditions for clinical trials due to the implementation of European legislation, there is some disparity on some key issues.
First of all, the age at which a child is considered sufficiently mature to understand information and to give his/her consent to participate in a clinical trial is not uniform. In fact, this is a question regulated only at a national level.
Considerable differences can also be found regarding the importance given to the minor's assent and explicit dissent, which are binding only in some States. Regulation (EU) 536/2014, unlike Directive 2001/20/CE, establishes that the explicit wishes of the minor shall always be respected by the researcher. However, not all the States analysed have yet to implement the Regulation.
A broader uniformity may be pointed out with regard to the information provided to the minor or their legal representative. Nevertheless, neither the European legal framework nor the considered national rules take into account the issue of the literacy of the minor involved in research, or that of his/her family. Moreover, a specific regulation for the protection of children's data is lacking, as only general rules on data handling are applicable. Finally, another issue on which there is no uniformity among the six Member States analysed is the question of infringement. In some cases, violations are punished only with an administrative sanction, while in other cases, a criminal penalty is also possible.
Some discrepancies exist on fundamental issues among the domestic laws of the States considered. Some States do not require the participation of the child in the decision-making process while others, inspired by supranational norms, require it. However, following the entry into force of Regulation (EU) 536/2014, there seems to be an ever greater consideration for the autonomy of the minor capable of discernment and for their assent in issues related to their health.

1.3.3 Gender-related issues: soft law

Not all International and European guidelines and recommendations reviewed specifically focus on gender considerations in informed consent to clinical trials. There are often scattered references to this topic in documents addressing women's participation in clinical trials or in ethical guidelines for research involving human subjects. It is possible to devise a number of common ethical standards resulting from the soft law review, as well as problematic issues where disagreement or gaps still remain.

Findings show that there are no specific guidelines focusing on methods and procedures adapted to a differentiated approach between women and men, in terms of effective communication strategies meant to improve the informed consent process. However, particular attention is devoted to raising awareness on safety methods and devising special sections within consent forms with inclusion/exclusion criteria relating to pregnant/breastfeeding women or of childbearing potential. There is often consideration for cultural or social aspects, which may lead to specific gender vulnerabilities, but these observations are not translated in particular tailored procedures to be implemented in consent forms.

The Permanent Working Party of Research Ethics Committees in Germany (Arbeitskreis medizinischer Ethik-kommissionionen), for instance, has developed and published templates for informed consent, which are documents for clinical trials with medicinal products on healthy volunteers or patients and for collecting materials for biobanking, recommended to sponsors. These samples are widely used. Even though they are not adapted to gender, they stress that the oral information process must take the individual background and abilities into account.

The UK Health Research Authority, in the Consent and Participant Information Sheet Preparation Guidance places significant emphasis on the useful role of new technologies, in order to innovate the informed consent process, but no differences are reported concerning how best to apply these technologies with regard to women and men.

In Spain, there are no specific guidelines in this context: reference is made to international documents, such as the Helsinki Declaration, the Council of Europe's Convention on Human Rights and Biomedicine and the ICH GCP Guideline.

Bioethics Committees in Austria and Italy have both issued Opinions on the topics with final recommendations, which raise awareness on the importance of including women in clinical trials with due consideration of their specific physiological condition: both countries have particularly stressed the significance of ensuring a balanced presence of women and men in the composition of ethics committees, in order to better understand and meet the needs of women enrolling in clinical trials. In addition, the Italian National Bioethics Committee also highlights a number of physiological, social, economic and cultural factors which may generate vulnerabilities with regard to their participation in research. Recommendations do not suggest gender-tailored informed consent processes.

France does not specifically deal with gender considerations in an ad hoc guideline; however, some scattered references to cultural and social elements affecting women's autonomy and freedom may be found in a number of Opinions released by

the French National Consultative Ethics Committee for Health and Life Sciences on the topic of transnational research. Here, again, no explicit mention is made of a gender-approach to the informed consent process.
Beyond the six-selected European countries, the research refers to documents of soft law in other countries, specifically dedicated to these topics, as interesting cases for a gender approach to informed consent. The United States soft law (issued by governmental and non-governmental bodies, scientific societies) devotes considerable efforts to promoting gender equality in clinical research recommending a sex-stratified analysis of research data and overcoming barriers to women's inclusion in all phases of clinical research. Health Canada emphasizes the importance of adapting the informed consent process to women's specificities through "user-friendly" models. Belgium Advisory Committee on Bioethics develops ethical reflections on two sensitive roles in the informed consent process: the role of the fertile or pregnant woman's partner in the consent process, as well as the role of a man's fertile or pregnant partner.

1.3.4 Gender-related issues: hard law

The regulatory analysis points out that in the Directive 2001/20/EC and in domestic laws of selected countries there is no legal sensitivity to gender issues, and no differentiated rules for the acquisition of informed consent can be found.
The Regulation (EU) 536/2014 shows a greater juridical sensitivity to the Directive with regard to vulnerable subjects participating in clinical trials.
However, in the Regulation there is a lack of specific provisions regarding women enrolled in clinical research. The only rules concerning women refer to specific vulnerability conditions (pregnant or breastfeeding women), and are aimed to balance the interests of both pregnant women and their foetus, as well as of nursing mothers and their children.
The Regulation as well as the implementing measures in French and in Spanish legislations, do not prescribe differentiated gender profiling processes. The case law of the European Court of Human Rights, of the Court of Justice and of the National Supreme Courts broadly evaluates the issue of informed consent: however, these Courts do not consider gender-related aspects regarding informed consent in clinical research.

2. Tables of Main Results

2.1 Age-related issues in informed consent to clinical trials

Soft Law

Common ethical standards	Problematic issues
Paediatric clinical trials are essential to gain knowledge about children's health condition.	Appreciation for minors involvement in clinical trials is expressed, but some documents ask not to involve minors if research can be conducted on adult subjects. Thus, appreciation for minors' involvement in clinical trials and for children's autonomy is evident, but has to be combined with parental and social moral duty to protect them. Recently the balance had shifted to specifically encouraging children's inclusion in trials taking into account the benefit they can obtain, both direct and indirect (see Nuffield Council on Bioethics). Nevertheless, discrepancies about the risk/benefit assessment and the importance of child's objection are still existing.
Duty to ask for parental permission and minor's assent.	Parental permission and minor's assent are not synonyms of informed consent and sometimes documents highlight the ethical difference between a parental permission given in the child's best interest and an informed consent given by an adult in his or her own interest. Assent too does not have the same value as informed consent, because given by a person unable to consent. Nevertheless, there are not unequivocal interpretations of these terms.
Assent is mandatory to carry out paediatric clinical trials, if the minor is capable.	Guidelines do not agree about the age to provide a valid assent. The assent's importance grows in relation to minor's age, his maturity and risks associated with clinical trials, but in soft law documents there are differences concerning age limits, age ranges and circumstances to consider (e.g. direct or indirect benefit for involved subjects).
Parental permission is required.	No indication in case of disagreement between parents.
A mature minor can decide independently, if research implicates minimal risks and burdens.	The parental authority defined by national law is however effective and is not easy to define minimal risks and burdens.
Informed consent is required not only for interventional studies, but also to carry out research on biological samples or health information.	Informed consent can be obtained for future research too, but if future research is undefined and not related to the one carried out in the present, the possibility of a blanket consent is ethically controversial.

Informed consent and assent are a process and not a form.	There are no clear standards about procedures to obtain parental permission and minor's assent.
Information must be understood.	There are no clear procedures to assess information comprehension.
Information should take into account cultural differences.	Cultural mediation is not always mentioned and documents are focused overall on translation of information.
Compensation and reimbursement cannot become undue inducement to be involved in clinical trials. Compensation cannot be related to the level of risk undertaken and cannot be presented as a benefit related to the involvement in the study.	There is no clear definition of "illicit compensation".

Hard Law

	AGE CRITERIA	MINORS YOUNGER	MINORS OLDER	ASSENT	DISSENT	NATIONAL LAW
UNITED KINGDOM	16	Consent must be provided by parents or legal representative	Is considered as a competent adult for decisions on clinical trial participation	Not expressly required	The explicit wish of a minor capable to form an opinion is considered by researcher	Medicine for Human Use Regulation of 2004
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 researcher	D.lgs. 211/2003
SPAIN	12	Consent must be provided by parents or legal representative	Children must give their consent in addition to the consent provided by parents or legal representative	Required for minor over 12 years old	The researcher must respect the minor's dissent	Royal Decree 1090/2015
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
FRANCE	18 or 16 in the case of emancipated minor, not living with parents and eventually having his 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)
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)

Similarities and differences between the Directive 2001/20/CE and the Regulation (EU) 536/2014

	DIRECTIVE 2001/20/CE	REGULATION (EU) 536/2014
Benefit of involving minors in clinical trials	Art.4: a clinical trial on minors may be undertaken only if some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors	Art.32: a clinical trial on minors may be undertaken only if there are scientific grounds for expecting that participation in the clinical trial will produce a direct benefit for the minor concerned outweighing the risks and burdens involved; or some benefit for the population represented by the minor concerned
Risk and Burden	Art.4: a clinical trial on minors may be undertaken only if clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored	Art.32: a clinical trial on minors may be undertaken only if clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition
Data Protection	Art.3: the right to confidentiality is determined by Directive 95/46/CE (no specific rules for minors)	Artt.28 and 93: the right to confidentiality is determined by Directive 95/46/CE (no specific rules for minors)
Incentive	Art.4: no incentives or financial inducements may be granted to reward research participation	Art. 32: no incentive or financial inducements are given to the subject or his/her legally designated representative
Paediatric expertise of Ethics Committes	Art.4: a clinical trial on minors may be undertaken only if the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol	-
Specific rules on informed consent in clinical trial involving minors	Art.4	Art.32
Definiton of Age Criteria	Defined in domestic law	Demanded to domestic law
Participation of the minor	-	Art.32: The minor shall take part in the informed consent procedure in a way adapted to his/her age and mental maturity
	Art.4: the minor receives information	Art.32: the minors receive information in a

Content of information	according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits	way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children
Consideration of explicit wish of the minor	Art.4: the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time **is considered** by the investigator or where appropriate the principal investigator	Art.32: the explicit wish of a minor who is capable of forming an opinion and assessing the information to refuse participation in, or to withdraw from, the clinical trial at any time, **is respected** by the investigator

2.2 Gender-related issues in informed consent to clinical trials

Soft Law

Common ethical standards	Problematic issues
Women should be included in clinical trials, in order to improve their health condition by gaining knowledge from research; differences between men and women should be regularly assessed to avoid discrimination	The variability in women's physiological condition raises concerns with regard to an adequate risk assessment prior to inclusion: e.g possible interactions between changes in hormonal status and the use of experimental substances in trials.
The role of women as research actors (both as researchers and representatives of patient associations) and as members of ethics committees should be fostered, to enable their active participation.	No specific strategies or methods are recommended to improve the informed consent process with a gender perspective.
The duty to protect fertile, pregnant or breastfeeding women: safety criteria must be included (with both references to women and foetuses, newborn baby) and clearly communicated in the informed consent process.	The exclusion of women of childbearing potential is accepted only in exceptional cases and it requires a detailed justification.
Women are not generally considered a "vulnerable population", except for specific physiological conditions (i.e. pregnancy or breastfeeding), which require special protection; or social and cultural patterns affecting their autonomy in the decision to participate in clinical trials.	There are guidelines highlighting that women in trials should be defined as "scientifically complex", rather than a "vulnerable population" (also if pregnant), as women have the decision-making capacity to opt for participating or not in specific research studies.
The self-determination of fertile women should be guaranteed in research participation, as long as they have been duly informed about the specific degree of risk involved.	Some documents raise the issue of contraception. The required methods, which are often prescriptive, have their own inherent risks and may not meet the woman's preferences and convictions.
Research conducted on pregnant or breastfeeding women may or may not have a potential direct benefit and it is allowed only when studies of comparable effectiveness cannot be carried out on other persons, there is a direct benefit, there is a benefit to other women in the same condition (with minimum risk and minimum burden as compulsory).	Some guidelines stress that when the social value of research for pregnant or breastfeeding women or their foetuses or infants is compelling, and the research cannot be conducted on other persons, a research ethics committee may allow a minor increase "above minimal risk". Definitions of minimum risk and burden or over this minimum threshold are unclear.
A careful balance between benefits and risks for the mother and the foetus or the infant must be carried out before any	Challenging cases of enrolment are possibility of foetal loss, research directed at the foetus, which poses a risk to the

decision about trial participation is made.	mother. Different answers to this risk-benefit assessment reflect the ethical pluralism concerning the status of the foetus. No kind of research may be conducted without an explicit consent of the woman involved.
There is broad consensus on the fact that in no case permission by the woman's partner may replace the individual informed consent of the woman herself, since this would result in a violation of the principle of respect for the person.	Some guidelines state that it is ethically permissible, and in some contexts highly advisable, for the woman to consult the partner. The extent to which the father of the unborn child should be involved in the informed consent process is controversial. Other problematic issues may become from cultural contexts where the community dimension may coerce women into participating or not participating in clinical trials, affecting their freedom to decide.
The accuracy and clarity of the information provided is key to ensuring prospective participants' full understanding of the potential benefits and the extent of risk involved.	Very few documents emphasize the need to adapt consent forms to women's specificities and literacy levels. Women living in a social context of patriarchal authority may adopt a passive behaviour with regard to enrolment procedures. The role of cultural intermediation in bridging communication gaps is not considered in relation to gender issues.
The involvement in a clinical trial is a benevolent act, which should not be induced by monetary or other forms of compensation, in order to avoid exploitation. Reimbursements are considered ethically acceptable, as long as they do not result in undue inducement	Determining the ethical acceptability of compensation is problematic, as the possibility it may exert an undue inducement to participate in research depends on a number of different variables, such as prospective subjects' economic status.

Hard Law

	NATIONAL TRANSPOSITION MEASURES OF DIRECTIVE 2001/20/EC AND DOMESTIC LAW	IMPLEMENTATION MEASURES OF CLINICAL TRIAL REGULATION (EU) 536/2014
SPAIN	Royal Decree 223/2004 BOE n° 33 of February 2004; Law 41 of 14 November 2002; Law 14/2007;	Royal Decree No. 1090/2015;
ITALY	Legislative Decree 211/2003, amended by Decree 158/2012, converted by law no. 189 of November, 2012;	
UNITED KINGDOM	The Medicines for human use (Clinical Trials) Regulations 2004 No. 1031, amended by Statutory Instrument 2006 No. 1928; Statutory Instrument 2006 No. 2984; Statutory Instruments 2008 No. 941 Regulations 2009 No.1164;	
GERMANY	12th Amendment of the Medicinal Product Act (Arzneimittelgesetz - AMG) , June 30, 2004; GCP-Verordnung - GCP-V of August 2004;	
FRANCE	Law no. 2004-806 on 9 August 2004; Decree no. 2006-477 on 26 April 2006;	Decree concerning Research Involving Humans No. 1537 of 16 November 2016; Decree No. 1538 of 16 November 2016; Ordinance No. 800/2016;
AUSTRIA	Arzneiwareneinfuhrgesetz 2002 und das Bundesgesetz über die Errichtung eines Fonds geändert wERDEN, BGBl I. No. 35/2004; the Medical Devices Act (Medizinproduktegesetz, MPG) No. 143/2009; the Hospital Act (Krankenanstaltengesetz 2002); the University Act (Universitätsgesetz) (BGBl. I No. 120/2002); the Data Protection Act (*Datenschutzgesetz* 2000) (DSG).	

	SPECIFIC RULES RELATED TO ENROLMENT OF WOMEN	GENDER RELATED-ASPECTS REGARDING TO INFOMED CONSENT
SPAIN	Some provisions about pregnant or breastfeeding women, mainly aimed to the protection of the foetus	Regulations do not provide different provision by gender with respect to the consent.
ITALY	No explicit reference to women	Regulations do not provide different provision by gender with respect to the consent.
UNITED KINGDOM	No explicit references of women	Regulations do not provide different provision by gender with respect to the consent.
GERMANY	Specific requirements for pregnant women and nursing mothers. Clinical trials should be designed in a way to allow conclusions on possible different effects of the tested product on men and women	Regulations do not provide different provision by gender with respect to the consent.
FRANCE	Specific provisions for pregnant women and nursing mothers	Regulations do not provide different provision by gender with respect to the consent.
AUSTRIA	No explicit references to women	Regulations do not provide different provision by gender with respect to the consent.

3. Data analysis and discussion

3.1 Age-related issues in informed consent to clinical trials (Soft Law)

3.1.1 Children's participation in clinical research

The context of children's participation in clinical trials

According to WMA Declaration of Helsinki (2013) "While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects" (art. 8), therefore a voluntary and informed consent is a necessary condition. However, if trials need to involve persons unable to consent, duty to protect them becomes pivotal. A strict interpretation of this duty could leave groups of vulnerable people without significant benefits and knowledge about their condition, so the involvement of minors and people unable to consent in clinical trials needs to be justified.

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.

Nowadays, children's participation in clinical trials is considered insufficient, in view of low involvement rates: "The reasons for these deficits are to be found in a lack of interest on the part of the pharmaceutical industry, firstly because of the lower economic potential (smaller markets) and secondly because studies involving children are more complex, time-consuming and expensive. This is enhanced by the fact that the conditions of trials change depending on the different stages of childhood development and the related risks are therefore more difficult to assess" (Austrian Bioethics Commission 2013, 34).

It is important to involve in research people unable to consent, and children too, in order to make them access to benefits for their own health, balanced with related risks. For these reasons institutional documents highlight the importance of informed consent, risk assessment and inclusion criteria in clinical trials on 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 (EMA 2016).

The first issue is to determine if paediatric clinical trials are necessary, or if research on adult subjects is sufficient to increase knowledge: should paediatric clinical trials be considered an exceptional procedure? Institutional documents ask to involve children in research first of all for scientific reasons: "Growth and maturation processes, as well as certain specific diseases are unique to children. Specific consequences of medical interventions may be seen in children and may only appear long after exposure" (EMA, 2008, 4). Yet, from an ethical point of view, their involvement in clinical research has not to be viewed as necessary evil: "In the past,

many new products were not tested in children or adolescents although they were directed at diseases also occurring in childhood. In some cases, this resulted in children or adolescents being exposed to interventions that were either not effective or harmful. In general, this lack of information results in higher risks for children and adolescents from being exposed to interventions where little is known about their specific effects or safety in this population. Therefore, it is imperative to involve children" (CIOMS 2016, Commentary on Guideline 17). Nevertheless, minors' involvement in clinical research is not suggested if trials can be carried out on adult subjects. If involvement is necessary, researchers should include first of all less vulnerable subjects (EMA 2008, 5). About the order of involvement in research, it is often preferable to conduct research on adults before children but CIOMS doesn't establish such a strict requirement, because sometimes children face different health issues and minor's specific conditions have to be taken into account. However, older children having more capacity to consent should be involved before younger children, unless there are thorough scientific reasons to involve them before (2016, Commentary on Guideline 17).

Trials involving minors are essential to test the effects of therapies and interventions, or to develop observational studies (Austrian Bioethics Commission 2013, 36). Particular physiological characteristics and health needs make paediatric clinical trials necessary to offer tailored and better healthcare for children. CIOMS (2016, Guideline 17) states that "Children and adolescents must be included in health-related research unless a good scientific reason justifies their exclusion". Minor's condition requires a series of specific protections, overall because the person is unable to consent, but an exclusion needs to have sound scientific basis concerning risks and benefits of involvement in a trial.

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 (2015, paragraph 4.28). 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.

Risk/burden and benefits (direct and indirect)

Clinical research on human subjects has allowed a great increase of therapeutic and diagnostic opportunities, but it is structurally uncertain, because is built on a scientific hypothesis which needs to be confirmed through investigation. Parents and society are in charge of protecting children and this requires risk and burden minimization (see below), as well as benefit for people involved (ICH 2000; WHO 2011; European Commission 2013; CIOMS 2016). Hence researchers have to minimize risks and burdens, balancing these factors with expected benefits for subjects involved and improvement of knowledge.

Risk assessment is a fundamental aspect of a research protocol. In paediatric clinical trials it requires strict control: "Risk assessment includes the evaluation of the risk of the medicinal product tested or the control, the risk of withholding active treatment in some cases, the risk of the disease itself. Potential harms would include

invasiveness and intrusiveness of research, the severity as well as seriousness of potential harms, the reversibility of adverse effects and reactions, and their preventability. The accumulation of research projects in the same population (over-studied population) is another potential harm. Multiple clinical trials in an individual should be discouraged" (EMA 2008, 17).

Major risks in clinical trials are related to the health of involved subjects and data reliability. Health-related risks depends 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 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 (French National Consultative Ethics Committee for Health and Life Sciences 2003a, 3-5). Dealing with clinical practice direct benefit is essential to justify therapeutic interventions, but in clinical trials this topic has to be taken into consideration too: "In scientific research projects, a potential direct benefit also plays a key role in the ethical evaluation of the trial" (Austrian Bioethics Commission 2013, 39).

However, as mentioned above, research can have no direct benefit for subject involved, but it doesn't mean that has no benefit at all: "imply that such research has no benefit, but it serves for the general increase in knowledge, the progress of medical science and consequently the health of other people. In some cases the person on which research is conducted, or the patient group to which this person belongs, may draw benefit from the research results obtained at a later time (potential indirect benefit), which means these results are in the patient's interest. For this reason, research projects may have a group benefit or may – in a broader sense – be of general social value where no direct benefit is produced" (Austrian Bioethics Commission 2013, 39).

General knowledge produced through the investigation can be usefully applied to 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: "Obtaining knowledge of the effects of medicinal products in paediatric patients is an important goal. However, this should be done without compromising the well-being of paediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole" (ICH 2000, 2). When the benefit is referred to society as a whole, the ethical assessment needs to be stricter and it's really important to evaluate the risk factor: the risks must be minimized and no more than minimal. (Austrian Bioethics Commission 2013, 40; CIOMS 2016, Guideline 17).

CIOMS Guideline 17 adds: "When the social value of the studies with such research interventions and procedures is compelling, and these studies cannot be conducted in adults, a research ethics committee may permit a minor increase above minimal risk".

Usually "minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than

those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. However, this definition also lends itself to ambiguous interpretations.

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.

Concerning burden minimization, ICH (2000, 12) requires:

- Personnel knowledgeable and skilled in dealing with the paediatric population and its age-appropriate needs, including skill in performing paediatric procedures.
- A physical setting with furniture, play equipment, activities and food appropriate for age.
- The conduct of studies in a familiar environment such as the hospital or clinic where participants normally receive their care.
- Approaches to minimize discomfort of invasive procedures, such as: topical anaesthesia to place IV catheters; indwelling catheters rather than repeated venepunctures for blood sampling; collection of some protocol-specified blood samples when routine clinical samples are obtained.

