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Paediatric Research under the New EU Regulation on Clinical Trials: Old Issues New Challenges

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Abstract

Regulating paediatric research means searching for the balance between two valuable goals: protecting children while ensuring they benefit from safe and efficient medicines. Different legal instruments were adopted in the EU in order to regulate clinical trials, foster paediatric research and promote European and international ethical guidelines. However a new Regulation on clinical trials was adopted in 2014, and might change the current framework of paediatric research. How does the new Regulation 536/2014 foster research on children taking into account both the EU Paediatric Regulation and the EU Ethical Recommendations? Does it live up to the standards of the Directive 2001/20/EC and does it represent a step forward in accordance with international ethical guidelines? This article shows that, despite the adoption of new rules, many clarifications are still needed. Stakeholders involved in paediatric research have to play a driving role in the implementation process of the new Regulation.

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1 Introduction

Regulating paediatric research means striking the right balance between two valuable goals: protecting children because they are vulnerable, and making sure they benefit from safe and efficient medicines. After the outrageous medical experiments performed on humans during the Second World War, there has been a tendency to exclude any vulnerable participants from clinical trials. With time, this well-intentioned reaction showed its limitations. Due to the fact that children's bodies could react differently to drugs as compared to adults but there has been a dearth of data regarding testing in children, many drugs were used off-label. Thus calls for safe and efficient medicines specifically for children arose.

The Directive 2001/20/EC¹, implementing ICH-GCP international guidelines, introduced for the first time specific provisions² aimed at favouring the conduct of ethically acceptable clinical trials in children³. These provisions were enhanced by the ICH-E11 specifically devoted to paediatrics⁴. In 2006, the Paediatric Regulation established "a system of both obligations and rewards and incentives"⁵ with the aim of fostering paediatric research⁶. One key measure of this Regulation is the institution, at the European Medicines Agency, of the Paediatric Committee (PDCO), in charge of giving advice and examining Paediatric Investigation Plans (PIP)⁷. Finally in 2008, EU Ethical Recommendations were developed with the aim of implementing non-binding ethical guidelines for Directive 2001/20/EC in the paediatric population.

However, the European legal framework and especially the Directive 2001/20/EC was deemed partly responsible for a dramatic increase in bureaucracy, costs and delays for launching clinical trials in the EU, leading to a 25% decrease in trials⁸ as well as to their off-shoring to emerging countries⁹. Those problems led to the elaboration and adoption of the new EU Regulation 536/2014¹⁰ on clinical trials, which repeals the Directive 2001/20/EC, and will be directly binding and applicable for all EU-Member States by 2016. The major changes are as follows: first, the application procedure will be simplified, notably for multinational clinical trials, thanks to a unique application submitted to a single submission portal¹¹. Second, assessment of the application is split in two: one part for the Reporting Member State (RMS), the other one for each Member State concerned by the trial¹². Third, a new category of clinical low-intervention trials was created in order to facilitate research, notably academic trials, when the drug being tested is already authorized and additional procedures involve only minimal risk and burden¹³. Finally, there are several provisions that could impact paediatric research. For example, there are new

¹ 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 (Hereafter "Directive 2001/20/EC")

² Directive 2001/20/EC, Article 4.

³ "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". Directive 2001/20/EC, Recital 3.

⁴ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Clinical Investigation of Medicinal Products in the Pediatric Population, E11, Geneva, 2000 (Hereafter "ICH E11").

⁵ Regulation (EC) N° 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 (Hereafter "Regulation 1901/2006"), Recital 6.

⁶ European Medicines Agency (EMA), Successes of the Paediatric Regulation after 5 years. August 2007-December 2012, EMA/250577/2013, London, 2013.

⁷ Paediatric Investigation Plans are documents "upon which the development and authorisation of medicinal products for the paediatric population should be based". Regulation 1901/2006, Recital 9.