Healthy children should not be involved in clinical trials, because they are unable to provide a proper informed consent. Prevention trials or vaccine trials are justified exceptions, because in this case they are preventive measures with good risk/benefit ratio both for individual and for society, but they must be carried out following high safety standards.

Another important issue related to risks and benefits is the use of placebo in paediatric clinical trials. According to WMA (2013, art. 33) and Italian Committee for Bioethics (2010, 3) the use of placebo is justified only for scientific reasons and with the informed consent of the patient, but should be restricted in paediatric clinical trials, because randomization and procedure's risks are not easy to be understood by parents and children. Placebo shouldn't be used if effective treatments are available: "The use of placebo may be warranted in children as in adults when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain, hay fever). As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases" (EMA 2008, 15).

According to DH-BIO (2012, 31) questions to consider when using placebo are:

- Is there a compelling scientific reason to carry out a placebo-controlled study?
- Is there a known treatment of proven effectiveness?
- If so, is it safe for the participants to go without such treatment for the period required by the project? In other words, is the additional risk acceptable?

- Is the additional burden imposed on the participant by unrelieved symptoms acceptable?
- Would there be an additional burden as a result of the participants' condition on their families/carers?
- Will the participants be informed about the possibility that they may be assigned to a placebo group?
- Does the study involve participants not able to consent? Is the level of the additional risk and burden within the acceptable limits for research on such participants?
- Are there measures in place for early detection of a seriously unfavourable course of the disease in participants on placebo that would necessitate appropriate intervention?
- Is there provision for an appropriate timely interim analysis?
- Once the research is over, will the participants be told which group they were assigned to?

Research integrity, ethical review and undue inducement

Exploitation of people unable to consent is unacceptable and a mandatory ethical review by ethics committees is an essential requirement (DH-BIO 2012, 40). Research integrity needs to be considered too, to guarantee compliance with ethical principles and professional standards (EGE 2015).

Research ethics committees have an important role in protocols review and their focus is on "ethical acceptability" of the research (WHO 2011, 12). 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 Committee or competent authorities do not give permission to proceed.

Parents could need to consult their child's physician about the chance to participate in a clinical trial. If the investigator is the physician too, particular attention needs to be paid to undue influence and conflict of interests: the will 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 minor involved in 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 (Nuffield Council on Bioethics 2015, xxxiii).

Biobanks, access to data and confidentiality

During clinical trials often biological samples (specimen) and personal data are collected, thus protection is required to guarantee individual right to confidentiality, through anonymization or codification of stored information (CoE 2016; UNESCO 2008, 24; French National Consultative Ethics Committee for Health and Life Sciences

2003b). Research can be carried out on biological samples, tissues or health data collected and stored for clinical practice purposes. In this case, informed consent has to be obtained in addition to informed consent to diagnosis or intervention and the subject needs to be informed about conservation and anonymization/codification systems, risks for confidentiality or disclosure in certain circumstances.

Italian Committee for Bioethics affirms that "samples should not be rendered anonymous irreversibly and the authorisation of the parents or legal representative should not be 'broad', but rather given for a specific research or one directly related to it ('partially restricted consent'), after receiving detailed and full information, so that the giver can assess the aims, duration, place and manner of implementing the scientific project in which the sample is used. Parents, therefore, retain, 'control' over the use that is made of the biological material of their child, so as to be able to request an informative report and its destruction following the withdrawal of consent" (2014, 10).

Minors should be listened to in relation to their maturity and capacity to understand and must later be informed about the use of their biological material, even a long time after the donation, overall if they reach the age to consent: "Children and adolescents who reach the age of maturity during the research project should be given the opportunity to give informed consent for the continued storage and use of their material and related data, and they should also be able to withdraw consent for future research. An informed, opt-out system in which such persons are alerted to their right to withdraw could also be acceptable" (CIOMS 2016, Commentary on Guideline 11).

Other guidelines ask for informed consent limited to future research related to the one carried out in the present.

Research on already collected biological samples or health data can be carried out without consent if processing is necessary and does not imply significant risk, or when is impossible to contact the minor or his/her parents, provided that a research ethics committee has approved the project (Italian Committee for Bioethics 2014, 11-12). According to CIOMS (2016, Guideline 11) "When researchers seek to use stored materials collected for past research, clinical or other purposes without having obtained informed consent for their future use for research, the research ethics committee may consider to waive the requirement of individual informed consent if: 1) the research would not be feasible or practicable to carry out without the waiver; and 2) the research has important social value; and 3) the research poses no more than minimal risks to participants or to the group to which the participant belongs". These recommendations, valid for biological samples, can also be applied to health data collections (CIOMS 2016, Guideline 12).

Recently, the concept of "dynamic consent" has been introduced to indicate a process or an interactive tool allowing to give consent to the use of personal biological samples over a long period of time. Specimens and data are tracked across research studies and a system is provided for re-contacting individuals to be involved in other studies, so that the relationship with each participant is continuous (European Commission 2012, 57-58).

Research on biological samples and health data can implicate collective utility and significant increasing of knowledge about a clinical paediatric condition: "Accordingly, even if a minor does not directly and immediately benefit from the

research, it appears justified from the point of view of personal benefit, since it could in future determine some benefit in terms of health to the minor donor, but also from the ethical perspective, as it is necessary for society" (Italian Committee for Bioethics 2014, 12).

Children and their families are entitled to know any health information about them collected during the trials. Researcher should also clarify if feedback of incidental information or findings to the subject is foreseen, even if the biobank has no diagnostic purpose. In case of incidental findings, only important information has to be disclosed. "This implies that life-saving information and data of immediate clinical utility involving a significant health problem must be offered for disclosure" (CIOMS 2016, Commentary on Guideline 11); "In this case – in the face of actual and potential benefits – there is the researcher's duty to inform and a right/duty to know on behalf of the parents/legal representative in the interests of the minor, even if this entails a burden in terms of costs and on an organisational level for biobanks, as well as a psychological burden for the parents themselves" (Italian Committee for Bioethics 2014, 14).

Parental right not to know can be limited if there is a real possibility of effective preventive or therapeutic intervention, but if incidental findings regard genetic diseases of late onset, for which there are no preventive measures of proven benefit or no current treatments, a common ethical criterion is not clear. Adequate counselling is recommended when information is fed back. If total data anonymization is provided, information feedback is not possible, whereas partial data coding allows that feedback, so this issue has to be made clear.

Confidentiality on health data is mandatory and should be ensured also within the family in some circumstances, without sharing information with parents about minors if not necessary. This issue becomes more important for adolescents and health data: "The specific aspects of disclosure to parents of information concerning adolescents should therefore be taken into consideration for clinical trials in this age group and should be transparent to the adolescent concerned, as well as emancipation status, and age to consent to medical care" (EMA 2008, 12).

3.1.2 The children's and families' autonomy

Vulnerability

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 from adults, first of all from parents, but from researchers and society too. Hence, specific protections are required.

CIOMS (2016, Guideline 17) states that, before starting a paediatric clinical trial, researchers and ethics committees should make sure that:

- a parent or a legally authorized representative of the child or adolescent has given permission; and
- the agreement (assent) of the child or adolescent has been obtained in

keeping with the child's or adolescent's capacity, after having been provided with adequate information about the research tailored to the child's or adolescent's level of maturity.

All institutional documents assume vulnerability as a major issue. 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. Nuffield Council on Bioethics challenges the association between vulnerability and childhood and asks researchers to work in partnership with children and parents, not to protect children "from" research (2015, paragraph 4.59). 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.

The role of parents

The role of parents is very important, both from a legal and from an ethical point of view. It could not be interpreted only as a right to decide or a duty to protect, but as assistance and support to children's evolving autonomy too. Parental decisions should evaluate "child's best interest", a complex concept determined on a case-by-case basis, considering individual needs and rights. In the field of research involving minors the notion of "avoidance of harm" may offer a more solid basis than the concept of "best interest". The "best interest" approach generally promotes an effort to be more objective, weighing the potential benefits and burdens for a particular child. In the case of clinical research, however, it is too generic, as it lends itself to ambiguous interpretations.

Nuffield Council on Bioethics (2015, paragraph 4.10) asks parents to make decisions on behalf of their children taking into account:

- Respect for children as individuals, regardless of their age or capacity. This may, for example, be expressed through consideration of children's wishes and respect for their bodily integrity, although children's wishes may not always be determinative.
- Recognition of children's developing capacity for autonomous agency and the supportive or educational role of parents in helping their child develop and 'practise' decision-making skills and confidence.
- Concern for children's immediate and longer-term welfare.

Since clinical trials are not only focused on participant's interest, Nuffield Council on Bioethics (2015, paragraph 4.33) 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 minor's "best interest", fundamental in clinical practice, override other ethical values and become the only issue to consider in decision-making.

However, 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. In cases of chronic disease minors can have more experience and capacity to understand risks, burdens and benefits of a clinical trial than parents.

If parental permission is impossible to obtain and the study is emergency research, investigators can ask an approval to the ethical review committee and must inform and involve parents as soon as possible, but if minor is able to understand and decide, his decision should be respected (Nuffield Council on Bioethics 2015, paragraph 6.35).

According to U.S. National Academy of Sciences (2004, 201), ethical review committees can consider waiver of parental permission for adolescent's involvement in clinical trials when:

- the research is important to the health and well-being of adolescents and it cannot reasonably or practically be carried out without the waiver or
- the research involves treatments that State laws permit adolescents to receive without parental permission and when
- the investigator has presented evidence that the adolescents are capable of understanding the research and their rights as research participants and
- the research protocol includes appropriate safeguards to protect the interests of the adolescent consistent with the risk presented by the research.

Parents cannot ask for involvement of their children in clinical studies without a sound scientific background, adequately assessed by researchers and research ethics committees.

Children and mature minors: different age, different issues

As age advances, maturity and capacity to understand become more valid, as well as the importance of individual autonomy. 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. Minor's 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" (Austrian Bioethics Commission 2013, 44).

Some documents propose an age-based classification. ICH distinguishes new-borns (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 (2000, 7). EMA make no distinction between minors and children, using these terms as synonyms (2008, 7). Nevertheless, the document deals with the issue of consent and its value according to age groups and subject's level of maturity: for children from birth to 3 years 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; from the age of 9 children are considered able to better understand 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" (EMA 2008, 12). Researchers must however assess that adolescents have understood information provided.

If research implies minimal risks and minimal burden for minors involved, Austrian Bioethics Commission (2013, 46) asks for parental permission only for children up to the age of 14: "For minors aged 14 or older (mature minors), the Bioethics Commission does not envisage such a requirement as mature minors are allowed to act independently also in the case of other comparable medical measures. Group benefit research shall be enabled for this group of persons beyond the scope of the special laws".

Without fixing rigid age thresholds, Nuffield Council on Bioethics (2015, paragraph 4.5) distinguishes three different situations when we deal with the broad concept of "childhood":

- 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.
- 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.
- 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 assent has particular value, such as an actual informed consent: "We recommend that, where children and young people have sufficient maturity and understanding, but are not yet treated as fully 'adult' by the law of their country, professionals should, wherever possible, seek consent from both the children or young people concerned, and from their parents." (Nuffield Council on Bioethics 2015, Recommendation 13).

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" (2016, Commentary on Guideline 17).

UNESCO states that "criteria for the capacity to consent have included the ability to understand the issues involved in the decisions at stake, the ability to evaluate these rationally, a reasonable outcome of the decision and evidence of a decision being made" (2008, 28).

In some jurisdiction is recognized the status of "emancipated" minor, that is minor not living with parents and eventually having his own family. Emancipated minors can be married or parents themselves, so their protection can request involvement of adults that are not their parents. "If an adolescent aged 16 to 18 is no longer a

minor as defined in national law, or is an 'emancipated minor', then written informed consent is required from these individuals as for any adult capable of giving consent. Under these conditions, informed consent is no longer required from the parents/legal representative, although an adolescent is still vulnerable and may require additional discussions and explanations" (EMA 2008, 10).
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 legal age to consent (EMA 2008, 10; Italian Committee for Bioethics 2014, 11; ICH 2016, 5).

Parental permission and assent

To be legally and ethically justified, clinical trials need to be freely accepted by subjects involved, on the basis of an adequate information about relevance, purpose, risks and burdens of the envisaged procedures (DH-BIO 2012;WMA 2009, 2013; UNESCO 2008). Subjects must have a clear idea that they are going to be involved in research and not in normal clinical care, even though benefits are expected. Participation to clinical trials should not be seen as an opportunity to gain better care immediately (U.S. National Academy of Sciences 2004, 167).
According to WHO Research Ethics Review Committee (2017) obtaining informed consent in paediatric clinical trials should follow some essential rules:

- 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.
- 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.
- 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".
- 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 (Spanish Bioethics Committee 2013, 15-16), 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" (2008, 8).

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" (EMA 2008, 11). 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.

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 parent's views to determine risks, benefits and burdens, taking into account child's maturity and capacity to understand; in Case Three young child could potentially make decisions for himself, even if parents still have moral and legal duties to protect him. In that third circumstance the individual autonomies could collide, so it is important to seek protection for family autonomy as a whole: "this should normally be a shared family decision. In other words, we are making the claim that there is a morally significant difference between 'competent children' and 'adults', which may potentially justify differential treatment. Children, however intellectually capable, do not have full adult powers – and the corollary of that is that they also do not have full adult responsibilities. Parents are there, both ethically and legally, to share that responsibility until the agreed threshold of adulthood is reached" (Nuffield Council on Bioethics, 2015, xxii-xxiii).

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: "Information should be given by an experienced investigator, or his adequately trained delegate, to each parent, or the legal representative, on the purpose of the trial and its nature, the potential benefits and risks, and the name of investigators(s) who are responsible for conducting the trial with background professional information (such as education, work experience) and direct contact details (telephone and e-mail) for further information regarding the trial. The parent/legal representative should be given sufficient time and necessary information to consider the benefits and risks of involving the child in the clinical trial" (EMA 2008, 9). 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, merely providing information. Nevertheless, 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.

Information given need to be understood and it is important to assess

comprehension of quantitative information. Communication strategies are important too: "Information presented in relative terms (e.g., a 50 percent increase or decrease in some outcome) tends to be more 'persuasive' than information presented in absolute terms (e.g., decrease from 2 in 10,000 to 1 in 10,000) […] framing quantitative information about possible outcomes in positive terms (e.g., a 3-in-4 chance of improvement or survival) rather than negative terms (e.g., a 1-in-4 chance of deterioration or death) may encourage individuals to choose less risky options […] Providing quantitative descriptions of probabilities (e.g., a 1-in-4 chance) rather than or in addition to verbal descriptions (e.g., a moderately low chance) may reduce inconsistency in the interpretation of risk information and encourage more deliberative thinking" (U.S. National Academy of Sciences 2004, 163).

Consent can be withdrawn at any time, during a procedure too, unless when there is a serious danger for the subject's health. Withdrawal of consent does not provoke the end of relationships between researchers and subjects involved: "It must be emphasised that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the investigator needs to assure appropriate treatment and follow-up" (EMA 2008, 11).

Informed consent should be obtained from the subject involved once he 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.

If assent and parental permission are impossible to be obtained, the consent can be waived, but this waiver needs to be approved by an independent research ethics committee. CIOMS (2016, Guideline 10) 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.

Research protocols can be designed for emergency situations too, with 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 locate, research can be carried out only if an ethics committee had 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, 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. (CIOMS 2016, Guideline 16). Italian Committee for Bioethics recommend the constitution of ad hoc independent ethics committees for clinical trials in emergency situations (2012).

Compensation and inducement to clinical trials

The principle of gratuitousness is pivotal to protect subjects involved in clinical trials,

because prevents undue exploitation of vulnerable persons. Nevertheless, clinical trials can be long and burdensome, thus some kind of reimbursement is fair for subjects involved, to reduce barriers that may discourage participation. The compensation has to respect certain ethical criteria to keep informed consent actually free: "Compensation must not be so large as to induce potential participants to consent to participate in the research against their better judgment ('undue inducement'). A local research ethics committee must approve reimbursement and compensation for research participants" (CIOMS 2016, Guideline 13). According to ICH "Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant. Reimbursement and subsistence costs may be covered in the context of a paediatric clinical study. Any compensation should be reviewed by the IRB/IEC" (ICH 2000, 10).

Monetary reimbursements can cover direct costs, such as travel or time spent. It is not easy to determine if financial benefit is undue, because influence may vary depending on family income. Reimbursement for time spent is not easy to define too, because is related to work and may vary depending on the individual wage. Furthermore, unpaid workers (e.g. housewives) or unemployed persons may be excluded. However, compensation cannot be related to the level of risk undertaken and cannot be presented as a benefit related to research involvement.

Children and persons unable to consent are vulnerable and could be exploited for financial gain by other subjects, so they need additional protection: "A legally authorized representative asked to give permission on behalf of a person who is incapable of giving informed consent must be offered no compensation other than reimbursement for travel and other direct or indirect expenses. Where it would be reasonable to provide compensation to the participants themselves, their lack of decisional capacity must not preclude researchers from doing so. When participants are incapable of giving informed consent, compensation must be provided in a way that participants themselves can benefit from it" (CIOMS 2016, Commentary on Guideline 13).

Compensation for research-related injuries is instead perfectly licit and parents should be informed about available insurance policies too. Parental permission and assent to be involved does not mean waiving right to compensation for any research-related injury.

Compensation to clinicians in charge of providing care to minors for children's involvement in clinical trials raises instead ethical concerns and should be avoided and considered negatively by ethics research committees (U.S. National Academy of Sciences 2004, 223).

3.1.3 Main challenges to the proper acquisition of informed consent

Improving children's participation in clinical trials

The main purpose of assent and informed consent is to involve children and families,

not to obtain a signature in order to avoid legal liabilities. Thus, researchers should focus on subject's participation process than in providing detailed information and recording consent through the forms. This does not mean that there is no need to make efforts to provide clear consent forms, but this commitment has to be addressed to the whole communication process too: "It is important to realise that consent is a dynamic, continuous process, and should therefore not only be obtained prior to enrolling a child in a trial but should be maintained during the trial on a continuous basis. This could be done for example, by a brief discussion during each repeat visit. It is recommended to document this process in the medical records or equivalent. The discussion is part of the ongoing dialogue between children, parents and investigators and should focus on all aspects of the trial but in particular on any new information that arises in relation to the trial and that might affect the willingness of the parent and child to continue" (EMA 2008, 10).

Professionals interacting with children and families need to have both technical and non-technical skills to communicate adequately. A proper ethical attitude is important too. Nuffield Council on Bioethics (2015, paragraph 5.8) identifies a brief list of professional virtues, aimed at promoting research with children according to ethical standards. These virtues are:

- Trustworthiness: "children and parents will only feel able to take part in research if they can trust both the researchers with whom they are interacting, and the way the research is organised. Any functioning system of governance must also be able to trust the researchers who are subject to that governance".
- Openness: "researchers need to share information clearly and honestly with children and parents – when inviting them to take part in research, during the research itself, and afterwards. They also need to be willing to collaborate with, and learn from, other sectors of the research community, and across countries and continents".
- Courage: "some research is difficult to do, and it may seem easier just not to do it. But if research is not carried out, then children will not have the best possible healthcare, and may even be given treatments that are harmful, because no one has done the research to find out. The proper involvement of children and young people in the research process, which involves at least some degree of transfer of power between adults and children, also involves courage".

The role of ethical review committees is also important in improving children's participation to clinical trials: the action of these bodies could be not only protective, but facilitative too, as highlighted by Nuffield Council on Bioethics (2015, xxv) that emphasizes the ethical value of paediatric research. Nevertheless, parents and children should be made aware that refusal or withdrawal of consent will not result in any prejudice or discrimination against the minor, whose interest is the main value to protect.

According to EMA "Strong and definitive objections from the child should be respected" (2008, 13) and this especially when no direct benefit is prospected by researchers. Some exceptions are proposed by ICH, just 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 paediatric 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" (ICH 2000, 11). Conversely, child's objection has more value than parental permission when research has no direct benefit for subjects involved. Silence or absence of objection cannot be considered as assent (ICH 2016, 5).

Shared decision-making

Clinical trials have to be carried out "with" children and not "on" children. Shared decision-making is an approach emphasizing the importance of the 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 minor's 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. Hence 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, overall when conflicts arise within the 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 familiar counselling.

If disagreement between family members is impossible to solve, it's difficult to choose who to listen to. In these cases, it is not clear if child's objection to research is binding. When shared decision-making is a major value, disagreement becomes a barrier to informed consent acquisition. In this case, Nuffield Council on Bioethics (2015) recognizes determinative value to dissent, both expressed by parents or by children: "Where children (even young children with limited understanding of what is proposed) explicitly and consistently dissent, there will generally be both ethical and practical reasons why it would be right for professionals to accept that dissent, despite parental willingness to proceed.

The more children are able to understand what is involved in a research proposal, the greater the justification needed to act against their clearly expressed wishes. The multiple factors in play in such cases, however, make simple 'yes' or 'no' answers as to how professionals should approach these difficult decisions impossible to offer" (paragraph 6.24); "Similar issues may arise where children or young people in Case Three wish to participate in a research study, but their parents do not agree. In such cases, professionals have an important role in seeking to inform and encourage parents. However, if these attempts prove unsuccessful, then in most cases participation in research should not go ahead" (paragraph 6.25). Affirming this, Nuffield Council of Bioethics moves 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.

According to U.S. Presidential Commission for the Study of Bioethical Issues

"Parental permission cannot override a child's sustained meaningful dissent" (2013, 84). CIOMS too, dealing with children's "deliberate objection", highlights the importance of child's wishes in decision making, but asks to consider expected benefits. So 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" (2016, Commentary on Guideline 17).

Conversely, in other circumstances parental involvement can appear inappropriate, "or might undermine the research objective or even threaten a young person's wellbeing". In such cases "it may be ethically acceptable to approach children and young people in Case Three without parental knowledge or involvement. However, such approaches should be subject to specific review by a REC" (Nuffield Council on Bioethics 2015, paragraph 6.7). Case Three is referred to minors able to understand and consent (see above).

Families coming from different cultural background

When families come from different cultural background, the first issue is to provide understandable information for people speaking other languages. U.S. Food and Drug Administration recommends to provide information in language that is understandable to the parents and not to use the child as a translator (for communication between researchers and parents) even if he is fluent and able to assent. If child assent is required, the information given should be in language understandable to him (FDA 2014, 37). Qualified interpreters, aware of cultural factors too, should be provided. Information sheets and consent forms should be adapted and translated. Research sponsors should recognize related costs (U.S. National Academy of Sciences 2004, 199).