⁸ European Commission, Impact assessment report on the revision of the "Clinical Trials Directive" 2001/20/EC, VOLUME I, Working Document Commission Services, SWD(2012) 200 final, Brussels, 17 July 2012, (Annexes), p. 9.

⁹ The 2013 EMA report shows that, between 2005 and 2011, only 38.1% of the patients in pivotal trials submitted in marketing authorization applications to the EMA were from the EU. EMA, Clinical trials submitted in marketing-authorisation applications to the European Medicines Agency ; Overview of patient recruitment and the geographical location of investigator sites. Containing data from 2005 to 2011, EMA/INS/GCP/676319/2012, London, 2013, p. 9.

¹⁰ Regulation (UE) n° 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 (Hereafter "Regulation 536/2014")

¹¹ Regulation 536/2014, Article 5.

¹² Regulation 536/2014, Articles 6 and 7. The whole process is submitted to strict timelines sanctioned by the tacit agreement principle. *Ibid.*, Preamble Recital 8.

¹³ Regulation 536/2014, Article 2.2(3).

criteria for the representativeness of subjects' age and sex to be similar to that of future patients¹⁴, the possibility to conduct trials with minors in emergency situations¹⁵, and the status of the PDCO.

How does the new Regulation foster paediatric research, taking into account the framework set up by the EU Paediatric Regulation? Does it implement the EU Ethical Recommendations; live up to the standards of the Directive 2001/20/EC; and represent a step forward in accordance with international relevant legal texts and guidelines?

This article will deal with specific novelties that might require further attention regarding their implementation in paediatric research, such as the concept of minimal risk introduced in the new EU regulation as a requirement to authorise paediatric trials (2); the new category of low-intervention trials and its applicability (3); the role and expertise of Ethics Committees in paediatrics (4), the newly introduced possibility of secondary use of children's data (5), as well as other internationally recognised ethical standards relevant to paediatrics that necessitate some clarification in the implementation of the new EU Regulation on clinical trials (6).

2 Minimal Risk: A Key but Still Heterogeneous Concept to Authorize Paediatric Trials

Whereas Directive 2001/20/EC only required risks to be minimized for children, the new Regulation introduces the criteria of minimal risk and minimal burden that now must be assessed "in comparison to the standard treatment of the minor's condition"¹⁶.

Except for the ICH-GCP¹⁷, many ethical guidelines consider "minimal risk" as a prerequisite for paediatric research (e.g. Declaration of Helsinki¹⁸, CIOMS guidelines¹⁹, UNESCO Declaration on Bioethics and Human Rights²⁰, EU Ethical Recommendations²¹). This is also the case for legal instruments such as the Oviedo Convention of the Council of Europe²² and its Additional Protocol on Biomedical Research²³, as well as most national laws in Europe (e.g. Austrian law²⁴, Danish

¹⁴ Regulation 536/2014, Article 6.1(b)i.

¹⁵ Regulation 536/2014, Article 35.2(a).

¹⁶ Regulation 536/2014, Article 32.

¹⁷ In the ICH guidelines, the requirement for conducting trials with persons who are not able to consent is that the foreseeable risks are low. ICH, Guideline for Good Clinical Practices, E6(R1), Geneva, 1996, § 4.8.14.b, p. 17.

¹⁸ WMA (World Medical Association), Declaration of Helsinki - Ethics principles applicable to medical involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Hereafter "Declaration of Helsinki"), §28.

¹⁹ "Minimal risk – that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination". CIOMS (Council for International Organizations of Medical Sciences), International Ethical Guidelines for Health-related Research Involving Humans, in collaboration with the World Health Organization (WHO), Geneva, 2002 (Hereafter 2002 CIOMS Guidelines), Guideline 10.

²⁰ United Nations Educational, Scientific and Cultural Organization (UNESCO), Universal Declaration on Bioethics and Human Rights, 2006, Article 7.b).

²¹ Ethical considerations for clinical trials performed in children. Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, final 2008, §11.1.

²² 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, Oviedo, 4 April 1997, ETS n°164, (Hereafter "Oviedo Convention"), Article 17.2.

²³ Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, Strasbourg, 25 January 2005, CETS n°195, (Hereafter "Additional Protocol"), Article 15.2.

²⁴ *Arzneimittelgesetz* (AMG), §42(2)2 ; as well as *Medizinproduktegesetz* (MPG), §51(2)2.

law²⁵, French law²⁶, German law²⁷, Dutch law²⁸, or Spanish law²⁹) and abroad (the US³⁰ and Canada³¹). However, most of these texts do not define what constitutes minimal risk. When definitions are provided, there is a lack of consistency among them. However, there exist two main interpretations of minimal risk: the US "absolute interpretation" (2.1) and the Council of Europe "relative interpretation" (2.2). The EU Ethical Recommendations introduce a third, compromise approach (2.3). Questions remain as to how the Clinical Trials Regulation 536/2014 interprets minimal risk criteria (2.4).

2.1 The US Absolute Interpretation of Minimal Risk

In the Code of Federal Regulations (CFR), 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"³².

This "absolute interpretation"³³, or "healthy child interpretation"³⁴, was first criticised because it could hinder valuable research by limiting acceptable risk to the very low risks that a healthy child faces in his daily life. Additionally, this interpretation, although restrictive in general, would not be protective enough in some cases. For example, healthy children might live in geographically or socially dangerous areas, which would lead to their inclusion in research of relatively high risk, which could still be minimal in comparison to their daily life³⁵. Even if several suggestions exist as to how to interpret the absolute definition of minimal risk³⁶, ambiguities remain as well as a lack of consensus on what is "small", "moderate", or "serious" risk of harm or "considerable" discomfort³⁷. The comparator of "daily-life" itself also has often been questioned³⁸.

²⁵ Act on Research Ethics Review of Health Research Projects as updated on 9 October 2013, Section 19(3)3.

²⁶ Code de la Santé Publique (CSP), Article L 1121-7.

²⁷ AMG, §41(2)2.d).

²⁸ Act of 26 February 1998, containing rules on medical research involving human subjects (Medical Research Act), Section 4.1.

²⁹ Law 14/2007, of 3 July 2007, on biomedical research, Article 20.2)b). Royal Decree 223/2004, of 6 February 2004, Article 4.b).

³⁰ Code of Federal Regulations (CFR), Title 45, Section 46.404 Research not involving greater than minimal risk.

³¹ Canadian Institute of Health Research (CIHR), Natural Sciences and Engineering Research Council of Canada (NSERCC), and Social Sciences and Humanities Research Council of Canada (SSHRC), Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 2010, Articles 3.7.a and 6.12.

³² CFR, Section 46.102 (i); This is almost similar to the previously mentioned definition of the CIOMS, except that the 2002 CIOMS guidelines do not refer to the daily-life but only to medical and psychological examinations. 2002 CIOMS Guidelines, Guideline 10.

³³ Westra A. E. *et al.*, "How best to define the concept of minimal risk", *Journal of Pediatrics*, Vol. 159, n°3, 2011, p. 496.

³⁴ Binik A., "On the minimal risk threshold in children", *American Journal of Bioethics*, Vol. 14, n°9, 2014, p. 3.

³⁵ *Ibid.*, p. 4.

³⁶ For instance: to "limit the comparison of risks in nontherapeutic research to the risks posed by activities in daily-life that are designed to benefit others". Wendler D., "Justice and nontherapeutic pediatric research", *American Journal of Bioethics*, Vol. 14, n°9, 2014, pp. 13-15; or to distinguish between minimal risk of discomfort and minimal risk of harm. Westra A. E. *et al.*, "How best to define the concept of minimal risk", *op. cit.*, p. 497.

³⁷ *Ibid.*, p. 500.

³⁸ *Ibid.*, p. 497.

This restrictive interpretation of minimal risk is balanced with possible exceptions. Specific conditions have been required in the CFR³⁹, but more importantly, a crucial role is given to the IRB in the assessment of risk and the approval of the trial in accordance with these conditions⁴⁰.