It is also important to provide a cultural mediator's support to families coming from different cultural background, during the process of obtaining informed consent (Italian Committee for Bioethics 2017, 2011; EMA 2008, 10). Social and cultural differences may influence people's understanding and commitment in deciding about children involvement in research. Cultural mediation thus can be useful to help persons to decide with respect to their values and preferences, because risk and benefit perception may vary considerably depending on different communities. Even their rights perception may change in relation to this: "Research protocols must always take account of these factual situations and therefore require prior study and sociological investigation (human sciences) before any medical or scientific steps are taken." (French National Consultative Ethics Committee for Health and Life Sciences 2003c, 17).

Furthermore, is very important to understand how the notion of "childhood" is perceived in different cultures, because this can affect the children's protection and autonomy level in some communities: "Such differences may be accompanied by

significant differences in family hierarchies and the extent to which children and young people may normally expect to have their voices heard and their wishes considered. The perceived ending of childhood may also be affected by factors such as the usual age for marriage in a particular culture, or the absence or death of parents. Some jurisdictions include a concept of 'mature minors' where young people below the domestic age of legal majority are treated in law as no longer minors if they are married, have children themselves, or are household heads. The extent to which children or young people in these situations have the freedom or authority to make their own decisions in practice will, of course, vary" (Nuffield Council on Bioethics 2015, 20). It's not easy to justify the lack of autonomy in decision-making about health issues for minors who are autonomous in other fields of daily life.

According to French National Consultative Ethics Committee for Health and Life Sciences, tutoring provided to people from different cultures by other members of their community, but not family members, is not suitable in healthcare decisions: "With the agreement of those concerned, the tutor would help them to understand their situation and the options open to them. This tutor could be someone with special moral authority, such as a religious or secular local figure. However since medical information would have to be made known to the tutor, the principle of medical confidentiality would be violated. There is no reason to accept this violation in the name of cultural dissimilarity" (2003 c, 18).

ICT and clinical trials, mobile health research, video informed consent

Interactive technologies offer enhanced access to information and can be usefully used in healthcare both to inform people and to record informed consent and assent, but also to update and share information about research development (EGE 2012, 33; WMA 2015). The information format has to be targeted at allowing an effective involvement and compliance to the trial. Electronic devices can be used also to inform subjects about modifications of clinical trials they are involved in and to confirm their informed consent to participation. These materials should be appropriate to the participant's age and may include tools to assess the subject's understanding.

Interest about processes and instruments replacing paper-based acquisition of informed consent is increasing. According to U.S. Presidential Commission for the Study of Bioethical Issues, which refers to scientific literature, "children demonstrate better understanding of study procedures and possible risks – and in some cases adults demonstrate better overall comprehension –when information is delivered in a multimedia format compared to the traditional written format" (2013, 85).

U.S. Food and Drug Administration (2016, 2) specifies that is possible to use "electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent". These tools can be used to obtain assent too, or parental permission if required in paediatric clinical trials.

Nevertheless, specific problems arise when ICT are used to obtain informed consent

to clinical trials: “the informed consent displayed on screen and not on paper, leads to clicking in an immediate way without sufficient time for making an informed choice and without the possibility of ascertaining actual voluntariness. Furthermore, the multiplication of consent may lead to irritating the user or often to giving consent just in order to speed up the procedure, without - here as well - adequate awareness” (Italian Committee for Bioethics 2015, 12-13).
Hence the information need however to be understandable and adequate time has to be spent to present new information tools to subjects and how long the process will take. If tools are addressed to minors, specific requirements must be met to guarantee simple information, friendly use and educational contents. Parental and medical control is however essential.
Electronic devices can be also used to supplement and not only to replace paper-based process. Subjects should have the chance to choose and to be assisted during the use of innovative tools. Both remote and on-site informed consent must provide enough time to the subject to ask questions and consider the involvement in research: “This may be accomplished by in person discussions with study personnel or through a combination of electronic messaging, telephone calls, video conferencing, or a live chat with a remotely located investigator or study personnel” (FDA 2016, 6).
If the informed consent process takes place remotely, identification of subject can be an issue and the authentication of signature can be realized through personal security questions, biometric methods or visual methods (FDA 2016, 5). The acquisition process of informed consent through ICT and electronic tools (scientific contents, electronic forms, informational materials, videos, web presentations, methods to assess the subject’s comprehension) must be approved by an ethical committee and subsequent modifications too. Data management must be secured with restricted access, to protect confidentiality.

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3.2 Age-related issues in informed consent to clinical trials (Hard Law)

3.2.1 The participation of children in clinical research: the European legal framework

The need to adequately protect minors without depriving them of the benefits deriving from clinical research has resulted in a majority of legal rules prohibiting research on minors if trials can be conducted on non vulnerable subjects.
About this issue, art. 16 of Council of Europe Convention on Human Rights and Biomedicine (1997) establishes that "Research on a person may only be undertaken if all the following conditions are met: I. there is no alternative of comparable effectiveness to research on humans (…)". Directive 2001/20/CE further specifies that "persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down" (Preamble § 3).

Interests of minors as research subjects: burdens, risks and benefits

Article 2 of the Convention on Human Rights and Biomedicine establishes the general principle "the interests and the welfare of the human being shall prevail over the sole interest of society or science".

Further provisions, which can be specifically applied to clinical trials involving children, derive from this general principle. Art. 6 of the Convention states 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/her direct benefit". In article 17, it also establishes that "exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub- paragraphs i, iii, iv and v above, and to the following additional conditions: 1. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, 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; 2. the research entails only minimal risk and minimal burden for the individual concerned".

The Additional Protocol on the Convention on Human Rights and Biomedicine concerning Biomedical Research (25 January 2005) clarifies the notions of minimal risk and minimal burdens.

According to art. 17 "for the purposes of this Protocol it is deemed that the research bears a minimal risk if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned. It is deemed that it bears a minimal burden if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned. In assessing the burden for an individual, a person enjoying the special confidence of the person concerned shall assess the burden where appropriate" (The §111 of Explanatory Report to the Additional Protocol illustrates minimal risk as taking a single blood sample from a child).

In the European legal framework, the EU Directive 2001/20/CE specifically tackles the issue of the child's interest by requiring that the research must generate direct benefits for participants. Art. 4 (e) requires that, in addition to any other applicable restrictions, a clinical trial on minors may be undertaken only if the group of patients can obtain "some direct benefit"; furthermore, the "research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors".

Art. 4 (g) of the EU Directive 2001/20/CE provides that clinical trials involving minors must be designed to “minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage”. This norm must be read together with the following provision of art. 4 (I) which sets forth that the interest of the minor must always prevail over those of science and society in order for clinical trials on minors to be undertaken. Risks and benefits associated with clinical studies involving minors is an ethical principle which is considered by the law at both supranational and national levels. In this context, the concept of the best interest of the child taking part in research assumes particular importance. The best interest of the child is a key principle of children's rights and derives from Article 3 of the UN Convention on the Rights of the Child, approved by the United Nations General Assembly on 20 November 1989, under which “1. In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration. 2. States Parties undertake to ensure the child such protection and care as is necessary for his/her well-being, taking into account the rights and duties of his/her parents, legal guardians, or other individuals legally responsible for him or her, and, to this end, shall take all appropriate legislative and administrative measures. 3. States Parties shall ensure that the institutions, services and facilities responsible for the care or protection of children shall conform with the standards established by competent authorities, particularly in the areas of safety, health, in the number and suitability of their staff, as well as competent supervision”. The rationale of this principle is that persons who have not reached physical and psychological maturity need greater protection. Its purpose is to improve conditions for the child, and it aims to strengthen the minor’s right to the development of his/her personality.

The principle of best interest requires that adequate consideration be given to the condition of the child. In particular, the immaturity of minors makes them vulnerable, such that their right to development can only be enjoyed with the assistance and protection of their family and competent institutions (the right to protection is a fundamental right established by art. 25 of Declaration of Human Right of 1948 and art. 24 of EU Charter of Fundamental Rights of 2000). In the context of paediatric research, the notion of best interest refers to the principle of benefit (see above, Soft Law section). The parents or legal representative should decide what would benefit the child most. Issues connected with the burdens, risks and benefits of clinical trials involving minors are taken into account by the law at a international, European and national level.

The Regulation (EU) 536/2014 establishes in art. 28 concerning general rules for the protection of subjects and informed consent that "a clinical trial may be conducted only where all of the following conditions are met: (a) the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored; (e) the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subject and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored". This issue is also regulated in relation to the conditions of minors: "A clinical trial on minors may be conducted only where, in addition to the conditions set out in article 28, all of the following conditions are met: g) there are scientific grounds for expecting that participation in the clinical trial will produce: (i) a direct benefit for the minor concerned outweighing the risk and burdens involved; or (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition". The rule specifies that the primary condition for the conduct of a clinical trial involving a minor is the presence of a direct benefit. However, unlike art. 4 of Directive 2001/20/CE, this regulation considers the possibility of indirect benefits, allowing clinical trials only if risks and burdens are minimal in comparison with standard treatments. The Directive 2001/20/CE takes into account the issue of indirect benefit at art.3 that lays down a general rule that is not specifically referred to minors.

The domestic laws of member States also give particular attention to the balance between risks and benefits in the context of clinical trials involving minors.

In the United Kingdom, the Medicine for Human Use (Clinical Trials) Regulations of 2004 establishes that "Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks" (Schedule 1 part.2) .

Moreover, it is necessary that "The clinical trial relates directly to a clinical condition from which the minor suffers or is of such a nature that it can only be carried out on minors. Some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial" (Schedule 1 part. 4).

Art. 3 of the Italian Legislative Decree 211/2003 requires that the foreseeable risks have been weighed against the benefits for the subject involved in the trial and those for other current and future patients. "In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if (d) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors; (f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored" (art.4).

In the Spanish legal system, art. 3 of Royal Decree 1090/2015 establishes that "the anticipated benefits for the subjects or public health justify the foreseeable risks and inconveniences and compliance with this condition is constantly monitored. However, the rights, safety, human dignity, and well-being of the subjects prevail over any other interest". Moreover, "the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the trial subjects and both the level of risk and the degree of discomfort are specifically defined in the protocol and constantly monitored" (art.3 (e)).

Germany has a more restrictive approach to clinical trials than the Directive 2001/20/CE. The German Medicinal Products Act of 2005 specifies that clinical research may only cause minimal risk and minimal burden to the minor concerned. Moreover, a research intervention must entail: "1. minimal risk if this intervention will result, at most, in a very slight and temporary impairment of the minor's health; 2. minimal burden when it is to be expected that the discomfort for the minor will be, at most temporary and very slight" (Chapter 6, Section 40 and 41) .

Austrian Medicinal Product Act 185/1983 requires that the benefit to the subject concerned outweigh the risk involved, unless when the trial aims at generating a substantial progress in scientific understanding of conditions, disease or disorder from which the minor suffers and only entails minimal risks and minimal burdens.

Article L-1121 of French Public Health Code establish that children may not participate in medical research if it is possible to carry out comparable efficacy tests on adults: "Les mineurs ne peuvent être sollicités pour se prêter à des recherches mentionnées aux 1° ou 2° de l'article L. 1121-1 que si des recherches d'une efficacité comparable ne peuvent être effectuées sur des personnes majeures et dans les conditions suivantes: -soit l'importance du bénéfice escompté pour ces personnes est de nature à justifier le risque prévisible encoure; -soit ces recherches se justifient au regard du bénéfice escompté pour d'autres mineurs. Dans ce cas, les risques prévisibles et les contraintes que comporte la recherche doivent présenter un caractère minimal".

Data protection

A question closely related to the provision of informed consent is that of the handling of personal data. In the case of clinical trials, the data involved must be considered sensitive data, including information on the health status of the subject involved in the research. Children, like adults, have data protection rights; however, they may not be in a position to independently exercise these rights, depending on their level of maturity and understanding and their age. These rights exist independently of the minor's ability to exercise them.

In this context, art. 16 of the UN Convention on the Rights of the Child of 1989 recognises that "No child shall be subjected to arbitrary or unlawful interference with his/her privacy, family, home or correspondence, nor to unlawful attacks on his/her honour and reputation".

Referring to the context of clinical trials, art. 3 of Directive 2001/20/CE, like artt. 28 and 93 of Regulation (EU) 536/2014, establishes the right to confidentiality as determined by the Directive 95/46/CE. Moreover, art. 93 of the Regulation states that "without prejudice to Directive 95/46/EC, the sponsor may ask the subject or, where the subject is not able to give informed consent, his/her legally designated representative at the time when the subject or the legally designated representative give his or her informed consent to participate in the clinical trial to consent to the use of his/her data outside the protocol of the clinical trial exclusively for scientific purpose. That consent may be withdraw at any time by the subjects or his/her legally designate representative". Directive 95/46/CE does not explicitly mention the privacy rights of minors. These legal instruments apply to all natural person, including children.

It is worth mentioning that Regulation (EU) 2016/679 on the protection of natural persons with regard to the handling and free movement of personal data, which will enter into force in May 2018 and repeal Directive 95/46/EC, makes an explicit reference to minors. Art. 8 of Regulation states that:

"1.Where point (a) of Article 6(1) applies, in relation to the offer of information society services directly to a child, the processing of the personal data of a child shall be lawful where the child is at least 16 years old. Where the child is below the age of 16 years, such processing shall be lawful only if and to the extent that consent is given or authorised by the holder of parental responsibility over the child. Member States may provide by law for a lower age for those purposes provided that such lower age is not below 13 years.

2.The controller shall make reasonable efforts to verify in such cases that consent is given or authorised by the holder of parental responsibility over the child, taking into consideration available technology.

3.Paragraph 1 shall not affect the general contract law of Member States such as the rules on the validity, formation or effect of a contract in relation to a child".

Domestic laws regarding privacy do not provide specific norms on to the condition of minors who exercise these rights through their legal representatives. Examining 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.

Consent to data handling and the right to confidentially is about enabling autonomous decision making. If the minor is unable to make the decision, then autonomy is not an issue; however if we think of confidentiality not just in terms of autonomy but as a right to privacy, this right exists whether or not the person is autonomous.

The informed consent is also necessary when biological samples or health data are collected and stored for clinical practice purposes. Biobanking is an important issue to consider in relation to clinical trials. During a clinical trial there is the possibility to collect and examine samples, as for example blood of trial subjects, which can then be stored in biobanks for research purposes. Privacy and data protection in biobanking is essential for securing acceptance of biobank research across Europe.

The art.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 2004/23/EC 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 art.1).

Incentives and financial inducement

Art. 21 of the Council of Europe Convention on Human Rights and Biomedicine establishes the general principle of the prohibition of financial gain, under which "the human body and its parts shall not, as such, give rise to financial gain".
The European Union has a clear policy with regard to the payment of minors who are research subjects. Art. 4 of Directive 2001/20/CE establishes that no incentives or financial inducement, except for compensation, may be granted to reward research participation. This requirement is adopted in all domestic implementations of the Directive.
In particular, the UK Medicines for Human Use Regulation of 2004 establishes that "No incentives or financial inducements are given:

1. (a) to the minor; or
2. (b) to a person with parental responsibility for that minor or, as the case may be, the minor's legal representative,

except provision for compensation in the event of injury or loss" (Schedule1 part.4).
Art. 1 of the Italian Legislative Decree 211/2003 establish that "It is forbidden to offer, grant or request incentives or financial benefits for the participation of subjects in clinical trials, with the exception of any allowances for healthy volunteers".
Chapter 6, Section 41 of German Medicinal Product Act of 2005 establishes that "with the exception of adequate compensation, no advantages may be granted".
§ 42 of Austrian Medicinal Product Act 185/1983 sets forth that in the case of clinical trials involving children, it is illegal to grant any advantage for taking part in the clinical trial. In addition, both the custodian for medical affairs and the custodian for monetary affairs, if present, have to be informed about the clinical trial because of the special insurance that is provided in case of medical experimentation on humans.
Article L-1121 of French *Code de santé publique* establishes that all economic incentives in favour of the child involved in the clinical trial are forbidden, with the exception of compensation for damages.
The Regulation (EU) 536/2014 addresses the problem under the norm dedicated to the protection of subjects, stating as a general rule that "no undue influence, including that of financial nature, is exerted on subjects to participate in clinical trial".

The principle that prohibits economic incentives for research participants in European law, transposed by national legislators, is intended to protect research subjects and prevent the human body from being subject to financial interests. This principle is even more relevant with regard to the condition of the minor, and is further strengthened in those national disciplines which prohibit the payment of financial incentives to the legal representatives of minors.

Paediatric expertise of Ethics Committees

The European legislator has assigned an essential role to research ethics committees for checking the compliance of research protocols with the legal requirements established by the Clinical Trial Directive.
Article 4 of Directive 2001/20/CE requires that ethics committees either have paediatric expertise, or seek their advice on clinical, ethical and psychosocial problems in the field of paediatrics.
EU member States provide specific requirements with regard to the paediatric expertise of ethics committees. The same rule is not stated in the Regulation (EU) 536/2014.

3.2.2 Informed consent in paediatric clinical trials: international and EU law

The Council of Europe Convention on Human Rights and Biomedicine and the Additional Protocol

In addition to the general principles regarding the participation of minors in a clinical trials, the Council of Europe Convention on Human Rights and Biomedicine of 1997 establishes the principle of informed consent. Which is enforceable and therefore binding only for States ratifying it. The Convention sets forth the principle that a person must give the necessary consent for treatment expressly and in advance, except in an emergency, and that such consent may be freely withdrawn at any time. The treatment of persons unable to give their consent, such as children and people with mental illnesses, may be carried out only if it could produce real and direct benefits to their health.
The Convention establishes at art. 5 general rules on informed consent, while at art. 6, it specifically addresses the issue of paediatric research.
Article 6 of the Convention states that “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/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/her age and degree of maturity”. This norm must be considered together with art. 16 and 17 about the necessary condition to involving minors in a clinical trial.

The Additional Protocol on the Convention on Human Rights and Biomedicine concerning Biomedical Research of 25 January 2005, after further specifying the principle of informed consent in Articles 13 and 1 , establishes at article 15.IV that "the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law, and after having received the information required by Article 16, taking into account the person's previously expressed wishes or objections. An adult not able to consent shall as far as possible take part in the authorisation procedure. The opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity". The Explanatory report to the Additional Protocol clarifies that "The purpose of the Protocol is to define and safeguard fundamental rights in the field of biomedical research, in particular of those participating in research. Biomedical research is a powerful tool to improve human health. Freedom of research is important in and of itself, but also because of the practical benefits it brings to the healthcare field. At the same time, it is always necessary to protect human beings participating in research. Research participants are contributing their time to the research and may be subjecting themselves to risks and burdens. Particular attention must be paid to ensuring that their human rights are always protected and their altruism is not exploited" Referring to art. 3 of Additional protocol, the report specifies that the entire Additional Protocol, the aim of which is to protect human rights and dignity, is inspired by the principle of the primacy of the human being, and all its Articles must be interpreted in this light.

Referring to art. 13 of Additional Protocol, the Explanatory report highlights that the information must be sufficiently clear and comprehensible to the person who is to take part in the research. The information should be provided in a way to make it understandable, taking into account their level of knowledge, education and the psychological state of the potential participant. Where necessary, the information should be provided in a language appropriate to the participant/group of participants or in a form appropriate to those with sensory disabilities.

With regard to informed consent, in case of clinical trials involving people not able to consent to research (art. 15 Additional Protocol), the Explanatory report clarifies that "the research must be potentially beneficial to the health of the person concerned. The benefit must be real and follow from the potential results of the research, and the risk must not be disproportionate to the potential benefit. (…) Recourse to research on persons not able to consent must be, scientifically, the sole possibility. This will apply, for instance, to research aimed at improving the understanding of development in children or improving the understanding of diseases affecting these people specifically, such as infant diseases or certain psychiatric disorders such as dementia in adults. Such research can only be carried out, respectively, on children or the adults concerned".

The Charter of Fundamental Rights of the EU

The Charter of Fundamental Rights of the European Union of December 2000, also known as the Nice Charter, contains an explicit reference to informed consent, thus providing it with an important legal basis. With the entry into force of the Treaty of Lisbon, the Charter of Nice has the same legal value as the Treaties.
The Charter is fully binding for all the European institutions and the Member States. In the first article, the Charter sets forth the principle of the inviolability of human dignity, which must be respected and protected by states. The dignity of the human person is not only a fundamental right but constitutes the basis of all fundamental rights. The result is that none of the rights laid down the Charter may be used to harm the dignity of another person, and that the dignity of the human person is part of the substance of the rights it contains.
Article. 3, placed in Chapter I devoted to dignity and entitled the "Right to the integrity of the person" states that "Everyone has the right to respect for his/her physical and mental integrity. In the fields of medicine and biology, the following must be respected in particular: the free and informed consent of the person concerned, according to the procedures laid down by law". In this way the Charter identifies informed consent as a fundamental right.
The EU Charter of Fundamental Rights expressly governs the rights of the child, stating explicitly the concept of the best interest of the child. According to art. 24, "Children shall have the right to such protection and care as it is necessary for their well-being. They may express their views freely. Such views shall be taken into consideration on matters which concern them in accordance with their age and maturity. In all actions relating to children, whether taken by public authorities or private institutions, the child's best interests must be a primary consideration" . This legal provision has particular relevance because, in addition to clarifying the concept of the best interest of the minor, it makes this principle a cornerstone of the decision making process in the context of informed consent, and assigns importance to the expression of minor's opinion in accordance with his/her age and maturity.

The EU Directive 2001/20/CE

A more effective attempt to harmonizing the provisions on clinical best practice in the EU Member States is found in the EU Directive 2001/20 / EC on Clinical Research. The Directive was intended to be incorporated and made effective in member States' national laws by 1 May 2004. The Directive chiefly aims at the harmonization of the provisions on good clinical practice, recalling the principles already affirmed by the Helsinki Declaration and underlining the need to protect people who are unable to validly give their consent to participation in clinical trials .

Art. 3 states that “This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein. Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent”. Nevertheless, several EU Member State, including Italy, Portugal and Romania, have opted for an almost verbatim implementation of the text of this Directive.

Moving to the analysis of the legislative text, the European legislator, after restricting the scope of the Directive to clinical trials carried out on humans (art.1.1), is concerned with providing a clarification of the meaning of Informed consent (art.2 [j]) by defining it as the “decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his/her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation”.

The Clinical Trial Directive, after setting forth rules for the protection of subjects of clinical trial in general (art. 3), addresses the specific issue of paediatric research in art. 4. Like the European Convention, the Clinical Trial Directive includes specific provisions on the involvement of minors in clinical research in which the ethical concerns of informed consent is addressed.

Article 4 (a), in particular, states that researchers must ensure that “the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor”. This informed consent must represent the presumed will of the minor and may be revoked at any time without detriment to the minor.

The standard must be read in conjunction with the one provided for in art. 4 (b) according to which it is necessary that “the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits”.

Moreover, the same article at point (c) establishes that “the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator”. Even if these are the rules imposed by the directive, its nature as a subsidiary act has led to the existence of considerable diversity in the national provisions on the conduct of paediatric clinical research across the European Union.