2.2 The Council of Europe Relative Interpretation of Minimal Risk

According to the Council of Europe⁴¹, research is deemed to bear 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"⁴².

It is further specified that "minimal risk and minimal burden depend on the current state of knowledge and availability of procedures, and less invasive procedures should be utilised once they become available"⁴³. Precise examples clearly show that the interpretation of minimal risk is relative, which means that it depends on each individual, his/her condition and treatment. This is the case, for instance, of taking small additional tissue samples "at the time when tissue samples are being taken, *i.e.* a surgical operation".

This interpretation is "relative"⁴⁴ because it has to be assessed on a case-by-case basis, for instance distinguishing between the daily risks of healthy children versus sick children⁴⁵. It depends on the specific risks that the research subject faces in his/her daily life. Therefore this interpretation of minimal risk is called "subject of research interpretation"⁴⁶. The advantage and danger of this interpretation is that it permits to conduct research with higher risks in sick children. It might promote knowledge about their disease, but it also results in weaker protection of yet particularly vulnerable children. Can illness be a legitimate reason for treating children differently⁴⁷? In any case, in both its texts, the Council of Europe excludes trials for children with any increase over minimal risk. The Council of Europe specifies that "any consideration of

³⁹ CFR, Section 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects. CFR, Section 46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition. CFR, Section 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

⁴⁰ In summary, "greater than minimal risk" is allowed when there is a prospect of direct benefit, if the balance risk/benefit is at least as favourable as that presented by available alternative approaches. But it can also be allowed without prospect of direct benefit to the child, if it is likely to yield generalizable knowledge about the subject's disorder or condition and if the procedures involved in the research are "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations" (45 CFR 46.406). In this case, the risk has to represent a "minor increase over minimal risk", according to the IRB (Institutional Review Board) evaluation. Finally, it could be possible to carry out "research not otherwise approvable" if it presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of the child and if it will be conducted "in accordance with sound ethical principles" (45 CFR 46.407). In any case, adequate provisions have to be made for soliciting the assent of the children and permission of their parents or guardians.

⁴¹ The Oviedo Convention does not exactly define the minimal risk for children, but provides a long list of examples in its Explanatory report. For instance: "obtaining bodily fluids without invasive intervention, e.g. taking saliva or urine samples or cheek swab; at the time when tissues samples are being taken, for example during a surgical operation, taking small additional tissue samples; taking a blood sample from a peripheral vein or taking a sample of capillary blood; minor extensions to non-invasive diagnostic measures using technical equipment, such as sonographic examinations, taking an electrocardiogram following rest, one X-ray exposure, carrying out one computer tomographic exposure or one exposure using magnetic resonance imaging without a contrast medium". Explanatory report to the Additional Protocol, §100.

⁴² Additional Protocol, Article 17.1.

⁴³ Explanatory report to the Additional Protocol, §96.

⁴⁴ Westra A. E. *et al.*, "How best to define the concept of minimal risk", *op. cit.*, p. 495.

⁴⁵ "However, for certain participants, even these procedures might entail risk or burden which cannot be considered minimal. Assessment on an individual basis must therefore be carried out". Explanatory report to the Additional Protocol, §100.

⁴⁶ Binik A., "On the minimal risk threshold in children", *op. cit.*, p. 4.

⁴⁷ *Ibid.*, p. 5.

additional potential benefits of the research shall not be used to justify an increased level of risk or burden"⁴⁸.

2.3 The EU Ethical Recommendations: A Compromise Approach Toward Minimal Risk

The EU Ethical Recommendations allow research with children when there is minimal risk and a prospect of benefit for the individual or for the group with the same condition. A minor increase over minimal risk is permitted when there is a benefit for the individual or for the group, but only if the risk/benefit ratio is at least as favourable as that of available alternative approaches. Finally, the Recommendations allow a greater than minor increase over minimal risk, but only when there is a benefit for the participant, and only if the risk/benefit ratio is especially favourable in relation to available alternatives approaches for the individual condition.

The EU Ethical Recommendations for paediatric research released in 2008 tried to find a balance between the two existing approaches. They refer to the texts of the Council of Europe and use a relative interpretation of minimal risk as they compare it to the risks of the participant's condition and treatment⁴⁹. However, without referring to risks in daily-life, the EU Ethical Recommendations also seem to be aligned with the US absolute interpretation. The EU Ethical Recommendations consider "minimal risk" in a literal way, *i.e.* as a risk that would be minimal in every possible situation, similar to interpretation by the CFR. This explains why the Recommendations' examples of minimal risk⁵⁰ are in sharp contrast to those from the Oviedo Convention and on the contrary, why the EU Ethical Recommendations define exceptions to minimal risk⁵¹, similarly to the CFR.

As a consequence, European legal texts referring to the criteria of minimal risk are inconsistent: on the one hand there is the Oviedo Convention and its "relative interpretation" of minimal risk, while on the other hand, the EU Ethical Recommendations offer a compromise between this interpretation and the 'absolute interpretation' inspired by US regulations. This inconsistency can lead to differences in the assessment of paediatric trials and consequent approval of the same research protocol⁵². One example demonstrates that the EU Ethical Recommendations are not protective enough because of this possibility to authorise a minor increase over minimal risk⁵³,

⁴⁸ Additional Protocol, Article 15.2 ii.

⁴⁹ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, 12.1.

⁵⁰ "No or minimal risk: history taking, clinical examination, auxological measurements, tanner staging, behavioural testing, psychological testing, quality of life assessment, venepuncture, heel prick, finger prick, subcutaneous injection, urine collection with bag, breath condensate collection, collection of saliva or sputum, collection of hair sample, collection of tissue removed from body as part of medical treatment, topical analgesia, stool tests, Bio-impedancemetry, transcutaneous oxygen saturation monitoring (pulse oxymetry), blood pressure monitoring, electroencephalography, electrocardiography, vision or hearing testing, ophthalmoscopy, tympanometry, lung function tests (peak flow, exhaled NO, spirometry), oral glucose tolerance test, ultrasound scan, digitally amplified chest or limb X-ray, stable isotope examination)". Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, Annex 4, p. 30.

⁵¹ "Minor increase over minimal risk: Urine collection via endoluminal or suprapubic catheter, Arterial puncture, Umbilical catheter, pH metry, Nasogastric tube insertion and use, Transcutaneous oxygen or carbondioxide tension monitoring, Electrophysiological measurements (using stimulation), Exercise testing (ergometry, spiroergometry), Raised volume pulmonary function testing (infants), Peripheral venous lines, Polysomnography, Fasting (≥ 1 meal), Spinal CSF tap, Bone marrow aspiration, MRI scan, X-ray other than digitally amplified chest or limb X-ray, CT scan*, X-ray DEXA bone density measurement, Use of contrast media, Paracentesis, Skin punch biopsy, Airways or skin hyperreactivity challenge test"; "Greater than minor increase over minimal risk: Heart catheterisation, Endoscopy, Biopsy, Surgery or modification of standard surgical procedure carried out as part of medical treatment, Sedation, Anaesthesia, Systemic analgesia, Hypoglycaemia test, Unstable isotope usage, PET scanning". Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, Annex 4, p. 30.

⁵² Westra A. E. *et al.*, "Drug development for children : How adequate is the current European ethical guidance ?", *Archives of Disease in Childhood*, Vol. 95, n°1, 2010, p. 3.

⁵³ *Ibid.*, p. 5.

which is not even the highest risk that the document allows. The Oviedo Convention, supposedly more permissive with a relative interpretation of minimal risk, was on the contrary too restrictive and thus more likely to limit research.