The Regulation 1901/2006 on medicinal products for paediatric use

In order to address the need to protect children by ensuring high quality research in the development of paediatric drugs, that drugs must receive specific authorization for prescription to children and that high quality information on such medicinal products is available, the European Union submitted Regulation 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) 1768/92, Directive 2001/20 / EC, Directive 2001/83 / EC and Regulation (EC) 726/2004.

As the Report from the Commission to the European Parliament and the Council "Better Medicines for Children-From Concept to Reality" has pointed out, "there are several reasons for the lack of paediatric medicines. It would, however, be too simplistic to pin the blame on pharmaceutical companies for not carrying out enough research and development (R&D) to adapt medicinal products to the needs of the paediatric population. This reluctance has long mirrored a general social and ethical paradigm that children should be protected from clinical research. Only in the last two decades has there been a shift to the current consensus of better protecting children through clinical research".

To address this problem, the Regulation establishes a system of obligations, rewards and incentives, together with horizontal measures, to ensure that medicines are regularly researched, developed and authorised to meet the therapeutic needs of children. The Regulation aims: to encourage high-quality research into the development of medicines for children; to ensure that the majority of medicines used by children are specifically authorised for such use; to guarantee the availability of high-quality information about medicines used by children.

The Regulation encourages better and safer paediatric research through the requirement of developing and discussing with the Paediatric Committee a paediatric investigation plan, which normally should be submitted, at the latest, upon completion of the human pharmaco-kinetic studies in adults. This obligates companies to think about paediatric use early on so as to avoid any delays in general product development.

Differently from the European Convention and the European Directive, the Paediatric Regulation is specifically intended to discipline clinical research in minors. In the preamble, the Regulation states that any concerns about conducting trials in the paediatric population should be balanced by ethical considerations about giving medicinal products to a population in which they have not been appropriately tested. Public health threats from the use of untested medicinal products on children can be safely addressed through the study of medicinal products for the paediatric population, which should be carefully controlled and monitored through the specific requirements for the protection of this vulnerable group.

To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population and in order to increase transparency, information on the results of these studies, as well as on the status of the paediatric investigation plans, waivers and deferrals should be included in product information.

With the Resolution 2902 of 15 December 2016, the European Parliament has noted that insufficient progress has been made in a number of fields, in particular paediatric oncology and neonatology, despite the fact that following the adoption of Regulation 1901/2006 there was an improvement of the overall situation, including a considerable increase in the number of paediatric research projects, leading to tangible benefits for treatment of a series of childhood diseases. For this reason, the Parliament requested that the Commission consider making changes, including through a legislative revision of the Paediatric Medicines Regulation, that would give due consideration to: "(a) mechanism-of-action-based, rather than only disease-type-based, paediatric development plans, (b) disease and drug prioritisation models that take account of unmet paediatric medical needs and feasibility, (c) earlier and more feasible PIPs, (d) incentives that better stimulate research and more effectively serve the needs of the paediatric population, while ensuring there is an evaluation of the research and development costs and full transparency of the clinical results, and (e) strategies to avoid paediatric off-label use where authorised paediatric medicines exist".

Regulation (EU) 536/2014

The Regulation (EU) 536/2014 of the European Parliament and of the Council on Clinical Trials on medicinal products for human use, repealed the Directive 2001/20/CE.

The new Regulation is part of a European legislative framework in which the European Commission intends to give a strong impetus to scientific research, redefining the legislative approach to clinical trials in Europe and addressing the need of simplification and harmonisation. The first important change is found in the type of normative instrument adopted. The legal form of a Regulation presents the advantage of minimizing differences of approach among Member States by allowing for the direct application of its provisions. Unlike the Directive that lays down an objective for Member States to achieve, the Regulation must be applied directly in all Member States, responding in this way to the necessity of standardisation.

Moreover, under Regulation (EU) 536/2014, the issue of safety in clinical trials is central. As stated in paragraph 11 of the preamble, "the risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention".

The importance of this issue is confirmed by article 3 of the Regulation that establishes the general principle that a clinical trial may be conducted only if: (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable and robust data.

As observed in the preamble of the Regulation, in a clinical trial is necessary to give a primary position to the rights, safety, dignity and well-being of subjects.

Article 10 of Regulation takes in to account the involvement of vulnerable populations, and in particular minors, in a clinical trial, establishing that “where the subjects are minors, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics”.
According to article 28, a clinical trial may be conducted only when all of the following conditions are met: “- the anticipated benefits to the subjects or to public health justify the foreseeable risks and inconveniences and the compliance with this condition is constantly monitored; - the subjects (or where subjects are not able to give informed consent, their legally designated representative) have been informed;
- the rights of the subjects to physical and mental integrity, to privacy and to the protection of the data concerning them are adequately provided for; - the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored;
- the medical care provided to the subjects is the responsibility of an appropriately qualified medical doctor or, where appropriate, a qualified dental practitioner; - the subject or, where the subject is not able to give informed consent, their legally designated representative, has been provided with the contact details of an entity where further information can be received in case of need”.
Furthermore, any subject, or their legally designated representative when the subject is not able to give informed consent, may withdraw from the clinical trial at any time by revoking their informed consent, without any resulting detriment and without having to provide any justification.
Article 2 of Regulation defines informed consent as a “subject's free and voluntary expression of his/her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial”.
Article 29 of the Regulation sets forth the general framework for informed consent:
“Informed consent shall be written, dated and signed by the person performing the interview referred to in point (c) of paragraph 2, and by the subject or, where the subject is not able to give informed consent, his/her legally designated representative after having been duly informed in accordance with paragraph 2. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his/her legally designated representative shall be provided with a copy of the document (or the record) by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his/her legally designated representative to consider his/her decision to participate in the clinical trial”.

Informed consent must include:- the nature, objectives, benefits, implications, risks and inconveniences of the clinical trial;- 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.
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 provides foran interview with an investigator.
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".
As well as Directive 2001/20/CE, the Regulation leaves the legislators of Member States free to identify the age criteria. Moreover, as stated in article 29.8, the Regulation should be without prejudice to national law requiring that "in addition to informed consent given by legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, should himself assent in order to participate in a clinical trial".
Article 32 of the Regulation provides a specific discipline for clinical trials involving minor. First of all, the article establishes that a clinical trial on minors may be conducted only when, in addition to the conditions set out in Article 28, all of the following conditions are met:
- the informed consent of their legally designated representative has been obtained;
- the clinical trial is intended to investigate treatments for a medical condition that only occurs in minors or the clinical trial is essential with respect to minors in order to validate data obtained in clinical trials on persons able to give informed consent or by other research methods;
- the clinical trial either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
- there are scientific grounds for expecting that participation in the clinical trial will produce:
a) a direct benefit for the minor concerned outweighing the risks and burdens involved;
b) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.
The minor must take part in the informed consent procedure in a way adapted to his/her age and mental maturity. In particular, minors must receive the information from investigators or members of the investigating team who are trained or experienced in working with children in a way suited to their age and mental maturity.

The explicit wish of a minor who is capable of forming an opinion and assessing the information to refuse participation in, or to withdraw from, the clinical trial at any time, must always be respected by the investigator. This norm points out a key difference compared to the provisions of Directive 2001/20/ EC, under which the wish of the child to refuse participation is only taken into account by the investigator. Hence, the regulation seems to assign a more binding character to the child's refusal.
If the minor reaches the age of legal competence to give informed consent, as defined in the law of the Member State concerned, during a clinical trial, his/her express informed consent must be obtained before they can continue to participate in the clinical trial.
Article 76 of the Regulation expressly disciplines compensation for damages derived from the clinical trial: "Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk. The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State concerned where the clinical trial is conducted. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for low-intervention clinical trials, if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place".
It should be specified that according to art. 32 additional monetary incentives for minors are not allowed.
The Regulation refers to Member States the task of setting forth rules sanctioning infringements of the Regulation, and imposes on states the duty to take all measures necessary in order to ensure that these rules are implemented. The penalties must be effective, proportionate and dissuasive. In any case, the Regulation does not affect national and EU laws on the civil and criminal liability of a sponsor or an investigator.
Analysing the European legal framework, it is noted that the specific issue of informed consent in the context of clinical trials involving minors, allows us to identify some key points of the issue: a) the rule takes into consideration, identifying it as a general rule, the proxy consent that must be provided by parents or other legal representatives; b) the directive requires the child to receive appropriate information about the trial, the risks and the benefits, 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.

Among the different domestic laws that implement the Directive in member states, diversity exists regarding all the requirements mentioned. In addition, there is diversity in relation to the definition of the age criteria for establishing the decision-making capacity of the child involved in the research, which is an issue not explicitly covered by the Directive. This heterogeneity also persists under Regulation (EU) 536/2014. As a general rule, all individuals who have not reached the age of 18 years can be regarded as minors in the decision process concerning participation in clinical trials, but several EU Member States define different age criteria.

Additionally, legal capacity does not always coincide with the factual capacity to make a decision, which is often taken into account in determining whether the child is able to give valid consent to the specific field of clinical trials. In the case of a minor who is unable to independently give his/her consent, this may be obtained from the parents or another legal representative.

Within the domestic law of the EU Member States, there are considerable differences on the proxy requirements for representing the will of the child. A first difference relates to the subject who must grant their informed consent: in some States, the law requires the participation of both parents, while in others it is sufficient, under certain conditions, to hear from only one of the parents. Moreover, depending on the age limit defined in domestic legislation, the assent of a minor may be required in addition to the proxy consent granted by parents or legal representative. The content of the information also varies in relation to the age criteria adopted by the different States, as does the concept of capacity of understanding.

3.2.3 Domestic law on informed consent to paediatric clinical trials: Austria, France, Germany, Italy, Spain and United Kingdom

Austria

The Austrian Medicinal Product Act 185/1983, amended on 29 April 2004 to implement Directive 2001/20/CE, does not refer to a specific age criteria in relation to clinical research.

Consequently, for the purpose of participation in a clinical trial, all persons who have not reached the age of 18 are considered as minors (ABGB, §21).

However, §21 of the Austrian Civil Code-ABGB states that until the age of 14 years the minor must be considered immature.

As a result, fourteen years of age can be considered as the age criterion for assessing the maturity of the child and his/her ability to express his/her consent.

The minor's maturity has to be assessed individually in every case (Austrian Medicinal Product Act 185/1983, §42).

Consequently, as general rule, the consent of parents or legal representative of the minor is necessary for his/her participation in a clinical trial.

In the Austrian legal order, the clinical trial requires the informed written consent of the parents or legal representative (Austrian Medicinal Product Act 185/1983, §42). The consent has to consider the well-being of the child.
If the minor over 14 years of age and considered mature is capable of understanding the nature, significance and implication of the clinical trial and of forming a rational decision in the light of the received information, then they must give their assent in addition to that of their parents or legal representative (Austrian Medicinal Product Act 185/1983, §42).
According to § 42 of Austrian Medicinal Product Act 185/1983, contrary to the regulation before the amendment of 2004, there is no strict time limit for assuming the minor's capacity to consent, but the minor's maturity has to be assessed individually in each case.
The same norm establishes that the dissent of the child considered sufficiently mature must be take into account.
If the minor lacks the capacity to consent, he or she at least has the right to express a veto, which has to be taken into account by the investigator.
According to §42 of Austrian Medicinal Product Act 185/1983 the legal representative and the minor must be informed about the nature, significance, risk and implication of clinical trial as well as about the right to withdraw from the clinical trial at any time without consequences.
The minor always has to be informed by an investigator who is experienced in dealing with minors, who must take in to account the stage of maturity of the child.

France

Article L- 1122 of the Public Health Code of 1953 as amended by the Law 806/2004 which implemented the Directive 2001/20/CE in French legal order and Ordinance 800/2016, establishes that "Les mineurs non émancipés, les majeurs protégés ou les majeurs hors d'état d'exprimer leur consentement et qui ne font pas l'objet d'une mesure de protection juridique reçoivent, lorsque leur participation à une recherche impliquant la personne humaine est envisagée, l'information prévue à l'article L-1122-1 adaptée à leur capacité de compréhension, tant de la part de l'investigateur que des personnes, organes ou autorités chargés de les assister, de les représenter ou d'autoriser la recherche, eux-mêmes informés par l'investigateur". Consequently, the norm indirectly identifies an age criterion by referring to the figure of the emancipated minor.
According to the French Civil Code, majority is reached at the age of 18, while the minor can be declared emancipated, and therefore considered as an adult for informed consent, at the age of 16 and following an assessment of the his/her maturity by a Court. When research involving the human person is carried out on a non-emancipated minor, consent is given by holders of parental authority .
In the event that a minor turns 18 in the course of their participation in a clinical trial, confirmation of their consent is required after the provision of appropriate information. When the minor participant in the clinical trial has acquired legal capacity before the end of the research, he personally receives the information provided by the researcher or the promoter.

According to article L-1122 of Public Health Code, when research involving the human person is carried out on a non-emancipated minor, consent is given by holders of parental authority. However, such consent may only be given provided that the following conditions are met:
- research involves only minimal risks and constraints;
- the child is not subjected to research as a healthy volunteer;
- the other holder of parental authority may not grant his authorization within a period which is compatible with the specific methodological requirements for carrying out the research in the light of its objectives.
If medical research involving a child creates a serious risk to privacy or to the integrity of the human body, the committee referred to in art. 1123 of the Public Health Code evaluates the need for the approval of the family council, if it exists, or of a judge in addition to the consent of the parents or the legal representative. In any case, the opinion of the child that is sufficiently mature is always considered by the investigator.
The emancipated minor is considered as an adult in the expression of informed consent.
Article L-1122 of Public Health Code establishes that dissent or revocation of consent by the non-emancipated minor must always be taken into account by the investigator.
Article 1122 of the Code de santé public, establishes in general that the information provided by the investigator to the participant in the clinical trial or to his/her legal representative has to include:
- the objective, methodology and duration of research;
- the expected benefits and foreseeable risks, even if the trial ends earlier than expected;
- 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. The information provided are summarized in a written document given to the person whose consent has been requested.
At the end of the research, the participant has the right to be informed of the overall results of this research.

Germany

In Germany, any person under the age of 18 is considered as a minor (Title1, Section 2 BGB). Generally, minors are unable to give valid consent. The exception to the general rule is the emancipated minor, who acquires a limited legal capacity on the condition that he or she has reached the age of sixteen (§1303 BGB).
As general rule, Section 1629 of German Civil Code establishes that parents are representatives of the child.

Chapter 6, Section 40 (4) of the Medicinal Product Act of 2005 that implemented Directive 2001/20/CE in the German legal order, establishes 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 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 risk and benefits, in so far as this is possible taking into account the minor's age and mental maturity".
Hence, if the minor is capable of understanding the nature, meaning and consequences of the clinical trial and able to act accordingly, his informed consent is required.
The law does not determine a specific age for this threshold between the requirement of simple assent and full consent, as this depends on the individual capacity of the minor concerned. Consequently, the minor's ability to comprehend should be assessed on a case by case basis as their consent is required if they are able to comprehend the nature, significance and implications of clinical trial and to form a rational intention in the light of the information given.
Chapter 6, Section 40 (4) of Medicinal Products Act of 2005 establishes that in the case of clinical trial involving children, consent is granted by their legal representative after being informed about the significance, risk and implications of the clinical trial, as well as the right to withdraw from the clinical trial at any time.
Furthermore, the legal representative and the child have the opportunity to have a counselling session with an investigator or a member of the investigating team who is a doctor. The consent expressed by the representative of the minor must correspond to the minor's presumed will where such a will can be ascertained.
Before the start of the clinical trial, the minor must be informed by an investigator who is experienced in dealing with minors about the clinical trial, taking into account the minor's age and mental maturity in so far as this is possible.
If the minor is in a position to comprehend the nature, significance and implications of the clinical trial and to form a rational decision in the light of the information, then his/her consent is also be required. Consequently, the assent of the child is not a necessary requirement, but must proceed on a case-by-case assessment.
According to Chapter 6, Section 40 (40) of Medicinal Products Act of 2005, the minor's refusal to his/her participation in a clinical trial must be respected: " (…) the consent is granted by the legal representative after being informed pursuant to sub section 2. It must correspond to the minor's presumed will where such a will can be ascertained. (…) in so far as this is possible taking into account the minor's age and mental maturity, should the minor declare or express in any other way that he/she does not wish to take part in the clinical trial, this must be respected. (…) If the minor is in a position to comprehend the nature, significance and implication of the clinical trial and to form a rational intention in the light of these fact, then his/her consent shall also be required".
According to Chapter 6, Section 40 (4) of Medicinal Products Act of 2005, the legal representative and the minor must be informed by an investigator who is a doctor and who is experienced in dealing with minors, about the nature, significance, risks and implication of clinical trial as well as about the right to withdraw from the clinical trial at any time.

An opportunity for a counselling session must be offered not only to the legal representative but also to the minor.

Italy

According to Italian law any person under 18 years of age must be considered a minor (Civil Code, art.2). Consequently, only those who have reached the age of majority are able to express a valid, free and conscious consent. The general rule regarding the informed consent of the minor is therefore the proxy consent.
It should be mentioned that, in 2001, Italian Parliament drafted a bill (Nr 4983, February 2001) on the "Standards for the consent of the minors to healthcare". The project included an article allowing the possibility that the consent of the minor may be sufficient if the child had adequate psychological and intellectual maturity in relation to the specific treatment to be implemented. However, the bill has not yet been approved. The emancipated minor is an exception to the general rule, who acquires a limited legal capacity on the condition that he or she has reached the age of sixteen and that the competent Court has recognized their physical and psychological maturity after a case-by-case assessment (Civil Code art. 390).
According to art. 2 l) of Legislative Decree 211/2003, in the context of clinical trials, informed consent is defined as the decision of a candidate subject to be included in a trial, written, dated and signed, taken spontaneously after exhaustive information on the nature, meaning, consequences and risks of the experiment and after having received the appropriate documentation. The decision is expressed by a person who is able to give consent, or, in the case of a person who is unable to do so, by his/her legal representative or by an authority, person or body in compliance with the applicable legal provisions in the field. If the subject is unable to write, he or she may exceptionally provide oral consent in the presence of at least one witness, in compliance with the applicable law.
The Legislative Decree does not explicitly set out an age criterion for experimentation, therefore reference should be made to the general framework provided by the Civil Code and the relevant guidelines. Until reaching the age of majority, the law establishes that consent for therapeutic treatments on the child is expressed by both parents (Civil Code art. 316) or, in the event of absence of parents or of their inability to consent, the Guardian or the Court (Civil Code art. 343 cc). In cases in which one of the parents cannot express their consent because of absence, legal incapacity or other impediment, parental rights are exercised exclusively by the other parent (Civil Code art. 317).
In this matter, the Constitutional Court has stated that the Constitution has overthrown the conception that the child is subjected to absolute and uncontrolled power, affirming the right of the child to the full development of his personality and functionally, linking to such interest the duties that, in addition to the rights, are inherent in the exercise of parental power (Constitutional Court nr. 132/1992).
According to art. 4 of D.lgs 211/2003, the informed consent of the legal representative of the minor must however reflect the will of the child and must be able to be withdrawn at any time without compromising the continuation of necessary treatment.

The assent of the minor in addition to the consent of the parents or the legal representative is not expressly required. Moreover the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in paragraph b) to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or the principal investigator (D.lgs 211/2003 art.4).

Article 3 of Legislative Decree 211/2003 establishes that the person participating in the trial, or their legal representative if the subject is unable to provide informed consent, must have the opportunity, in a preliminary counselling meeting with one of the experimenter, to understand the objectives and risks of the experimentation, the conditions under which it will be implemented, and their right to withdraw from the trial at any time.

In addition, in case of a clinical trial involving minor subjects, 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

In Spain, any person under the age of 18 is a minor (Constitution art.12; Civil Code art 315). Generally, minors lack the legal capacity to take legally binding actions because they are considered incapable of giving legally binding consent. However, Spanish civil law recognises that the sufficiently mature child, in accordance with the law, may act on his own behalf. Consequently, consent given by a minor, considered sufficiently mature, is legally valid.

According to art. 10 of the General Act on Health 14/1986 prior written consent is necessary before any medical intervention. This general principle provides for an exception in the event that the subject is not mentally capable, in which case the family members or the legal representative must be present.

In the case of a minor, this rule must be read in conjunction with the applicable provisions of the Civil Code and the Criminal Code. In particular, article 162 of the Spanish civil law code establishes that parents who have custody of their children also represent them legally, except in cases referring to the rights of person, when the child, in accordance with the law and being sufficiently mature, may act for himself.

Article 155 of Spanish penal law specifies that, in so far as bodily harm is concerned, any consent given by a minor or person considered incompetent will not be accepted as valid.

The Royal Decree 1090/2015 governing clinical trials involving human subjects, which repealed the Royal Decree 223/2004 implementing Directive 2001/20/CE in the Spanish legal system, defines the minor as a trial subject who is, according to Act 41/2002 of 14 November regulating patient autonomy and rights and obligations in terms of clinical documentation and information, under the age of legal competence to give his/her informed consent (art.2).

The Law 41/2002 regulating the autonomy of the patient in relation to obligations regarding information and clinical documentation, as amended in 2015, addresses the issue of the autonomy of the child in the context of informed consent to art. 8.3.

According to that norm, the proxy consent should be given when the minor is not intellectually or emotionally capable of understanding the scope of the treatment. In this case, consent will be given by the legal representative of the child after having heard his opinion if he is twelve years old.
In the case of children who are not disabled or incapacitated, but emancipated or aged sixteen years, such proxy consent is not permitted. However, in the event of a serious risk, according to the doctor's opinion, the parents must be informed and their opinion will be taken into account in the final decision.
The Royal Decree 1090/2015, after providing a definition of informed consent (art.2), at article 5 states that when the minor has reached twelve years of age they must also give his/her consent to participate in the trial.
In conclusion, is possible to distinguish three different situations:
a) minor under 12 years old: it is always necessary to obtain proxy consent provided by parents or a legal representative. The minor must be heard if he or she has sufficient judgment;
b) minor of 12 years old or older: the minor should give his/her assent in addition to that given by parents or legal representative;
c) minor of 16 years old or older: the minor, if is not disabled or incapacitated, has to give his/her consent, except in the event of a serious risk, when the opinion of parents or legal representative should be taken into account.
This case may create controversy about the age of informed consent in the area of clinical trials, because there is conflict between the general regulation of patients' rights and the specific regulation of clinical trials.
A possible solution is to consider the participation in the clinical trial as a serious risk to the life or health of the minor, with a consequent need to take into account the legal representative's opinion.
Art. 9.3 of Law 41/2002 on the patient autonomy and the rights and obligations regarding clinical information and documentation takes into consideration the hypothesis of proxy consent by distinguishing three different situations:
a) the proxy consent is issued by the legal representative when the child is not intellectually and emotionally able to understand the scope of the treatment;
b) the legal representative must take into account the opinion of the child who is 12 years of age;
c) when it comes to children, disabled or not, who are emancipated or have reached the age of 16, it is not possible to proceed with the proxy consent; however if the treatment involves particularly serious risks, the physician may, at his/her discretion, consider the opinion of the parents.
While this is the general rule, the Royal Decree 1090/2015 specifically dedicated to the discipline of the clinical trial should also be taken into account .
According to art. 5 of Royal Decree 1090/2015, in the case of involvement of the child in clinical trials, the informed consent of the child's legal representative is required. The informed consent form of the parents shall be valid provided it is signed by one of them with the express or tacit consent of the other, which should be adequately documented, as stipulated in article 156 of the Civil Code. If the minor is under 12 years old, they must be heard if he or she has sufficient judgment. In any case, when the minor is twelve years of age or older, they must also give their assent to participate in the trial.

Moreover, in accordance with article 4 of Royal Decree 1090/2015, "In the case of minors or incapacitated persons, where consent has been given by their legally designated representative, when their capacity to give their consent has been attained or recovered, their consent must be obtained to continue participating in the clinical trial".

With regard to the issue of the explicit dissent of the minor, unlike the previous Royal Decree 223/2004, that at art.7.3 determined expressly that the investigator has to accept the minor's explicit wish to not participate in the trial, the Royal Decree 1090/2015 refers to the new Regulation (EU) 536/2014.

As will be seen below, according to article 32 of Regulation (EU) 536/2014, the investigator must respect the explicit refusal to participate in a clinical trial of a minor capable of forming an opinion and assessing all the information received.

Articles 3, 4 and 5 of Royal Decree 1090/2015 establish that the subject of the trial must give his/her consent after having understood the objectives of the research, the risks and disadvantages, the conditions under which the trial is conducted, and its right to withdraw from experimentation at any time without any prejudice following a meeting with the researcher or a member of the research team.

The consent is documented in an information form signed by the subject. The document must contain all relevant information, expressed in clear and comprehensible terms for the subjects, and be written in the language of the person involved. In the specific case of child involvement in research, the minor must receive such information from professionals experienced in dealing with children and in an manner appropriate to their capacity of understanding.

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.

United Kingdom

In the UK there are two parallel legal systems on clinical trials for minors: the common law and the discipline deriving from the implementation of European legislation established by the Medicine for Human Use Act of 2004, to which, in the case of minors, the Family Law Reform Act of 1969 is added.

Where the common law applies, the law states that the age of majority is 18 (Family Law Reform Act of 1969, Section 1). Although they cannot be considered adults, young people between the ages of 16 and 18 are presumed to be competent to give consent for medical treatment. The Family Law Reform Act 1969, section 8, states that children aged 16 and 17 can consent to treatment in the same way as an adult. The law has a limited scope of application, and refer to diagnosis and procedures ancillary to treatment alone (Family Reform Act of 1969, Section 8.2).

If the procedure is not a treatment, as in the case of clinical trials, 16 and 17 year olds can consent if they can show that they are Gillick competent (Family Law Reform Act of 1969, Section 8.2). The decision Gillick v West Norfolk Area Health Authority (House of Lords, [1985] 3 All ER 402) first considered the notion of a competent child, establishing that a competent minor must:

a) understand the nature and implications of the treatment, which would include the likely effects and potential side effects;
b) understand the implications of not pursuing the treatment, including the nature, likely progress and consequences of any illness that would result from not receiving the treatment;
c) retain the above information long enough for the decision making process to take place.
These requirements were reaffirmed by subsequent judgments and in particular from those made in the cases CR (Axon) v Secretary State for Health (High Court of Justice, Queen's Bench Division [2006] QB 539) and An NHS Foundation Trust v A & Others (High Court of Justice,[2014] EWHC 920 (Fam)) that, in particular, established the additional requirement of sufficient intelligence and maturity to weigh up the information and arrive at a decision. While the general rule allows researchers to undertake experimentation in the event that they have obtained the consent of a Gillick competent child or of someone with parental responsibility for the child (referring to paragraph 3.2), it is unclear whether the general rules dealing with children and medical treatment apply in the special context of clinical trials.
In the case Re W (All ER 627 [1992]), the Court declared that is improbable that a Gillick competent child could consent to a medical procedure that did not benefit him or her.
In particular, in the opinion of the Court, it is not clear whether a parent can exercise parental responsibility by consenting to a procedure that it is not in the child's best interests in the case of clinical research (referring to paragraph 3.2).
Where the research involves a clinical trial of a drug, the Medicines for Human Use Act of 2004 applies. The Act provides express rules that operate in relation to children, establishing that a minor is a person under the age of 16. A minor can participate in a clinical trial only if the investigator obtains the consent of the parent or the person with parental responsibility. In the case of trials of emergency treatments, if there is no person with parental responsibility available, a personal legal representative can give the consent. This person should not have links with the research and must have a tie with the child in order to act in his best interest. If no person with these features is available, a professional legal representative should be appointed.
The Medicines for Human Use Regulation of 2004, which as mentioned identifies the minor who is 16 years of age as a competent adult in decision-making on clinical research participation, disciplines the issue of proxy consent at the Schedule 1, Pt 4.
The Regulation establishes that "a person with parental responsibility for the minor or, if by reason of the emergency nature of the treatment provided as part of the trial no such person can be contacted prior to the proposed inclusion of the subject in the trial, a legal representative for the minor has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted".
Is possible to distinguish three subjects that can give the proxy consent, identifying them according to a hierarchical order:
a) Parent: a parent or person with parental responsibility. Should always be approached if available.

b) Personal legal representative: a person not connected with the conduct of the trial who is suitable to act as a legal representative by virtue of their relationship with the minor, and who is available and willing to do so. May be approached if no person with parental responsibility can be contacted prior to the proposed inclusion of the minor, by reason of the emergency nature of the treatment provided as part of the trial.
c) Professional legal representative: the doctor primarily responsible for the medical treatment of the minor who is not connected with the conduct of the trial, or a person nominated by the relevant health care provider (e.g. an acute NHS Trust or Health Board). May be approached if no person suitable to act as a personal legal representative is available. Informed consent must be given before the minor is included in the trial.
Where a minor is recruited in an emergency situation without prior informed consent, steps must be taken to seek informed consent from a person with parental responsibility or a legal representative as soon as practicable after the initial emergency has passed. Where consent is withheld, the subject must be withdrawn from the trial.
If the parents refuse to consent to the minor's participation in the clinical trial, it is not possible to appoint a legal representative for obtaining the consent. The person with parental responsibility or the legal representative may, without the minor being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking their informed consent. The explicit refusal to participate in or wish to be withdrawn from the clinical trial by a minor who is capable of forming an opinion and assessing the information must be considered by the investigator at any time, but this opinion is not binding on the researcher. Informed consent given by a person with parental responsibility or a legal representative to a minor taking part in a clinical trial represents the minor's presumed will.
In United Kingdom, according to Schedule 1, Pt 4 of the Medicine for Human Use Regulation of 2004, in the case of children under the age of 16 " the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in the previous paragraph to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator". However, the rule does not clarify the true weight of the refusal of the minor who is not yet 16 years old.
On this point, in the decision An NHS Trust v A,M and I (High Court of Justice[2014] EWHC 920 (Fam)), the judges stated that "a competent young person under the age of 16 years who is able to understand all the relevant advice and the consequences of that advice, is to be treated as an autonomous individual and respected as such. That of course would not mean her views would be determinative, but they would be given great weigh".
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.

3.2.4 References

International Law

UN Convention of the Rights of the Child, 1989.

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.

Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research, 2005.

EU Law
Charter of Fundamental Rights of European Union, 2000 (2000/C 364/01).

Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (Text with EEA relevance).

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 (Text with EEA relevance).

Regulation (EU) 679/2016 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).

European Parliament resolution of 15 December 2016 on the regulation on paediatric medicines (2016/2902(RSP)).

Austria

Bundesgesetz vom 2. März 1983 über die Herstellung und das Inverkehrbringen von Arzneimitteln (Arzneimittelgesetz – AMG).

France

Code de la Santé Publique.

Germany

Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG) 2005.

UK

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

Family Law Reform Act, 1969.

Italy

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.

Spain

Ley 14/1986, de 25 de abril, General de Sanidad.

Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.
Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos.

3.3 Gender-related issues in informed consent to clinical trials (Soft Law)

3.3.1 Women participation in clinical research

Women as research actors and participants

At the European level, not many guidelines shed light on the relationship between the protection of women's health and the need for "gender-oriented clinical trials": up to date, very few National Bioethics Committees in Europe have addressed this topic by developing a thorough reflection on the shortcomings of a low-rate participation of women in research, with a clear emphasis on the benefits and risks of their inclusion/exclusion from clinical research.

In Italy, the Italian National Bioethics Committee raised awareness on this issue in its Opinion on "Pharmacological Trials on Women" (NBC, 2008), in which it focused its attention on the state-of-the-art of pharmacological experimentation from a gender perspective and highlighted key bioethical problems in this field, within the context of avoiding any form of discrimination and promoting gender equality in healthcare and research. The issues relating to the pharmacological experimentation on pregnant women were not considered in the scope of the document. The NBC stressed that in clinical research "women appear to be "weak subjects", or at least they seem to be not subjected to adequate consideration, which should take into account their specificity both from a quantitative point of view (rates of women enrolled in trials compared to men) and a qualitative point of view (analysis of the data with regard to sexual differences)". Moreover, the Opinion discussed interesting outcomes concerning a number of studies being conducted in Italy on female pathologies, where the involvement of women is directly linked to the nature of the pathology. The data provided by the Italian Observatory on drug experimentation showed a progressive increase in studies specifically carried out on women, especially in phases II and III. However, women's involvement is mainly identified in relation to therapeutic strategies for specifically female diseases, such as breast cancer and the control of the post-menopausal osteoporosis. There are other areas in which the NBC devised a lack of pharmacological trials on female pathologies as well: particularly with regard to the substitutive hormonal treatment in post-menopausal women, where there are many risks of heart attack or breast cancer or cardiovascular toxicity of the chemotherapy drugs used to treat breast cancer. Although, the most critical under-representation is identified in those trials on drugs for diseases affecting both men and women: clinical research falls short on considering women's specific biological traits and their changing health condition, with a higher risk of suffering medication side effects. This is due to sex-based differences in pharmacokinetic and pharmacodynamics characteristics of drugs. Many researchers have not devoted adequate efforts to looking into sexual differences relevant for the study of symptoms, assessment of diagnosis and efficacy of treatments.

In this regard, the Italian Committee set out a number of bioethical

recommendations, which recalled the importance of implementing the key "ethical principle of fairness of a pharmacological trial on both men and women, in real conditions of equality, without unjustified exclusion, while stressing the necessity of identifying and removing the causes of this unfairness". Along with considering specific age-related vulnerabilities in pharmacological trials, it is equally fair and right to place the same emphasis on gender differences, which are likely to lead to diverse research results and require tailored trial approaches. The NBC called for an increased level of women participation in research, especially in studies aimed at better understanding women health conditions (i.e. common diseases, specific risk factors etc.), taking into account changes in the their psychological, social and cultural conditions, in order to devise gaps in those areas of the health care system where new and variable female needs are poorly taken care of. It also pointed out that an improved involvement of women would guarantee an effective condition of equality of care with respect to men, since a lack of sex-differentiated data results in a form of discrimination for women's health. According to the Italian Committee, the promotion of women's participation in clinical research should rely on providing adequate information on the negative consequences deriving from a lack of differentiated trials, as well as on the social importance of their enrolment in clinical research. Another way to devote greater attention to gender issues in trials is to foster the involvement of women as research actors (both as researchers and representatives of patient associations) and in ethics committees, so as to enable their active participation in the definition of research protocol procedures and, most interestingly, in the informed consent process.

In this context, the Austrian Bioethics Commission at the Federal Chancellery published, in 2008, Recommendations with Gender Reference for Ethics Committees and Clinical Studies, in which it recommended that "action be taken to: 1) ensure an even balance of the sexes in the composition of ethics committees and that such measures be applied equally with regard to all legally required representatives in an ethics committee; 2) guarantee the inclusion of men and women of all ages according to acknowledged scientific principles (prevalence of the disease) in all biomedical and other research projects and to accept the exclusion of women of childbearing potential in exceptional cases only.;3) ensure that the inclusion of women of childbearing potential in clinical trials (with due consideration to international guidelines) be formulated and discussed and that rules be provided which make provision for a women-friendly study design of the projects that are submitted"; 4) it also stressed that "the exclusion of women or men of any age from clinical trials should require a detailed justification". There are no specific recommendations regarding a differentiated approach to informed consent for women and men. It only stresses the need for an ethics committee to assess the appropriateness of the method of obtaining informed consent.

As for European soft law, reference is made to women's peculiarities in the general context of health, however, clear and specific guidelines or policies focusing on inclusion/exclusion criteria for women in clinical research (beyond reporting the lack of gender-based stratified data in this area) have not been issued yet. Among the awareness-raising guidelines, it is noteworthy to recall the Note for Guidance on General Considerations for Clinical Trials, published by the European Medicines Agency (EMA) in 1998, highlighting that "women of childbearing potential should be

using highly effective contraception to participate in clinical trials". In 2003, based on the conclusions of a European working group including female researchers and representatives of the pharmaceutical industries, it issued the Note for Guidance on the Clinical Development of HIV-Medical Products in which the EMA made recommendations for envisaging study protocols pointing out gender-based data analysis with a male-female comparative approach, alongside calling for statistically significant women's enrolment and appropriate medical training adapted to this protocol design. In 2005, the EMA published "Gender considerations in the conduct of clinical trials", which reviewed the International Conference on Harmonization (ICH) guidelines dealing with women issues. The EMA stressed the fact that "while women appear to be participating in all phases of study development, participation is lower in early (phase 1 – 1 / 2)". Although, these trials are important for determining safety, efficacy and changes in dosage based on gender effects. Nevertheless, unlike special consideration for age-related specificities in other documents, it argued against "the need for a separate ICH guideline on women as a special population in clinical trials", and stated that "relevant ICH and regional guidelines should be consulted for guidance on demographic considerations, including gender, in the design, conduct and analysis of clinical trials", while stating that "this issue may be revisited if future experience suggests a change from current practice". Considerations on relevant information to be included in a gender-based informed consent process are not provided.

Recently, the European Parliament adopted a Resolution of 14 February 2017 on promoting gender equality in mental health and clinical research (2016/2096 (INI)), which recognized that "specific strategies to implement guidelines for the study and evaluation of gender differences in the clinical evaluation of drugs have not been developed by the European Medicines Agency (EMA), despite the fact it has acknowledged that 'some of the factors that influence the effect of a medicine in the population may be important when considering potential differences in response between men and women' and that 'gender-specific influences can also play a significant role in drug effect". Therefore, it urged EMA to take action in this field by drawing up separate guidelines for women as a special population in clinical trials.

At the international level, guidance on women participation in research is embedded in the International Ethical Guidelines for Health-Related Research Involving Humans (as revised in 2016), prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). Guideline n° 18 focuses particularly on women as research subjects, informed consent and childbearing potential issues. As for the former aspects, it states that "women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman". However, this last aspect may become problematic for those women with cultural backgrounds where the community dimension prevails over the individual

one. Most likely, it will constitute a reason for reluctance to participate in clinical trials; hence, resulting in an exclusion criteria for specific population subgroups. This issue, as well as fertility and pregnancy aspects, will be further discussed later on in this report.

In 2010, the Department of Gender, Women and Health (GWH) of the World Health Organization (WHO) published a document on "Gender, women and primary health care renewal", which highlighted the fact that gender biases permeate health research through: 1) the lack of sex-disaggregated data; 2) designing research methodologies that are not tailored to gender and other social disparities; 3) methods used in clinical trials for new drugs that exclude women and girls from study populations and lack a gender perspective; 4) gender imbalance in ethical committees, research funding and advisory bodies; 5) differential treatment of women scientists. It also stressed that "in the European Union, efforts at including the gender perspective into health research had been effective with regard to increasing women participation in science (research by women), but not as effective in tackling problems of research for and about women". It firmly argued that research failing to examine the role of sex and gender in health is both "unethical" and "unscientific". Moreover, the WHO underlined that individuals need to be given information to enable meaningful participation, not always through the written word, but by using communication modes that are suitable to women and men. Health literacy initiatives would constitute an important component of empowerment.

Inclusion/exclusion of women in clinical research: the US experience

The report "Women's Health Research: Progress, Pitfalls, and Promise" issued by the US Institute of Medicine. Committee on Women's Health Research (2010) reviews the process of exclusion/inclusion of women with regard to clinical research in the United States. In 1977, the Food and Drug Administration (FDA) excluded women of childbearing potential from participating in phase I and early phase II trials, because of thalidomide and diethylstilbestrol tragedies. This was meant to avoid the possibility of exposing a foetus to a drug that had not satisfied preliminary safety and efficacy testing. Therefore, women of childbearing potential were allowed to participate in clinical trials only after evidence of a drug's effectiveness in humans was obtained (that is, in late phase II and phase III trials) and following data analysis from animal reproductive studies to check whether the drug caused birth defects; yet, women resulted in being underrepresented in the later phases as well.

In 1985, the Public Health Service Task Force on Women's Health Issues concluded that "the historical lack of research focus on women's health concerns had jeopardized the quality of health information available to women and the health care they receive." From the publication of that report, there have been pivotal changes in women's health research, especially with regard to government support, policy and regulations leading to the development of new scientific knowledge about women's health. This commitment was enhanced by the establishment of specific offices on women's health in several government agencies.

In 1986, the National Institutes of Health (NIH) designed a policy, which

recommended for the inclusion of women in clinical research. Besides Government reports, also documents from other organizations, including the Institute of Medicine (IOM), have emphasized the need to foster and monitor women participation in health research. Previously, little clinical research on women's health was carried out, due to existing concern about risks of possible foetal exposure to an experimental substance, the variability in hormonal status in women, comorbidities and legal issues. Nevertheless, perplexities remained that if FDA approved drugs on the basis of clinical trials in which women were underrepresented, their effectiveness and safety in women would not be known. In 1993, the NIH Revitalization Act basically strengthened existing NIH policies, but with a number of key changes: inter alia, the necessity of fulfilling the requirement for inclusion of adequate numbers of women, in order to guarantee a valid analysis by sex for phase III trials and detect differences in intervention effects, while making clear that cost should not be allowed as an acceptable reason for excluding this population group. In the same year, the FDA reversed its 1977 guidelines barring women of childbearing potential from participating in clinical research and published a Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs. The Guideline focused on: "1) encouraging inclusion of women in phase I and II studies; 2) requiring inclusion of women in efficacy studies; 3) requiring analysis of data on sex differences; 4) boosting consideration of effects of menstrual cycle on drug effect, effects of exogenous hormone therapy on drug effect, and effect of drug on the effects of oral contraceptives, when feasible".

The Committee on Women's Health Research noticed a gradual, although existing shift from a disease-centred approach to women's health and related research – merely focusing on disorders associated with the female reproductive system – to a woman-centred approach, which included other burdensome diseases in women's life (e.g. where differences between women and men are more evident in terms of frequency, seriousness, causes or manifestations, treatments or outcomes, morbidity or mortality). This broader concept of woman's health has equally showed variations in the extent of diseases among women from different sociodemographic groups, as well as an uneven distribution of benefits stemming from research developments and new treatments. Research has also expanded to encompass studies that take into account not only biological sex as a determinant of disease, but also gender, in the sense of emphasizing the importance of social, psychological and behavioural influences.

Nevertheless, women representation, consideration and reporting of sex and gender differences in the design and analyses of studies are still inadequate. This hampers advances in women's health research and its translation to clinical practice. The Committee, therefore, recommended mainstreaming women's health research, namely routinely assessing differences between men and women, as well as subgroups of men and women in all health research. It also urged the FDA to enforce compliance with the requirement for sex-stratified analyses of efficacy and safety for medical products (drugs, devices and biologics) that are coming to the market, alongside considering those analyses in regulatory decisions (US Institute of Medicine. Committee on Women's Health Research, 2010).

Ethical research conduct

The principle of justice is of paramount importance in conducting an ethical research, especially when selecting eligible participants to be enrolled in trials. In the context of this report, it may be translated in the researcher's duty to refrain from contributing to inequalities with regard to research designs not adequately taking into account gender-based needs and characteristics in the management of the trial process; or ensuring completeness and accuracy of the information conveyed to research participants, through gender-tailored communication strategies, sensitive to different literacy levels (this is directly linked to guaranteeing free and informed consent).

Protecting privacy and confidentiality is another key rule stemming from the principles of respect for the person, and beneficence according to which the latter should be informed about the use of personal data, in order to avoid any harm deriving from the publication of sensitive information. Nevertheless, the Declaration of Helsinki does not specifically refer to women peculiarities in relation to ethical principles for medical research, not even with regard to informed consent.

These principles are also included in other crucial international legal instruments in the field of bioethics and research ethics.

In the context of an ethical management of informed consent, it is important to recall that, in 2015, the Committee on Ethics of the American College of Obstetricians and Gynecologists issued the Opinion n° 646 on Ethical Considerations for Including Women as Research Participants, in which the responsibilities of researchers were clearly specified: " the researcher has an obligation to disclose to women and discuss with her all material risks affecting her; in the case of a pregnant woman, this includes all material risks to the woman and her foetus. Disclosure should include risks that are likely to affect the patient's decision to participate or not to participate in the research. Anything beyond minimal risk must be weighed carefully against the potential benefits to the woman (and the foetus, in the case of a pregnant woman) when the advisability of participation is considered. Because the process of informed consent cannot anticipate all conceivable risks, women who develop unanticipated complications should be instructed to contact the researcher or a representative of the institutional review board immediately".

3.3.2 Women's Vulnerabilities

Different Dimensions of Vulnerability

Institutional guidelines are generally keen on not considering women as vulnerable subjects, since this may fuel reticence towards their inclusion in research and hinder the possibility for them of reaping the benefits deriving from participation. However, there are a number of circumstances in which they could be vulnerable in research, such as studies with female sex workers, trafficked women, refugees and asylum seekers; or the case of women who live in a cultural context where they are not

permitted to consent on their own behalf for participation in research, but require permission from a spouse or male relative. When women in such situations are potential participants in research, researchers need to exercise special care (CIOMS 2016, Commentary on Guideline 15). Particularly, CIOMS guidelines stress the fact that "in many societies women remain socially vulnerable in the conduct of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions, and a cultural tendency to deny or tolerate pain and suffering. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits, as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them" (CIOMS 2016, Commentary on Guideline 18). Caution must be used if vulnerable subjects are enrolled in studies; their proposed participation in a research project must always be justified specifically. The general rule is that potential research participants should be the least vulnerable necessary to achieve the goals of the study and appropriate protection should be ensured in these specific cases, in order to guarantee the dignity and safety of women consenting to participate in research (CoE Steering Committee on Bioethics 2012, 10).