2.4 Minimal Risk in the New EU Regulation on Clinical Trials

The new Regulation's formulation, referring to the standard treatment of the minor's condition, suggests that the interpretation of minimal risk will be relative because it depends on the minor's condition and treatment. Does it mean that the level of acceptable risk can vary according to each child? If so, does it mean that children who are exposed to more risks should be exposed to even higher risks? Or does the notion of minimal risk entail only risks that are minimal in comparison to any treatment? Unfortunately, the Regulation does not provide any further indication on how to define minimal risks in practice.

This seems to be quite surprising given that the notion of risk is part of a broader challenge: implementation of a risk-adapted approach to clinical trials⁵⁴. Furthermore, the sole notion of risk causes implementation problems, as brought to the attention of the European Commission during the legislative process by the Bioethics Committee of the Council of Europe⁵⁵ as well as by EU Parliament members in their 2013 amendments⁵⁶.

Questions clearly remain and it is evident that the new Regulation could benefit from further clarifications or conceptualization on risk and minimal risk, especially if we consider that many other interpretations could serve as a guide for risk-adapted implementation of the Regulation 536/2014 such as those contained in the Canadian Tri-Council Policy Statement⁵⁷ or the recommendations of the Organisation for Economic Co-operation and Development (OECD)⁵⁸.

In this context, there is no doubt that heterogeneous interpretations of minimal risk, and more generally the vagueness of the notion of risk, could raise uncertainties with respect to evaluating trial protocols and assessing when a trial should be considered as low-intervention.

⁵⁴ It consists in building a framework which strictness would be proportionate to the level of risk involved in the trial. Rid A., "How should we regulate risk in biomedical research? An ethical analysis of recent policy proposals and initiatives", *Health Policy*, Vol. 117, n°3, 2014, pp. 409-420.

⁵⁵ Bioethics Committee (DH-BIO), "Commentaires sur la proposition de Règlement du Parlement européen et du Conseil relative aux essais cliniques de médicaments à usage humain et abrogeant la directive 2001/20/CE à la lumière de la Convention sur les Droits de l'Homme et la biomédecine et de son Protocole additionnel relatif à la recherche biomédicale", DH-BIO (2012) 24, 2012, , p. 4.

⁵⁶ Notably in order to distinguish between 1) risks for physical integrity, 2) risks for individual rights of the participants, and 3) risks for data integrity and public health (which are quite similar to the OECD recommendations). Willmott G., Committee on the Environment, Public Health and Food Safety (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369 – C7 0194/2012 – 2012/0192(COD)), A7-0208/2013, Strasbourg, 7 June 2013, Amendment 274, p. 136.

⁵⁷ The Canadian Tri-Council Policy Statement, define minimal risk as the risk in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that relate to the research. CIHR, NSERCC, SSHRCC, "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans", 2010, Chapter 2, section B.

⁵⁸ The OECD suggested to compare the additional or incremental risk for the subject participating in a trial with the risk of non-participation, *i.e.*, "the risk of usual care for patients (or the risk of daily life for healthy volunteers)". Organisation for Economic Co-operation and Development (OECD), "OECD Recommendation on the Governance of Clinical Trials", 2013, p. 23.

3 Low-Intervention Trials Notion and Applicability

One main novelty in Regulation 536/2014 is the introduction of a new category of clinical trials, the low-intervention trial. The Regulation aims to facilitate trials⁵⁹ with already authorised medicinal products either when used in accordance with their Marketing Authorization or their use is "evidence-based and supported by published scientific evidence"⁶⁰. In any case, any additional diagnostic or monitoring procedures have to pose no more than "minimal additional risk or burden to the safety of the subjects compared to normal clinical practice"⁶¹. The low-intervention trial category could become a very useful tool in paediatric research in order to properly test drugs in children and report on, after marketing authorization, off-label uses of drugs in paediatric medicine's daily practice. This procedure, which is more flexible and yet less consuming in terms of time and money, could also motivate sponsors to invest in research that focuses more on the needs of children, particularly academic sponsors for which clinical trials are far too expensive otherwise.