The concept of vulnerability is also mentioned in other international documents, such as in articles 19 and 20 of the Declaration of Helsinki (as revised in 2013) and Article 8 of the UNESCO Declaration on Bioethics and Human Rights (2005), which calls for both a "negative" duty to refrain from causing harm and a "positive" duty to promote solidarity and to share the benefits of scientific progress, highlighting the close relationship between respect for the integrity and dignity of persons, on one hand, and the vulnerability of persons on the other (International Bioethics Committee of UNESCO 2013, 5-9). In this context, the International Bioethics Committee of UNESCO (IBC) recognizes special vulnerabilities of women and girls ("gender-related vulnerabilities") concerning treatment in healthcare delivery and research, as they are "particularly exposed to the whole range of social, cultural, economic, educational and political determinants of vulnerability".

Beyond social and cultural patterns leading to vulnerable conditions for women, there are biological reasons: as recalled by the Italian NBC, female subjects' involvement in clinical trials has traditionally been deemed problematic, due to their physiological peculiarities (notably enzymatic and hormonal differences), variations during childbearing and non-childbearing age (i.e. menstrual cycle, pregnancy, breastfeeding, menopause), as well as the possibility of reliance on contraception, in order to avoid pregnancy or for therapeutic reasons; however, estrogens and progestins modify women's metabolism; particularly, estrogens may also interfere with the way genes work. This kind of variability is likely to affect the collection of clear data in mixed sex trials, with an ensuing negative impact on the statistical relevant of the research study. In addition, a possible pregnancy in fertile women is considered another problematic issue for the pharmaceutical industry, as experimental drugs could harm the foetus not only during an unexpected pregnancy during the trial, but also after the end of the process. Therefore, these possible negative effects discourage investments in research involving women, because of the extensive time required for the study development, as well as the rise in insurance

costs to cover the emergence of negative consequences.

In this regard, CIOMS guidelines point out that "pregnant women must not be considered vulnerable simply because they are pregnant", although recognizing that "specific circumstances, such as risks to the foetus, may require special protections" (2016, Commentary on Guideline 15). This view has been strongly stressed by the Committee on Ethics of The American College of Obstetricians and Gynecologists, which argues that one of the reasons for systematically excluding women from research is their perceived status as "vulnerable", and goes as far as suggesting that "pregnant women in research trials should be defined as a "scientifically complex" rather than a "vulnerable" population". This position relies on the fact that vulnerable individuals are those with a compromised ability to protect their interests and provide informed consent, whereas pregnant women do not, as a group, fall within this definition. They have the decision-making capacity to opt for participating or not in specific research studies. However, pregnant women are a "scientifically complex" group, in the sense that they require tackling a mix of physiologic and ethical complexity, which stems from "the need to balance the interests of the pregnant woman and the foetus. Maternal and foetal interests usually align, as appropriate care of the woman is necessary for the health of the foetus, but these interests may diverge in the setting of research, especially when it is not focused on concerns of pregnancy or foetal health" (Opinion n° 646, 2015).

Although, cultural issues and the scientific knowledge gap between researchers and participants, directly affecting the latter's capacity to clearly understand the underlying risks related to their specific health condition should be carefully weighed, especially in these sensitive circumstances.

The importance of taking into account the physiological conditions of women is equally highlighted in a set of ICH guidelines, which call for "including demographic variables, such as age, sex etc. in research protocols and identifying menstrual status as a possible relevant factor. Where studies are sufficiently large, data should be presented according to these subgroups. At the summary level, the demographic characteristics of patients across all efficacy studies should be provided. Adverse events, extent of exposure and safety-related laboratory measurements and vital signs, etc. should include demographic data such as the age and sex of patients" (ICH 1995, E3).

If on one hand classifying women as "vulnerable" in specific contexts should not limit their participation in research and restrict the potential value of findings beneficial for their health; on the other, leaving such a categorization aside must not lead to an under-estimation of risks, protection needs and necessary safeguards peculiar to women's health condition.

Fertility condition in women

International and European guidelines tend to acknowledge the ethical importance of including women of childbearing potential in clinical studies. It would be unjust to exclude them from clinical studies, since this hampers their chance to reap the benefits of new knowledge obtained from these studies and may result in the impossibility to safely use drugs not tested on women of this group, without

adequately protecting the foetus – in case of pregnancy – as they could take drugs available on the market and risk exposure would not be avoided, with potentially dangerous consequences.

A number of guidelines place a great emphasis on the self-determination of fertile women in making their own autonomous decision to enrol in clinical studies, as long as they have been duly informed about the specific degree of risk involved in participation. The need to protect the interests and health condition of women often overrides an appropriate consideration of foetus protection measures: according to CIOMS, "access to a pregnancy test, to effective contraceptive methods and to safe abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention. The informed consent process must include information about the risk of unintended pregnancy. Moreover, if the pregnancy is not terminated, women must be guaranteed a medical follow-up for their own health and that of the infant and child" (CIOMS 2016, Commentary on Guideline 18). Nevertheless, as stated in the UK Guidelines on the practice of ethics committees in medical research with human participants, "since all contraceptive methods have a very small failure rate, the inclusion of potentially fertile women in pharmacological studies creates a teratogenic risk" (Royal College of Physicians 2007, 61). Risk exposure may be high or low; its extent varies according to single studies. Even in the case of women of reproductive age (i.e. not pregnant), the Royal College of Physicians recommends that such risks should be discussed with their partners, also assessing the opportunity to request the latter's consent. It equally encourages researchers to provide appropriate advice concerning contraception precautions and about the existing option of "emergency contraception" if precautions have been omitted.

Nevertheless, this possibility is ethically problematic, since it is likely to deter women not willing to run the risk of jeopardizing a potential pregnancy and harming the foetus from participating in high-risk trials, entailing an under-representation of specific groups of women.

An ethical assessment of the frequency of a health condition in a particular age group also deserves specific consideration, in order to determine whether a study of a disease could be carried out without involving such individuals, because it is rare in this category of women (i.e. old-age diseases).

Women who become pregnant during research are removed from the study in cases where a drug or biological product is known to be mutagenic or teratogenic. As a consequence, medical care and follow-up are required throughout their pregnancy, in order to detect and monitor any foetal anomalies. In studies where there is no evidence of a potential harm to the foetus, women who become pregnant are usually not advised to leave the trial, but are given the opportunity to continue or end their participation. Sometimes it may be appropriate for a woman to stay in the study for safety monitoring, despite being removed from the drug study (CIOMS 2016, Commentary on Guideline 18).

Other guidelines are more cautious about the inclusion of women of childbearing potential in clinical studies and embrace a balanced approach, which takes into account benefits and risk for both the woman and the foetus: for instance, the Italian NBC emphasized the ethical and social relevance of fertile women participation, "provided that an adequate protection of the unborn child can be guaranteed",

alongside recommending a preliminary consultation about the trial, during which clear and accurate information on the goals of the study is provided, as well as a classification of benefits and risks that the study may involve for the participant, while highlighting the risks for the foetus in case of pregnancy. Whenever risks for the foetus are envisaged, the NBC underlined the importance of the woman's clear statement of a conscious and responsible commitment to honour abstinence from sexual activity, in order to avoid pregnancy. If there is insufficient evidence to exclude risks to the foetus, but the study may result in benefits for women in general and particularly to treat specific diseases, "requesting the commitment to take contraceptives as a safety measure believed necessary by the study's sponsor – to avoid pregnancy, as the trials could cause harm to the foetus – can be included in the criteria to participate in the study" (NBC 2008, 18). The NBC also highlighted that the informed consent must be guaranteed, giving women a fair amount of time and appropriate environmental conditions to decide, and that their individual consent cannot be replaced by the partner's consent. Nevertheless, in cases of possible interactions between experimental treatments and the contraceptive methods being used (e.g. certain drug trials can make hormonal contraceptive ineffective), the NBC recommends that the woman (and her partner) receive adequate information; recruitment should follow only if a commitment is clearly expressed in the informed consent "to avoid starting a pregnancy during the time of the trial and, in some cases, also for a certain time afterwards, a time to be defined according to the typology of the trials. The woman, on her part, must be available to carry out checks (pregnancy tests) that allow the experimenters to verify the conditions of safety to proceed" (NBC 2008, 19).

The use of contraception is highly controversial and ethically problematic in the Italian debate, as in many cases where fertile women are involved research sponsors consider it a mandatory requirement for participation. Despite the existence of a variety of stances on this issue, which reflects an ethical pluralism in our current society, it is possible to identify two main positions that oppose this mandatory requirement: a first one upheld by those who criticize the expectation of the pharmaceutical industry that women should use hormonal contraceptives, as this requirement would restrict women's freedom, intended as self-determination (e.g. the possibility to choose among different options); others also argue that relying on hormonal contraceptives as a mandatory requirement is not morally acceptable, since it would be detrimental to the freedom and responsibility of research participants, but inspired by a different perspective. This position, supported by those who believe in the inseparability of the unitive and procreative dimensions of the marital act, claims that the woman's explicit commitment to avoid pregnancy is sufficient, and that she should be able to choose birth control methods, respectful of her lifestyle and values, including abstaining from sexual intercourse (NBC 2008, 12-13).

The NBC's balanced approach aimed at protecting both the woman and the foetus is also upheld by the Austrian Bioethics Commission, which stressed that clinical trials on fertile women should be conducted in ways that avoid posing risks to the unborn child, while recommending the formulation of rules for a woman-friendly study design of research projects (the Austrian Bioethics Commission, 2008).

Both at the international and European levels, particular attention is given to the significance of clinical research involving pregnant women, insofar as it improves knowledge of conditions and treatments of diseases related to pregnancy. These diseases may affect the woman, the foetus or both (CoE Steering Committee on Bioethics 2012, 46). In this context, CIOMS highlighted the fact that "physicians prescribe medications for pregnant and breastfeeding women, but most often do so in the absence of studies involving such women and without adequate evidence of safety and efficacy. Such routine treatment includes medications that may have a prospect of serious harm to the foetus, such as radiation or chemotherapy for cancer. A direct consequence of the routine exclusion of pregnant women from clinical trials is their use of medications (both prescription and non-prescription) lacking data from clinical trials about the potential individual benefits and harms to themselves, their foetuses and their future children. Therefore, after careful consideration of the best available relevant data, it is imperative to design research for pregnant and breastfeeding women to learn about the currently unknown risks and potential individual benefits to them, as well as to the foetus or nursing infant" (CIOMS 2016, Commentary on Guideline 19).

As recalled by the Steering Committee on Bioethics of the Council of Europe in the Guide for Research Ethics Committees, research conducted on pregnant women may or may not have a potential direct benefit and are allowed only when studies of comparable effectiveness cannot be carried out on other persons; for research with potential direct benefit, the risk-benefit assessment must consider the specific situation of pregnancy, whereas research without potential direct benefit "must contribute to the ultimate attainment of results capable of conferring benefit to other women in relation to reproduction or to other foetuses. However, in such research the criteria of minimal risk and minimum burden are compulsory". In addition, if involving breastfeeding women, particular care is recommended to avoid any adverse impact on the health of the child.

The issue of "minimal risk" was particularly raised in the US ethical debate in relation to the definition provided in federal regulations (according to which, the likelihood and degree of harm or discomfort anticipated in the research, should not be greater than those experienced in daily life or during the performance of routine physical or psychological examinations). It was unclear whether "daily life" referred to that of the general population or of individual participants. Relying on the participant's daily life as the standard might make a higher level of risk acceptable; hence, the general population standard is advised (ACOG, 2015; National Bioethics Advisory Commission, 2001).

Although, CIOMS underlined that "when the social value of the research for pregnant or breastfeeding women or their foetus or infant is compelling, and the research cannot be conducted in non-pregnant or non-breastfeeding women, a research ethics committee may permit a minor increase above minimal risk". This last aspect requires research ethics committees (RECs) to act with particular caution: the safety of persons who consent to research should always be the primary concern of RECs

and researchers; as a general rule, this implies that all risks be carefully weighed against expected benefits. In any case, relying on evidence from prior animal experimentation is absolutely necessary (The French National Consultative Ethics Committee for Health and Life Sciences, CCNE, 1993).

The Royal College of Physicians identified a number of specific criteria for pregnant women inclusion in research, according to which, "pregnant or breastfeeding women should not participate in non-therapeutic research that carries more than minimal risk to the foetus or infant, unless this is intended to elucidate problems of pregnancy or lactation; while, as a general rule, therapeutic research should only be undertaken in pregnant or breastfeeding women with a view to: 1) improving the health of the mother without prejudice to that of the foetus or breast-fed baby; or 2) enhancing the viability of the foetus; or 3) aiding the baby's healthy development; or 3) improving the ability of the mother to nourish it adequately" (the UK Royal College of Physicians 2007, 62).

In this regard, the Committee on Ethics of the American College of Obstetricians and Gynecologists pointed out that "pregnant women who enrol in a research trial and experience a research related injury should be informed about their therapeutic options, including those related to the pregnancy. When a pregnancy has been exposed to more than minimal risk in the conduct of research, the woman should be encouraged to participate in any available follow-up evaluations to assess the effect on her and her foetus or child" (ACOG, 2015).

In the context of safety concerns before enrolling in clinical trials on investigational medicinal products, the European Clinical Trial Facilitation Group (CTFG) issued recommendations related to embryo-foetal risk mitigation and risk assessment during preconception and early stages of pregnancy. The CTFG stressed the need to clearly provide in the trial protocol the analysis of embryofetal risk for clinical trials with investigational medicinal products (IMPs), including recommendations for the level of contraception and frequency of pregnancy testing, as well as detailed information on the possibility for interaction between the investigational medicinal product or non-investigational ones and hormonal contraceptives, since this may reduce the efficacy of the contraception method.

However, as emphasized by the Committee on Ethics of the American College of Obstetricians and Gynecologists, "concerns about the potential for pregnancy in research trial participants have led to practices involving overly burdensome contraception requirements (such as the use of intrauterine devices or bilateral tubal occlusion), which are out of proportion to the actual risks of experimental drugs or interventions". Therefore, it advises consultation with an obstetrician-gynecologist or other gynecologic care provider regarding the efficacy and risk of contraception measures, since investigators generally fail to consider what is actually "reliable": the required methods, which are often prescriptive and potentially coercive, have their own inherent risks and may not meet the woman's preference. Highly burdensome contraception could be inappropriate based on the principles of respect for autonomy, beneficence and justice. In this sense, a woman should be allowed to choose a birth control method, including abstinence, according to her needs and values. In addition, in the Committee's view, "requiring specific contraception in a woman not sexually active violates a commitment to respect her as a person" (Committee on Ethics of the American College of Obstetricians and Gynecologists

2015, 103). This ethical position is in line with the concerns raised by the NBC.

As part of the consent process, the woman should be duly informed of all types of risks (including those risks impacting on her decision to enrol or not enrol in research), that could be affecting her and/or her foetus in case of pregnancy (ACOG, 2015).

If new scientific information arises during the research, this information should be conveyed to participants as soon as possible. In this case, the CoE Steering Committee on Bioethics recommends that participants be told whether the research ethics committee has asked researchers to prepare revised information/new consent forms regarding modifications to the project. At this point, as at any stage in the course of the research, subjects' right to withdraw consent must be respected.

For clinical trials including pregnant women because the medicinal product is intended for use during pregnancy, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. If experimentation is carried out on breastfeeding women, "excretion of the drug or its metabolites into human milk should be examined, where applicable; in this case, their babies should also be monitored for the effects of the drug" (EMA 1998, 10).

Maternal and foetal health in pregnancy: balancing benefits and risks

As discussed earlier, conducting clinical trials on pregnant women is an ethically problematic issue, since maternal and foetal risks are deeply interconnected and the decision to enrol this category of women in research entails balancing the risk of foetal harm with the potential for benefit and the importance of the information to be gained on the health of women and foetuses (ACOG 2015, 101).

Particularly, it may be highly problematic to decide whether to enrol in research directed at benefiting the mother in which the possibility of foetal loss cannot be excluded; in this case, it is a matter of weighing maternal welfare against foetal risk, as for studies of epilepsy or psychosis in pregnancy (the UK Royal College of Physicians 2007, 63).

In this context, it is noteworthy mentioning the controversial bioethical debate surrounding the status of the foetus, recalled by the NBC: some argue that when balancing the possible damage to the foetus (considered not yet to have dignity "in the strong sense") with the potential direct benefits to women, primary consideration should be given to the latter, since an a priori exclusion of women to protect the foetus results in injustice in research, given that women would not have the same opportunities as men in the treatment of certain diseases; others argue that where clinical research is likely to jeopardize the foetus's life and health (according to this stance, the foetus is recognised as a subject having dignity "in the strong sense"), even only hypothetically or potentially, it is ethically advisable for these women not to participate in trials, since the risk to the new life overrides the potential benefits to the women. (NBC 2008, 12-13).

The accuracy and clarity of the information provided in these sensitive contexts is key to ensuring the prospective participants' full understanding of the potential benefits and the extent of risk at stake.

Foetal protection and disease prevention research

Research into pathological conditions (such as toxoplasmosis, deformities, etc.) or treatments specifically aimed at the foetus may equally be the focus of research studies. The primary goals of these interventions is to improve the health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities. However, since this leads to unavoidable consequences for the woman's health and bodily integrity, it cannot be carried out without consideration of her wellbeing and without her explicit consent: "it is impossible to enrol the foetus in a clinical study without affecting the pregnant woman either physically (i.e. in the case of surgical treatments) or pharmacologically (as when drugs given to women cross the placenta to treat the foetus)", (ACOG 2015, 105).

The impact of cultural diversity on autonomy

Autonomy refers to a person's capacity to make personal choices and implies responsibility for taking decisions. The power to decide for oneself entails the very acceptance of the consequences of one's actions, which when we deal with health matters, can be particularly significant. Therefore, the UNESCO International Bioethics Committee emphasizes that a person needs to be informed of the specific outcomes deriving from his/her choice. "The close connection between autonomy and responsibility supposes that consent be freely given by the person concerned, the clearest possible information be provided, his/her faculties of comprehension be intact, that he/she has been able to assess the consequences of participating in a research project and the development of the entire process, as well as fully understanding the advantages and disadvantages of possible alternatives, also in terms of treatment" (UNESCO IBC 2008, 15).

However, there are a number of social and cultural aspects which may challenge the notion of autonomy in the informed consent process: many guidelines debate about the possibility of a "communal" consent, alongside the traditional "individual" consent, under specific circumstances, and whenever dealing with research participants of specific cultural backgrounds. These considerations are usually not elaborated with a gender perspective. However, the NBC stressed the fact that in some cultural contexts women tend to delegate decisions concerning their health to a partner, a male family member or the family group. In this regard, the IBC noted that "in some societies, the community is the entity in terms of which the individual is identified. The leaders of the community make decisions on behalf of its members and of the community and these are not questioned and discussed out of respect due to them because of their age, their wisdom, and also due to the fact they are deemed to be the guarantors of knowing what is best for the community. Therefore it is difficult to align the autonomy of individuals (as enshrined in Art. 5 of the UNESCO Declaration on Bioethics and Human Rights) with specific cultural settings where "communal autonomy" might be thought to prevail. The expression of an individual wish clashing with these decisions can be difficult or impossible either out of fear of negative consequences for the individual (such as social disapproval) or out of respect for the leader. Seeking consent from an individual is indispensable even if

the community is consulted, but the actual value of the consent of such individual, once the community as given its approval or disapproval often raises concern". Nevertheless, such reasons should not lead to the conclusion that cultural considerations pave the way to situations where, exceptionally, for members of some groups communal autonomy may override individual autonomy. Conversely, we should always bear in mind Art. 12 of the UNESCO Declaration, which states that "respect for cultural diversity and pluralism should not be used to infringe fundamental freedoms nor any of the principles set out in the Declaration" (UNESCO IBC 2008, 36). In this perspective, the Italian Committee for Bioethics, proposes an interpretation of the concept of autonomy in terms of "relational autonomy", which may be better tailored to an intercultural approach aimed at accommodating the value of the community dimension in certain cultural settings (i.e. African tribes) and respect for the person (NBC 2017, 38).

In the context of research participation, women living in a social context of patriarchal authority, having a low literacy level, may adopt a passive behaviour with regard to enrolment procedures or not seek interaction with researchers in case of insufficient understanding of the study evolution. Therefore, as stressed by the UK Royal College of Physicians, "research ethics committees should exercise special care in examining the proposed consent process to ensure adequate time and a proper environment in which a decision to participate can be made".

Concerning research involving pregnant women with the prospect of direct benefits for the health of the foetus, there may be cases where participants belong to communities or societies in which cultural beliefs place greater importance on protecting the foetus than the woman's health. In these circumstances, women may feel coerced into enrolling, or not enrolling, in research. Hence, special safeguards are recommended to prevent undue inducement to pregnant women to participate in research with potential benefits to the foetus, but not to the woman herself (CIOMS 2016, Commentary on Guideline 19).

There is broad consensus in international and European guidelines on the fact that in no case permission by the woman's partner may replace the individual informed consent of the woman herself, since this would result in a violation of the principle of respect for the person. However, if the woman wishes to consult with husband or partner before deciding to enrol in research, that is deemed to be not only ethically permissible, but in some contexts highly desirable.

In addition, different cultures may also have different views concerning privacy and personal data, which can impinge on the acceptability of certain aspects of research protocols, especially with regard to data collection, as well as the data subject's right of access and right to object (The European Group on Ethics in Science and New technologies, EGE, 2003, 13). Guidelines do not address privacy and confidentiality issues with a gender perspective, but only from a general point of view.

Socio-economic conditions affecting freedom and self-determination

Social and economic vulnerabilities may interfere with the self-determination of individuals and lead to a remarkably increased exposure to a number of risks: some contextual aspects that fuel social vulnerability in research concern poverty and low

educational levels, difficulty in accessing healthcare (i.e. whenever transnational research projects are involved), as well as the interaction between gender and marginalised racial and ethnic backgrounds (UNESCO IBC 2013, 27). In this regard, the French CCNE highlighted the special status of women in some developing countries, that generates "a situation of inequality in the gender relationship", which deserves particular attention, since it could compromise an actual understanding of health issues (CCNE 2003, 19).

Respect for free and informed consent acknowledges that potential research participants must not be coerced or unduly influenced by use of inducements or threats. For instance, the IBC discussed cases of poor women in developing countries deciding to enrol in trials after being informed that their children would be entitled to receive necessary medical treatments in this context. Therefore, these women's ability to provide a valid consent was in doubt, given their concern for their children's health. In addition, they become vulnerable to any risks involved in clinical trials, since they are likely to underestimate these aspects due to other priority interests.