However, the main problem with implementation of this new category is the interpretation of the notion of "normal clinical practice". Usually, trials in minors must entail only minimal risks and burden in comparison "with the standard treatment of the minor's condition" while for a low-intervention clinical trial, any additional risk or burden need to be compared with "normal clinical practice". At first sight, standard treatment of a minor's condition has a greater likelihood to entail higher risks (e.g., a standard treatment in paediatric oncology) as compared to normal clinical practice, when we understand normal clinical practice as "routine examination". Do the expressions "standard treatment" and "normal clinical practice" designate the same thing? If so, why do legislators use two different expressions? If not, what is the exact difference? Furthermore, should we consider normal clinical practice for a healthy or sick child? In the EU Regulation, normal clinical practice is defined as the "treatment regime typically followed to treat, prevent, or diagnose a disease or a disorder". This notion is crucial because it determines an acceptable level of risk in low-intervention clinical trials⁶².

It is understandable to harbour some doubts in relation to this notion, notably its vagueness. Does "normal" mean the statistically most frequent practice? If so, how are Ethics Committees going to gather empirical data on each type of practice? Or does "normal" mean the latest available treatment? The German Medical Association asserts that "the standard of care should be based on the most up-to-date scientific knowledge, not on normal clinical practice. The definition should be defined more precisely"⁶³. In the same direction, the OECD recommendations distinguish between "standard of care" as the "treatment regimen or medical management based on state of the art participant care"⁶⁴ and "usual care" (which could be similar to the EU normal clinical practice definition) defined as the use of a medicinal product "in accordance with the marketing authorisation"⁶⁵. Several associations also have concerns and suggest to instead employ the expression "best current evidenced-based intervention"⁶⁶. An amendment was

⁵⁹ There will be more flexibility in the content of the application, traceability, and in damage compensation system, shorter timelines and sometimes even simplified informed consent. Regulation 536/2014, Articles 76.3 and 3.3.c.

⁶⁰ Regulation 536/2014, Article 2.2(3)b.

⁶¹ Regulation 536/2014, Article 2.2(3)c.

⁶² Regulation 536/2014, Article 2.2(2).

⁶³ German Medical Association (GMA), "Response to the European Commission on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM/2012/369)", 2012, p. 11.

⁶⁴ OECD, "OECD Recommendation on the Governance of Clinical Trials", 2013, p. 44.

⁶⁵ *Ibid.*, 2013, p. 24.

⁶⁶ The term "best current proven intervention", defined as "the treatment regimen followed to treat, prevent, or diagnose a disease or a disorder according to current reliable scientific evidence" (amend Article 1(6) of the proposed Regulation), should replace the term "normal clinical practice" throughout the text. Association Internationale de la

presented in the parliamentary report in 2013, suggesting that the notion required concrete implementation guidelines from the Commission in order to avoid contrasting interpretations from each Member State⁶⁷. Unfortunately, the amendment was not adopted in the final version, and the notion was not more clearly defined. The assessment of low-intervention trials could be particularly complicated in paediatric research where the concept of normal clinical practice is even less clear, largely because of widespread "off-label" use of medicines in children.

4 The Role and Expertise of Ethics Committees in Paediatric Research

Trial applications must undergo ethical review⁶⁸, as conducted by an Ethics Committee (EC). Risk/benefit evaluation is to be carried out, within stringent and compulsory timelines, by the Reporting Member State (RMS) (Part I of the assessment), whereas the assessment of ethical and local aspects (such as the informed consent...) is to be carried out by all the Member States acting individually (Part II of the assessment). Risk-benefit is thus assessed only by the RMS and not also by the Ethics Committee at national level. It means that, despite the existing international guidelines and literature, the risk-benefit assessment is *de facto* taken out of the "ethical domain". While the RMS's assessment and decision are valid to all other EU Member States⁶⁹, the new Regulation could lead to sponsors giving preference to some states over others⁷⁰. This issue reflects the EU's general reluctance to address ethical issues in this regulation, such as the definition of ECs⁷¹, harmonization of different ethical review systems⁷², and practical and

Mutualité (AIM) *et al.*, Joint Analysis "New Proposal for a Regulation on Clinical Trials: - The protection of human subjects must be upheld - Citizens' right to information must be strengthened", 2013, p. 8.