As recalled by the CoE Steering Committee on Bioethics, "it is extremely difficult to achieve a complete lack of influence, but influence that would lead individuals to accept a higher level of risk than would otherwise be acceptable to them, would be considered undue. This kind of influence may be financial in nature, but could also include, for instance, attempts to influence family members" (as in the case of vulnerable women accustomed to social conditioning to submit to authority), or veiled threats (for example by researchers, medical staff or healthcare providers) to deny access to services to which individuals would otherwise be entitled, or expectation of any other retaliatory response from senior members of a group with a hierarchical structure in case of refusal to participate in a trial. Therefore, special care is needed in situations where participation in a research project may be the only way to access health care (CoE Steering Committee on Bioethics 2012, 10). The CoE Steering Committee on Bioethics does not refer to gender issues in this specific context.

In principle, the involvement in a clinical trial is a benevolent act, which should not be induced by monetary or other forms of compensation, in order to avoid exploitation (EGE 2003, 13). Although, it is considered ethically acceptable and appropriate to reimburse individuals for any costs associated with participation in research, including transportation or lost wages. A number of research ethics committees also believe that participants should receive compensation for their time devoted to research participation; however, WHO recommends that payments should not be so large, or free medical care or other forms of compensations so extensive, as to provide prospective participants with incentives to consent to research enrolment against their better judgment or to undermine their understanding of the research (WHO, Department of Ethics, Equity, Trade and Human Rights 2011, 14). However, determining the ethical acceptability of compensation is problematic, as the possibility it may exert an undue inducement to participate in research depends on a number of different variables, such as prospective subjects' economic status.

An ethical consideration of informed consent must focus on comprehension and free consent, as both elements are an essential part of the person's self-determination: it is all the more important when dealing with vulnerable categories of women that

potential participants are given clear information in language, which is understandable to them, particularly when subjects with linguistic or cognitive limitations are involved. This is a necessary aspect for freedom in consenting, therefore the Committee on Ethics of the American College of Obstetricians and Gynecologists advises those in charge of providing information "to be cognizant of participants' beliefs and values during the informed consent process" (ACOG Committee on Ethics 2009, 3).

3.3.3 Gender issues in the communication and understanding process

Gender peculiarities in communication

The Gender guide for health communication programs issued by the US Center for Communications Programs points out the importance of including gender concerns in health communication initiatives, aimed at making health messages more effective and foster awareness of the necessity of equity in terms of gender needs. A gender perspective in communication should take into account ways in which gender influences health needs and concerns, different roles and interests of women and men, as well as the reception of health messages. Seeking feedback on effective communication strategies is highly recommended, also by conducting evaluations in different cultural communities. It is critical to speak to women and men separately to obtain reliable gender-informed perspectives.

Oral vs. written consent in differentiated literacy rates

The issue regarding comprehension of information conveyed by investigators or practitioners is often raised in developed countries where illiteracy can be a minor problem, but where inability to understand is due to the complexity and length of documents submitted to research participants (however, also in clinical practice). More than empowering subjects through clear information, these documents may be interpreted as a way to protect healthcare professionals from being accused of delivering incomplete information. The International Bioethics Committee of UNESCO, therefore, recalls the importance of the clarity of the text submitted and its content, which should include necessary and sufficient information to decide either to consent or refuse to consent. This must be done in a language that is accessible to person concerned.

Other ethical challenges stem from the fact that in many cases, particularly in scientific research, it may be necessary to document in a written form that consent has been obtained. However, the implementation of this request is likely to face problems, in certain situations: for instance, in societies with an oral tradition, where the value of oral consent is unquestionable; as a consequence, written form

consents can be considered as a lack of trust or even as an insult; or in illiterate groups of people, "where a sign at the bottom of a page may not reflect a real agreement with the content of the document". Hence, there is wide recognition that, in principle, despite the need of an assiduous effort towards the possibility of obtaining written consent, based on the context, it is appropriate to explore other ways of demonstrating that consent has been actually and consciously expressed (UNESCO IBC 2008, 35). Nevertheless, the IBC does not specifically apply literacy issues to gender considerations.

In this context, the German Working Party of research ethics committees has developed and published samples for informed consent, which are documents for clinical trials with medicinal products on healthy volunteers or patients and for collecting materials for biobanking, recommended to sponsors. Even though they are not adapted to gender, these documents stress that the oral information process must take account of the background and abilities of the person concerned.

Education, multimedia and ICT

Whenever dealing with research participants of differentiated levels of education, it becomes more difficult to adequately handle the informed consent process, as especially in the case of illiterate subjects, opting for excessive simplification of information might lead to part of it being omitted. In this regard, the IBC noted that "a way of mitigating these challenges is to encourage information/educational/communication systems through a multicultural approach in communities, the development of suitable tools to convey information, as well as the training of healthcare professionals to deliver simple, accessible and reliable information" (UNESCO IBC 2008, 34).

In this context, the UK Health Research Authority suggests to apply a "layered approach" to informed consent, which encompasses: "1) providing potential participants initially with a short summary including sufficient, but brief, information needed to decide whether or not to take part in research; 2) adopting user-friendly methods of access to further, more detailed information (e.g. additional paper information sheets, and/or online information) presented in one or more additional layers (but not provided upfront). The primary information should clearly explain how this additional information may be accessed. In this way potential participants control the amount of information they access and can do so well aware that more comprehensive information is available to them to refer to at any time, before, during and after their participation". It also stresses the importance of choosing an appropriate layout and format, including the use of visuals if this may support explanation. The use of media or non-text based approaches are recommended, such as videos, cartoons, animations, infographic cards, flipcharts, brochures and audios, all tools that can be used as patient-friendly introductions to complement, or replace, the traditional paper information sheet. However, the UK Health Research Authority underlines that "while it is acceptable to rely on online text or multimedia material as primary means of informing potential participants, alternative methods of information should also be available for people who are unable or unwilling to access the internet or engage with multimedia. However, the method of information

provision used in a study should always be adapted to the visual or other needs of the specific group being recruited. With a view to ensure adequate levels of understanding are achieved, suggestions are made to use interactive questioning of subjects within the consent process, with tools highlighting areas that prospective participants could misunderstand. Testing participant information with an appropriate group of people (e.g. patient groups and/or other members of the public) is strongly encouraged, along with reliance on medical writers with experience of writing in plain language for the public (UK Health Research Authority 2017, 6). No specific gender-tailored process is suggested in this context.

On one hand, if these tools can be helpful to improve understanding in young women and girls, for instance, that highly rely on ICT and multimedia devices, on the other, their use may present a set of ethical problems in terms of protecting the privacy of users, as well as instructing them on issues related to security and privacy or ascertaining their identity in case of remote consent process, in this new field of application of informed consent procedures. In addition, as emphasized by the Italian National Bioethics Committee: "obtaining informed consent in the medical field presupposes symmetrical and reciprocal communication, namely when individuals are equally powerful in the interaction and also when the positions between those giving the information and those receiving it take place in the recognition of their respective autonomy"(NBC 2015, 13). This kind of relationship may be affected by a possible excessive reliance on these tools.

Moreover, appropriate strategies should be devised to avoid streamlining the process in ways that may lead potential participants to underestimate risks (i.e. also in terms of managing personal data collection) or overestimate benefits deriving from research. In this perspective, new methods of regular interaction between researchers and recruited subjects would need to be explored.

3.3.4 A controversial issue related to the acquisition of informed consent: the role of the pregnant woman's partner in the consent process

Clinical studies involving female or male reproductive health may raise issues surrounding the potential effect of the study on the participant's partner. According to the ACOG Committee on Ethics, "in the absence of a few specific scenarios, requiring participation consent from a woman's partner is neither warranted nor ethically justified" (for instance, in cases of general medical care or whenever pregnancy decisions are involved). It is deemed appropriate if there is a risk of the partner's exposure to an investigational agent and this is likely to carry more than a minimal risk or if data regarding him will be collected; or if testing of a partner is required for a woman to participate in a study (eg. semen analysis or testing for a sexually transmitted infection). Beyond these circumstances, the consent of the woman's partner in not advisable, since it may hinder the woman's decision with regard to health issues (ACOG Committee on Ethics 2015, 103).

Conversely, a more balanced position is expressed by CIOMS: as recalled earlier, even if it firmly states that a partner can never replace the consent of the woman, whenever the latter wishes to consult with her partner before enrolling in research,

this possibility “is not only ethically permissible, but in some contexts highly desirable”.

3.3.5 Other relevant sources

A developed ethical reflection on pregnancy issues in research and the consent process: soft law in Belgium

The Belgian Advisory Committee on Bioethics has dealt twice with the topic of pregnant women’s participation in research: in 2004, it issued a first Opinion regarding experiments on pregnant and breastfeeding women and, in 2015, a second one on The Ethical implications of the “Statute” of the Pregnant Partner of a Male Participant in a Clinical Trial, in which it provided a detailed description of key ethical and legal issues related to the informed consent process in the context of pregnancy.

In its Opinion n° 31 regarding experiments on pregnant and breastfeeding women, the Belgian Advisory Committee on Bioethics, noted that research ethics committees should take into account the various stages of pregnancy that are linked with a totally different set of risks (i.e. possible effects on germ cells or the implantation of fertilized eggs cells, potential teratogenic effects, possible embryotoxic effects and the impact on the physiological changes caused by pregnancy) when assessing protocols for experiments on pregnant women. Hence, in terms of safety, an appropriate analysis of the many underlying issues should differentiate the different stages involved in the process: before conception; the first week of the pregnancy; the second week up to and including the eighth week; the second and third trimesters and the delivery.

Research involving pregnant women may be conducted for different reasons, which raise a number of specific ethical issues, ranging from research into problems specific to pregnancy (i.e. pregnancy-related pathological complications such as repeated miscarriages) to physiological or physiopathological research (for instance, concerning circulatory changes during pregnancy). In this case, both the mother and the child may benefit from the study and its results, since they are relevant to the goals of the research. In other cases, trials can be carried out to look into pathological conditions that are not linked to pregnancy, but that occur in pregnant women and, therefore, result in diagnostic or therapeutic problems (for instance, the diagnosis or treatment of hyperthyroidosis). Here, concern is mostly for any adverse effects on the unborn child that could be caused by the drug used; whereas, the benefits to the foetus are generally less important.

The Belgian Committee equally recalled different types of research directed at benefitting the foetus (i.e. pathological conditions generally affecting the foetus). These studies may also include investigations into the extent to which treatment can protect mother-to-child transmission of HIV virus (The Belgian Advisory Committee on Bioethics 2004, 2).

Another open question, raised was whether or not the child or, later, the adult has the right to know if his/her mother has participated in a clinical study during

pregnancy and, if so, what compensation he/she would be entitled to receive for any harm deriving from this enrolment. The issue of the extent to which the informed consent of the mother involves her unborn child remains controversial.

In the context of interactions between gender and multicultural issues, emphasis was placed on the fact that an over-representation of women belonging to socially disadvantaged or minority groups should be avoided, as their decision to enrol in a trial may be influenced by receiving free medical care. Likewise, they should not be systematically excluded either; nevertheless, it is important to make sure they actually have fully understood the consent form presented to them (Belgian Advisory Committee on Bioethics 2004, 5).

Moreover, considerable attention has been focused on two problematic issues, namely the role of the pregnant woman's partner and of the man's fertile or pregnant partner in the consent process. Concerning the first issue, the Belgian Committee reflected on the extent to which the father of the unborn child should be involved in giving informed consent, when a pregnant woman is enrolled in a clinical trial: some members of the Committee believe that the autonomy of the pregnant woman must prevail in cases where there are therapeutic benefits either for the woman or for the child or for both; however, if there is a stable relationship they highly recommend that the father be consulted. Other members of the Committee contend that since pregnancy involves both parents, the responsibility of the father cannot be denied; therefore, participation should be ruled out in case of conflicts. If no direct benefit is envisaged for the woman or the unborn child, some argue that the partner's consent should be obtained before enrolling in a trial, while others believe that the autonomous choice of the woman can never be overridden (Belgian Advisory Committee on Bioethics 2004, 5).

The second issue arises from the fact that some drugs being tested in clinical trials are potentially toxic for gametes or foetuses, resulting in possible consequences for any offspring conceived during the study. The Belgian Committee addressed this topic in the context of toxicity caused by the sperm of a male participant or when toxicity affects the gametes of a male participant. Its focus was on whether it would be necessary to request the pregnant partner's consent prior to research participation.

Because of the sensitiveness of this issue, the Committee underlined the importance of a thorough and adequate informed consent process, with the duty to inform the male participant in a complete, clear and understandable manner regarding the potential medical risk of the test product for both the participant himself and his partner. In this perspective, it is primarily the responsibility of the sponsor to limit the risks related to the study to a minimum. In addition, a number of specific recommendations are made on the informed consent process, which should include: "1) the period of risk exposure; 2) that the pregnancy of the partner or a refusal to use double contraception are considered to be exclusion criteria; 3) that the participant is encouraged to inform his partner about his participation in a clinical trial; and that the sponsor of the clinical trial formally declares to be prepared to answer the questions of the participant's partner" (Belgian Advisory Committee on Bioethics 2015, 10). However, no compulsory requirement to obtain the consent of the male participant's fertile or pregnant partner is suggested.

The Italian NBC does not specifically address the issue of acquiring consent from a

male participant's partner, but equally recommends that the informed consent and commitment to avoid procreation should apply to men participating in a clinical trial, which carries a risk of harm to the foetus through their gametes (NBC, Pharmacological Trails on Women 2008, 19).

A gender approach to the informed consent process: Soft law in Canada

Canada has also carried out initiatives to provide guidance on women enrolment in clinical research by issuing a number of documents in this area, which are particularly interesting for their major focus on tailoring the informed consent process to female peculiarities in terms of communication skills: particularly, in 2006, the Canadian Working group on Women and Health Protection published a document on "The Inclusion of Women in Clinical Trials: Are We Asking the Right Questions?", placing a strong emphasis on the need to adapt consent forms to women's specificities and literacy levels and overcoming the "pro-forma" model. It made clear that "this requires attention both to informed consent material, and the informed consent process. Given literacy levels of women and the complexity of forms, there are concerns about women expressing truly authentic consent to trial participation. And even with women who are print literate, other factors related to expectations of medical care, understanding of random assignment, placebos, and of probability, can compromise the ability to give truly informed consent". The Working Group therefore recommended that efforts be made to ensure consent forms are "user-friendly", without leaving out important informational content in order to be able to give an actual consent, well aware of the benefits and risks related to enrolment.

In addition, Canadian guidelines raise awareness about the possibility of gender-based differences in how the informed consent process is carried out, due to potential gender and class-based differences in doctor-patient relationships. These guidelines equally stress the importance of making "reader-friendly" summaries of trial protocols easily available and envisaging the development and use of multiple means of communication (i.e. Internet, print, oral, multiple languages, etc.), to ensure all women can have access to complete and accurate information, combined with related materials (the Canadian Working group on Women and Health Protection 2006, 26-27). All these tools are meant to guarantee full understanding of the research process with a gender perspective.

Institutional documents particularly underline a number of key elements pertaining to the consent process, whenever enrolling women of childbearing potential: in this case, clinical trial participants should be duly informed, alongside all other risks, about the potential risks of reproductive and foetal toxicity, including teratogenicity and about pregnancy prevention, so that prospective subjects understand how and when to take precautions (i.e. use of reliable methods of contraception and/or abstinence, pregnancy testing) to prevent pregnancy, if necessary within the trial. Moreover, Health Canada recommends that a statement on the effectiveness of contraception methods should be included in all informed consent forms requiring contraceptive guidance, as well as a clear list of the contraceptive methods suggested. Whenever relevant information is not available from reproductive toxicity studies, the informed consent form should explicitly note that embryo-foetal risk

cannot be excluded (Health Canada 2013, 5).

3.3.6 References

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3.4 Gender-related issues in informed consent to clinical trials (Hard Law)

3.4.1 The principle of informed consent at international level

Convention on Human Rights and Biomedicine (1997) and Additional Protocol concerning biomedical research (2005)

Chapter II (Articles 5 to 9) addresses the need for informed consent before any biomedical intervention. The fundamental principle for research involving human beings is the free, informed, express, specific, and documented consent of the person participating in clinical trial. The Convention provides particular protection of people who are not able to consent (article 6), who have mental disorder (article 7), but no particular prediction about women enrolled in clinical research.

The Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research is intended to build on the principles embodied in the Council of Europe's Convention on Human Rights and Biomedicine, with a view to protecting human rights and dignity in the specific field of biomedical research. The Protocol is aimed to cover the full range of biomedical research activities involving interventions on human beings. Research on pregnant or breastfeeding women is covered by the Protocol (Chapter VI). Article 18 describes the conditions in where research on pregnant women may be undertaken. In particular research is possible if it produces direct benefit to women's health (or to her embryo, foetus or child after birth), or even if it does not have direct benefit provided that three conditions are met. First, the research must contribute to the attainment of results to other women in relation to reproduction (or to other embryos, foetuses or children); additionally, the research must entail only minimal risk and burden; furthermore, comparable effectiveness must not be possible to carry out on women who are not pregnant.

Regarding breastfeeding women, the research may be undertaken, but particular care must be taken to avoid any adverse impact on the health of the child.

3.4.2 The informed consent to clinical research in Directive 2001/20/EC of 4 April 2001 ("the Clinical Trial Directive") and in regulatory measures at the national level

The Clinical Trials Directive refers to the protection of clinical trial participants and sets up an Ethics Committee, in charge of providing its opinions before the start of a clinical trial.

Several articles in the Directive provide guidance regarding the protection of clinical trial subjects (Article 3). Special attention is paid to minors and incapacitated adults, as specified in article 4 ("Clinical trials on minors") and article 5 ("Clinical trials on

incapacitated adults not able to give informed legal consent"), but women are not specifically mentioned.
With specific regard to informed consent, article 3 of the Directive provides for legal guarantees. Participants must give a written consent (or oral if he/she is unable to write) after being informed of the significance, nature, implications and risks of the clinical trial.
Therefore, even if the Directive highlights the importance of the protection of trial participants, it does not give any different provision by gender with respect to the consent.
The National transpositions by the six selected Member States, as well as other domestic laws on clinical trials or other laws on clinical trials, show the importance of understanding the informed consent process as a whole, and the right of participants to have sufficient information about the research and any risks they may encounter. However, even these national rules do not give weight to gender differences and specific needs.
A common element in any transposition law regarding clinical trials on human beings is the requirement of proportionality: the risk for the participant cannot be disproportionate in comparison with potential benefits. This principle, along with that of prevalence of the subject's welfare over the interests of science and community, can be found in the Council of Europe's Convention on Human Rights and Biomedicine and in the 2001/20/EC Directive. However, even if the considered national legal systems pay attention to vulnerable subjects, the regulatory measures consider "vulnerable" only minors, incapacitated adults and pregnant or breastfeeding women. No consideration or specific requirement relating to the acquisition of informed consent of women in general is specified.
Specific provisions are given with regard to pregnant or breastfeeding women, in order to grant them accurate information on risks and recommended actions. In particular, a number of national regulations concerning research involving pregnant women require that any risk must be the least possible for women and foetuses, while achieving the objectives of the research. Each woman providing consent must be fully informed regarding the reasonably foreseeable impact of the research on the foetus or newborn.
Spanish law also provides that when research involves women with childbearing potential, the possible adverse impact on an unknown or later existing pregnancy must be taken into account as well as that on the health of the embryo, foetus or child.

Austria

The Directive has been transposed into Austrian law by the Bundesgesetz, along with the Arzneimittelgesetz (Drug Act), Bundesgesetz über Krankenanstalten und Kuranstalten (Federal Law on Hospital and Health Institution), the Arzneiwareneinfuhrgesetz (Drug Delivery Act) of 2002, and the concerning the institution of a Fund for Health Care "Österreichisches Bundesinstitut für Gesundheitswesen", amended in 2004.
Regarding the equality of men and women in ethics committees, the law that

transposed the Directive establishes that "Die Ethikkommission hat sich in einem ausgewogenen Verhältnis aus Frauen und Männern zusammenzusetzen" (§ 41), that is , the ethics committee must be composed of a balanced proportion of women and men.

No single legal instrument covers all biomedical research. Several national legislations cover various matters relating to informed consent in clinical trials. The following are relevant: Drug Act (Arzneimittelgesetz) 1983, which has been amended on several occasions, and also implementing the Directive 2001/20/EC; the Medical Devices Act (Medizinproduktegesetz, MPG) as amended by Federal Gazette I No. 143/2009; the Hospital Act (Krankenanstaltengesetz 2002); the Genetic Engineering Act (Gentechnikgesetz) - GTG (BGB1 Nr. 510/1994); the University Act (Universitätsgesetz) (BGBl. I No. 120/2002); the Data Protection Act (Datenschutzgesetz 2000) (DSG). It is based on Directive 95/46/EC on data protection (Data Protection Directive).

By the regulatory measures analysed, there are no differences between men and women in regard to the legal requirements.

France

The Directive 2001/20/EC on the conduct of clinical trials (Clinical Trials Directive) was implemented in France by Law n° 2004-806 of August 9, 2004 relating to public health policy and its decree of application n° 2006-477 of April 26, 2006.

Similarly to the Directive, the French transposition measures do not mention women.

Germany

The Directive 2001/20/EC was implemented into German Law in 2004 by the 12th Amendment of the Medicinal Product Act (Arzneimittelgesetz - AMG) and by the Directive concerning Good clinical practice in clinical research in the conduct of clinical trials on medicinal products for human use (Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung - GCP-V) vom 9 August 2004).

It should be noted that Germany is a Federal state, which results in legislative power being divided between the German Federation and the German Lands. This division is also seen in the area of clinical trials where the federation is responsible for the medical research in general, while the Lands are competent to regulate medical professions.

The Übersetzung durch den Sprachendienst des Bundesministeriums für Gesundheit (Medical product Act and Phatmaeceutical Act – Drug Law) (Arzneimittelgesetz – AMG), chapter 6, titled Protection of human subjects in clinical trials, introduces a set of requirements which are indispensable for clinical trials conduct. One of the basic instruments aiming to protect the trial subject is the obligation to obtain subject's informed consent.

With regard to the information, as well as contra-indications, corresponding

precautions for use, interactions with other medicinal products or other products, if they are able to influence the effect of the medicinal product, the special situation of specific groups of persons (such as pregnant women or nursing mothers) must be taken into account.
With regard to gender issues, Chapter 6 explains that "A favourable opinion may be refused if […] the clinical trial is unsuitable for providing proof of the safety or efficacy of a medicinal product, including a difference in the mode of action in women and men". The favourable opinion by the ethics committee shall be withdrawn if the modalities for selecting trial subjects no longer correspond to the current state of medical knowledge and, especially, the clinical trial is unsuitable for providing proof of the safety or the efficacy of a medicinal product including a difference in the mode of action in women and men.
There are no specific criteria in the Medicinal Product Act (Arzneimittelgesetz - AMG) for the participation of women in clinical trials. However, the Act on Medical Devices (MPG) contains specific requirements for pregnant women and nursing mothers (§ 20). More specifically, the clinical trial may be carried out only for prevent, recognize, heal or alleviate diseases in pregnant or breastfeeding women or an unborn child. The conduct of the clinical trial for the unborn child must not imply unacceptable risks.
The only specific rules regarding women deal with the requirement that clinical trials should be designed in a way to allow conclusions on possible different effects of the tested product on men and women and that men and women should both participate to an adequate degree in a given clinical trial.
Besides the laws analysed, the following laws contain provisions on the informed consent process for clinical research: StrahlenschutzVO (Radiation Protection Act) § 87 StrahlenschutzVO 88 Abs. 4 Nr. 3 StrahlenschutzVO; Röntgenverordnung (Radiography Regulation) § 28c RöV § 28d Abs. 4 Nr. 3 RöV, but none of these regulations contain gender-specific informed consent procedures.

Italy

In Italy the Directive was transposed into domestic Legislative Decree n° 211 del 24/6/2003 implementing the Directive 2001/20/EC on the application of good clinical practice in the conduct of clinical trials of medicinal products for chemical use.
The law provides for the protection of subjects subjected to clinical trials who must have been informed and given their consent, but this refers to the "subject" as a "person participating in clinical trial" without distinction between a man and a woman.
Such a Decree concerns the protection of subjects of experimentation: specific provisions concern the protection of subject who are unable to give their consent, and to minors, but there is no explicit reference to women, or pregnant or breastfeeding women.
This legislative decree 211 of 2003 was amended by the decree 13 September 158/2012 ('Urgent provisions to promote the development of the country through a higher level of health protection'), converted by law no. 189 of November, 2012, required each Italian region to reorganise its ethics committees by 30 June 2013 in

line with criteria laid down in the relevant decree subsequently published on 8 February 2013 under the title “Criteria for the composition and functioning of ethics committees”.
Then the criteria for the composition of the committees was established by Decree of Ministry of 12 May 2006 "Minimum Requirements for the Establishment, Organization and Functioning of Ethical Committees for Clinical Trials of Medicines". The legislation does not specify that there must be a balanced representation of both sexes, meaning here the women as a research subject. These criteria have been redefined by Decree of Ministry of Health, February 8, 2013. Under the latter decree, the members of the ethics committees must have documented knowledge and experience in clinical trials of medicines and medical devices and other matters within the competence of the Ethics Committee (Article 2, paragraph 5). This decree, in modifying the committee's composition criteria, does not establish that there must be a balanced representation of both sexes.

Spain

The Clinical Trials Directive was transposed into Spanish Law by the Royal Decree 223/2004, of February 6th, which regulates clinical drug trials. (Real Decreto por el que se regulan los ensayos clínicos con medicamentos, BOE 33, February 1st, 2004).
This Royal Decree takes into account the basic principles for clinical trials on humans based on the protection of human rights and the dignity of human beings.
The decree, moreover, takes into account the conditions of pregnant women or nursing mothers. Clinical trials without direct potential benefits for them may be carried out only when the clinical research Ethics Committee agrees that they don’t pose any risk to their health (or to foetus or child) (article 6).
Another Law that regulates biomedical research in Spain is Law 14/2007, of July 3rd, (Ley de Investigación Biomédica, BOE 159 of July 4th, 2007). This legislation is a response to ethical and legal concerns about the use of Biomedical Research.
With particular regard to the issues of informed consent, the Law provides for the right to inform the subjects participating in the research, and underlines the characteristics of informed consent, in general, by taking into account the research involving pregnant women and women during lactation.
Investigations involving pregnant women may be authorized only if the aim of the research is to contribute the production of beneficial results for women, embryos, foetuses or children; that research of similar efficacy is not possible to be undertaken in non-pregnant women; that the research entails a minimum risk and damage for the woman and, in its case, for the embryo, foetus or child; that the pregnant woman, or the legal representatives of the child, in its case, provides their consent in the terms provided in this Law (article 19).
Furthermore, when research is carried out on a woman during breast-feeding period, special care should be taken to avoid adverse impact on the child's health.
The Law also specifies that when research involves women in a fertile age, the possible adverse impact on an unknown existing pregnancy or a later one, as well as on the health of the embryos, foetuses or child shall be taken into account (Article 23).

The purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means. The consent of pregnant women must be obtained according to the informed consent regulations. The baby's father's consent is not needed.
The issue of informed consent is also governed by Law 41 of 14 November 2002, Fundamental regulation of patient autonomy and rights and obligations regarding clinical information and documentation (last modification of 2015).
The Law defines the informed consent as the free, voluntary and conscious consent of a patient, manifested in the full use of his faculties after receiving the appropriate information, but it does not specify any particular protection for women.

United Kingdom

The Directive 2001/20 EC was transposed into UK law by means of The Medicines for Human Use (Clinical Trials) Regulations 2004 – Statutory Instrument 2004 No. 1031.
In particular, the Regulation describes the provisions relating to giving informed consent on behalf of minors and adults who are unable to give a valid consent, but there is no mention of women.
Regulations 2004 has been amended many times (The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 - Statutory Instrument 2006 No. 1928; The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 – Statutory Instrument 2006 No. 2984; The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) - Statutory Instruments 2008 No. 941; The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009 No.1164; Clinical Trials of Investigational Medicinal Products (CTIMPS): EU Legislation), but no change has taken into account the particular gender issue.

3.4.3 The Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use and implementation measures

In relation to informed consent process, the content of the Directive 2001/20/EC has not been amended by the new legislation, except in the particular provisions for vulnerable subjects.
The category of "vulnerable persons" in biomedical research includes incapacitated subjects (Article 31), minors (Article 32), pregnant and breastfeeding women (Article 33), and patients in emergencies (Article 35). Most interestingly, Article 34 gives the possibility for Member States to organize a further protection for certain subjects in a situation of institutional or hierarchical dependency likely to inappropriately influence their consent ("persons performing mandatory military service, persons deprived of liberty, persons who, due to a judicial decision, cannot take part in clinical trials, or persons in residential care institutions").
Therefore, gender-related aspects are not addressed regarding informed consent: the rules related to women only refer to pregnant or breastfeeding women, not to

women in general.
In particular, the Regulation contains new legal provisions for including and protecting pregnant and breastfeeding women.
The article 33 defines the conditions under which pregnant or breastfeeding women can participate in clinical trials. The Regulation provides that the clinical trial on pregnant or breastfeeding women may be conducted only if, in addition to the conditions set out in Article 28 (general rules): “a) the clinical trial has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, foetus or child after birth, or b) if such clinical trial has no direct benefit, it can be conducted only if: (i) a clinical trial of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding; (ii) the clinical trial contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, foetuses or children; and (iii) the clinical trial poses a minimal risk ; (c) where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child”. It is also established that for pregnant or breastfeeding women no incentives or financial inducements are given to the subject except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial (article 33 letter d)).
The pregnant woman's consent is obtained, and she is enrolled in clinical trial, if the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the foetus, or no prospect of benefit for the woman nor the foetus, when risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge (that cannot be obtained by any other means).
With regulatory practice, Europe takes into account gender differences in the clinical trials, also providing for analysis of results according to sex. The principle is that "the subjects participating in a clinical trial should represent the population groups, for example gender ... groups, that are likely to use the medicinal product investigated in the clinical trial".
Annex I affirms that the protocol must include "a description of the groups and subgroups of the subjects participating in the clinical trial, including, where relevant, groups of subjects with specific needs, for example gender ...". Annex IV refer to presenting sex differences in the clinical trial results, specifying that it is necessary takes into account population of participants (including gender breakdown).
Some Member States, such as Spain and France, have already adopted implementation measures in order to adapt their national legislation to the Regulation (EU) 536/2014. By the domestic laws analysis come into light that the informed consent requirements are not tailored to gender-based elements.

The role of Ethics Committees

The Clinical Trials Directive sets up an Ethics Committee, in charge of providing its opinion before the start of a clinical trial.
The Directive provides that Member States take the measures necessary for establishment of Ethics Committees that give their opinion before a clinical trial

commences.
The Regulation aims to simplify procedures with only EU portal and to provide more useful results and experimental data to all participants in a very short time. Article 1 specifies that the Regulation applies to all clinical trials conducted in the Union and it does not apply to non-interventional studies. Article 4 affirms that a clinical trial must be subject to scientific and ethical review and, in subsequent articles, refers to the need of an authorization.
The process of “scientific review” involves coordination between all member States concerned, leading to a shared report at European level. In contrast, the process of "ethical review" remains limited within each Member State. The ethical review is introduced "out of procedure" and the ethics committee is understood as an "independent" body, which has to formulate a binding opinion for the Member State prior to starting a clinical trial.

Implementation in France

France adopted two decrees on 17 November 2016 in order to adapt its national legislation to the CTR. The first decree (Decree concerning Research Involving Humans No. 1537 of 16 November 2016) focuses on “research involving the human person” and produces many changes, also regarding the role of the national commission for research. The second decree (Decree No. 2016-1538 of 16 November 2016) focuses on the rules regarding contracts for clinical studies for commercial purposes conducted by sponsors in public health establishments. These two decrees complete a government Order dated 17 June 2016, which implemented the law no 2012-300, dated 5 March 2012, on research on human persons.
The Ordinance concerning Research Involving Humans (2016/800), dated June 16 2016, amended the Public Health Code.
Article L1121-5 explains that pregnant women, parturient and nursing mothers may not be involved in research except if "the importance of the expected benefit to themselves or to the child is such as to justify the foreseeable risk incurred; this research is justified in terms of the expected benefit for other women in the same situation or for their child and provided that research of comparable effectiveness cannot be carried out on another category of the population. In this case, the foreseeable risks and constraints of the research must be minimal".
Therefore French law dealing with pregnant women, women giving birth or who are breastfeeding expressly allows trials on this category of person provided that the individual benefit is particularly great in view of the risks and that the trial is useful to persons of the same category.

Implementation in Spain

The Spain issued a Royal Decree No. 1090/2015 to adapt at the future application of CTR and to develop those aspects, which the regulation leaves to national legislation.
The RD 1090/2015 provides for that to obtaining and content of informed consent shall follow the provisions of Article 29 of CTR, as well as Articles 8 and 9 of

Regulation Law 41/2002, of 14 November. The person participating in the trial, particularly people with special vulnerability, will be informed of the access routes to the usual clinical practice for their pathology.

There is not any special rule or prevision about women and informed consent beyond these concerning pregnancy. Nevertheless, the Preamble of the Regulation 1090/2015 affirms that: "At the same time, it is necessary to promote clinical research of medicinal products aimed at the treatment of population groups such as women, ... traditionally poorly represented in clinical research".

In particular, with regard to pregnant or lactating women, the Decree explains that clinical trial may be carried out only if, in addition to the conditions laid down this Royal Decree, all the conditions listed in Article 33 of CTR are respected.

Understanding clinical trials results: public consultations for the implementation of Regulation (EU) 536/2014

At European level, in view of the entry into force of the new Regulation, the European Commission through the Directorate General launched public consultations for Health and Food Safety (DG Santé). Consultations, through which stakeholders express their opinion on documents annexed to the Rules of Procedure (prepared by the Expert Panel on Clinical Trials Regulation), ended on August 31, 2016.

The four topics are: Risk proportionate approaches in clinical trials; Summary of Clinical Trial Results for Laypersons; Definition of Investigational Medicinal Products ("IMPs") and use of Auxiliary Medicinal Products ("AMPs")" (previously called "Guidance on Investigational Medicinal Products ("IMPS") and Non-Investigational Medicinal Products ("NIMPs")); and Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors.

In particular, the subject of the second consultation is the Summary of Clinical Trial Results for laypersons, Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) 536/2014 on clinical trials on medicinal products for human use, which aims to provide suggestions for the aspects of experimentation to be drafted in a language that is understandably accessible and accessible to the non-specialized public.

The main objective of this document will be to provide recommendations for the production by investigators of a summary of clinical trial results for laypersons, in accordance with Annex V of the EU Clinical Trials Regulation. According to Article 37 of the Clinical Trials Regulation (EU) 536/2014, it is necessary that sponsors provide a summary of clinical trial results to the EU Portal and Database, in a format that is understandable to laypersons. The considerations presented touch upon the development of the content, language and literacy level to meet the needs of the public. Therefore, this aspect concerns communication and comprehension of clinical trials results.

3.4.4 Case law

Patient's right to be informed about her or his health is in the centre of attention of the healthcare system and it is considered by National and European case law.
There are many judgments concerning patient informed consent in clinical practice. In particular, most of these focus on liability of health professionals for lack of full information to patient. However even if the jurisprudence is copious in matter of clinical practice, the same attention is not reserved to issues concerning informed consent in clinical trials.
More specifically, the case law found, in compliance with the research protocol criteria, do not address gender issues regarding informed consent in clinical research.

3.4.5 Biobanks and protection of personal data

The European Union's actual regulatory framework in biomedical research is full of gaps. More specifically, the Directive 2001/20/EC on clinical trials do not apply to biobank-based research; the Directive 2004/23/EC (on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells) does not cover research using human tissues. However biomedical research carried out by using personal data is regulated in the EU Data Protection Directive (95/46/EC). Regarding to the processing of personal data and the protection of privacy in the electronic communications there is a new regulatory framework, introduced by the European Data Protection Regulation, that repealing Directive 95/46/EC. This Regulation came into force on 24 May 2016, but will be fully implemented from 25 May 2018. The Regulation introduces clearer rules on information and consensus. More specifically, novelties concern: principle of accountability, data protection impact assessment, privacy by design, privacy by default, obligation to keep a register of the processing activities carried out, the new figure of Data Protection Officer, right to data portability, right to cancellation.
The principles contained in the clinical trials and data protection laws lay down the relevant procedural rules to ensure the protection of individuals participating in biobank-based research.

3.4.6 The Food and Drug Administration's perspective

The FDA's regulatory measures is certainly an example of good legal practice regarding the involvement of women in clinical trials and the attention to sex-specific issues in drug response. The Agency took important steps to ensure that new drugs are properly evaluated in women. The prerequisite is that responses to drugs are influenced by many factors, including sex, age, ethnic background, metabolic phenotype.
Important safeguards regarding women's health are contained in the Code of federal

regulations (CFR). In particular, the CFR supports and facilitates the participation of women in clinical research, on the assumption that medical products can affect men and women differently. Sometimes women have different side effects. It is important that women participate to show if products are safe and work well in both men and women.

For research involving pregnant women, foetuses, or neonates the IRB approves the conduct of the research only if it finds that the research meets the regulatory criteria of Part 46 of Title 45 of the Code of Federal Regulations ("Additional Protections Pertaining to Research, Development, and Related Activities Involving Foetuses, Pregnant Women, and Human In Vitro Fertilization").

Federal Law establishes that pregnant woman may be involved as a subject in a human clinical research project only in determinate cases. The section of 45 C.F.R. 46 reads "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as ... pregnant women, ..., additional safeguards have been included in the study to protect the rights and welfare of these subjects". One wonders what aspect of pregnancy renders women particularly vulnerable to "coercion" or "undue influence". Research involving pregnant women is permitted only if: "(1) the purpose of the activity is to meet the health needs of the mother and the foetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the foetus is minimal". The mother and the father are legally competent and both have given their consent after having been fully informed regarding the possible impact on the foetus.

The federal regulation barring the use of pregnant women in research except in limited circumstances (45 C.F.R. § 46.207) is an example of a neutral policy (gender-neutral because it does not explicitly exclude all women as a class) that arguably results in disparate treatment of women (only women can be pregnant). An important government objective is protecting potential life and there is no intent to discriminate against women in creating the pregnancy classification.

The major relevant FDA's regulatory measures are: 1997 FDAMA Section 115: Clinical Investigations (b) Women and Minorities Regulation, with the goal of including more women and minorities in clinical trials; 1998 Demographic Rule – Amendments to Content and Format of a New Drug Application (21 CFR 314.50 (d). This final rule revised the NDA content and format regulations at 21 CFR 314.50 to require effectiveness data to be presented by gender, age and racial subgroups and dosage modifications be identified for specific subgroups; 1998 Investigational New Drug (IND) Applications - Annual Reports (21 CFR 312.33), that requires the partition in annual reports by sex, age, and race of data regarding participation in clinical trials. 2000 Amendment to the Clinical Hold Regulations for Products Intended for Life-Threatening Diseases (21 CFR 312.42). The regulation allowing the agency to halt research on drugs for life-threatening diseases and conditions if men or women who have the condition are excluded from study based on a perceived risk to their reproductive potential. The rule does not apply to conditions relevant to only one sex or gender, and it does not require researchers to enrol a specific number of men or women with reproductive potential rather it seeks to remedy the historic exclusion of women with a potentially deadly condition. By regulatory analysis done it emerges that for the FDA is important to adopt a gender approach to health aims to counteract inequalities, prejudices and stereotypes in clinical trials.

3.4.7 References

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Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg 2005)
European Union Law
Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive")

Directive 2002/58/EC of the European Parliament and of the Council of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector (Directive on privacy and electronic communications)

Regulation (EU) 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

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)

Austria
Bundesgesetz, mit dem das Arzneimittelgesetz, das Bundesgesetz über Krankenanstalten und Kuranstalten, das Arzneiwareneinfuhrgesetz 2002 und das Bundesgesetz über die Errichtung eines Fonds "Österreichisches Bundesinstitut für Gesundheitswesen" geändert werden, 2004.

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France
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Germany
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Italy
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The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 Statutory Instrument 2006 No. 1928

The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 Statutory Instrument 2006 No. 2984

USA
US Food and Drug Administration (FDA) FDA Modernization Act Public Law.

4. Recommendations

Age-related issues

1) Children sufficiently able to understand the proposed research should have the opportunity to be informed about the nature and the purpose of the research, related risks and burdens, expected benefits (direct or indirect). They should also be heard in order to ask questions and to express their will to participate.

2) Assent which is denied by a child should be considered binding if the minor is mature and the risk is high. Parental permission, without minor's assent, is sufficient only if direct benefit is expected to be obtained (for the best interest of the child), risk and burden are minimal and the minor is not sufficiently mature to express a valuable objection.

3) Tools and methods to assess the minor's degree of maturity should be adopted.

4) Risk assessment and communication are fundamental, but burden is an important factor to evaluate and communicate too when children are involved in clinical trials. Overall pain and separation from parents during the research must be considered, because they can affect the child's neurological, psychological and physical development.

5) Parents and children must be free from undue pressure and be informed of the possibility to give and revoke informed consent to clinical research without any prejudice for healthcare.

6) The principle of gratuitousness is pivotal to protect subjects involved in clinical trials, because prevents undue exploitation of vulnerable persons. Only reimbursement of justified expenses may be ethically acceptable (such as travel costs or accommodation). Informed consent should explicitly say that any kind of payment for the experimentation (direct or indirect) is ethically illicit. An independent research ethics committee must review and approve any reimbursement and check that there is no privilege given to subjects of experimentation. Undue inducement cannot be used as a means to reduce barriers that may discourage participation.

7) Involvement in clinical research should not be presented as a way to obtain better healthcare, as cure and care is due to each patients, regardless of participation to experimentation.

8) Confidentiality on minor's health data is mandatory. In some circumstances, when the minor is mature, confidentiality should be ensured also within the family, without sharing information with parents about adolescents if not necessary or without his/her permission for health purposes.

9) Communication strategies and tools for comprehension assessment should be defined, also by relying on ICT and multimedia.

10) Translation and cultural intermediation should be provided for families coming from different cultural backgrounds.

11) Information material for children should be based on the minor's level of maturity and his/her capacity of comprehension, not only on his/her age.

12) Informed consent must specify if healthy subjects are involved in the study: clinical research on healthy subjects requires risk and burden minimization and this aspect has to be adequately explained during the acquisition of informed consent.

13) "Partially restricted consent" or "dynamic consent" should be introduced to give consent to the use of minors' biological samples or data in the future. Subjects who reach the legal age to consent during the research should be given the opportunity to give informed consent to the storage and use of their specimens or data.

14) Information must clarify that children and their families are entitled to know any health information about them collected during the trials. Incidental findings should be fed back if concerning data are of immediate clinical relevance on preventive, diagnostic and therapeutic level and there is an interest of the minor to obtain direct benefits from the information disclosure.

Gender-related issues

1) Possible interactions between changes in women's physiological conditions and the use of experimental pharmaceuticals should be clearly conveyed in the informed consent process, with reference to the implications related to the fertility condition and the possible pregnancy and possible damages to the embryos and foetuses .

2) The informed consent should highlight benefits and any possible risks (specifying the extent, envisaged or potential) for embryos and foetuses in case of pregnancy: a fertile woman should be aware and fully informed of methods to avoid pregnancy before, during and after the trial (the period of risk is to be defined and communicated according to the type of trial). This information should be clearly provided by the researcher, respecting the woman's choices and moral or religious convictions. Communicating contraception requirements should also include referring to any inherent risks related to its use.

3) The woman should be given a fair amount of time and appropriate environmental conditions to make her free and informed decision and be aware of the possibility for her to revoke consent, at any time, during research, as well as informed of any risks also after experimentation related to the period of time.

4) Definitions of minimum risk and burden or above this minimum threshold should be provided in the context of clinical research, especially when dealing with fertile,

pregnant or breastfeeding women. This information should be clearly explained and communicated before any decision to participate is made.

5) For clinical trials including pregnant women, follow-up of the pregnancy, foetus and child is essential, even for several months after the end of the study. This safety requirement should be clearly communicated during the informed consent process.

6) If research is carried out on breastfeeding women, participants should be adequately informed of the need to monitor the possible excretion of the drug into human milk, as well as their babies for the effects of the drug.

7) Pregnant or breastfeeding women should be encouraged to involve their partners in the informed consent process. The degree of involvement of partners may be adapted to participation risks and requires the elaboration of adequate criteria, which need to be explicitly mentioned before experimentation.

8) Men participating in research which is potentially toxic for gametes or foetuses should not only receive clear and detailed information on the risks linked to their enrolment, but also be requested to involve their fertile or pregnant partners in the consent process. Criteria for their involvement should be defined.

9) Researchers should make sure that women from vulnerable social contexts, and with low literacy levels, have fully understood all benefits and risks related to clinical research enrolment and freely consented to participate. The possibility of cultural intermediation with a gender approach should be considered, in order to bridge communication gaps.

10) Caution is needed whenever low-income women are enrolled in research, in order to make sure they have not been coerced (through social conditioning or pressures by medical staff or research team) or unduly influenced (financially or offering better healthcare) to participate, in ways that would lead these women to accept a higher level of risk than would otherwise be acceptable to them. It is of paramount importance to verify that there is no underestimation of such aspects due to other priority interests.