⁶⁷ Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*, Amendment 12, p. 12.

⁶⁸ Regulation 536/2014, Article 4.

⁶⁹ Member States can only opt-out from the trial, but without having any impact on the decision regarding the trial application. Regulation 536/2014, Article 8.2.c.

⁷⁰ The chosen RMS can only refuse this appointment if other Member States concerned manage to agree on one of them being appointed. Regulation 536/2014, Article 5.

⁷¹ Regulation 536/2014, Article 2.2(11). An Ethics Committee is defined as "an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions for the purpose of this Regulation, taking into account the views of laypersons, in particular patients or patients' organisations". This new definition seems to have undergone quite a few cuts, notably on the symbolic statement of the ECs role to "protect the rights, safety and wellbeing of human subjects" and "to provide public assurance of that participation" foreseen in Directive 2001/20/EC. Directive 2001/20/EC, Article 6.

⁷² The European Commission released a proposal in 2012 which had deleted any reference to ethics except for the provision stating that it is not part of the competence of the EU and should therefore be at the discretion of national laws (European Commission, "Proposal for a Regulation 2012/0192 of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, COM(2012) 369 final", Recitals 6 and 12.); Many reactions from the scientific and academic community lead to the reestablishment of the ECs thanks to parliamentary amendments. But as underlined, this reestablishment was only done half-heartedly; For more on the topic: Bioethics Committee (DH-BIO), "Commentaires sur la proposition de Règlement du Parlement européen et du Conseil relative aux essais cliniques de médicaments à usage humain", *op. cit.*; European Group on Ethics in Science and New Technologies (EGE), Statement on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM 2012) 369 final, 2012; Nys H., "New European rules regarding the approval of clinical trials, the role of ethics committees and the protection of subjects", *Archivum Immunologiae et Therapia Experimentalis*, n°60, 2012, pp. 405-414; Den Boer A. et Schipper I., "New EU regulation on clinical trials : The impact on ethics and safeguards for participants", *Indian Journal of Medical Ethics*, Vol. X, n°2, 2013, pp. 106-109; Heringa J. & Dute J., "The proposed EU-regulation on clinical trials on medicinal products : An unethical proposal ?", *European Journal of Health Law*, n°20, 2013, pp. 347-362; Global Research in Paediatrics (GRiP), Children matter: important amendments in the draft Clinical Trials Regulation, 2013; Westra A.E. *et. al.*, "New EU clinical trials regulation needs a few tweaks before implementation", *BMJ*, Vol. 348, 2014, pp. 1-2.

operational aspects of the assessment of part II⁷³. This reluctance is just one of many issues that ECs face with respect to paediatric research, including the question of their paediatric expertise (4.1), their collaboration (4.2), and interaction with Paediatric Committee (PDCO) PDCO (4.3).

4.1 Paediatric Expertise of Ethics Committees

The new Regulation did not really change the requirement from Directive 2001/20/EC that ECs have paediatric expertise or take "advice in clinical, ethical and psychosocial problems in the field of paediatrics" for trials on children⁷⁴. These provisions, however, were thoroughly supplemented by the EU Ethical Recommendations, by adding requirements for ECs' members to demonstrate proper documented education and experience in the various aspects of working in paediatrics⁷⁵. This document gives precise indications of what constitute paediatric expertise which goes "beyond having professionally worked with children and could be defined on the basis of education, training and experience on the various aspects of child development, ethics and psychosocial aspects"⁷⁶. It also recommends having a specialised EC in paediatrics "for the evaluation of trial protocols that are complex or in serious paediatric diseases"⁷⁷.

The new Regulation does not yet satisfy these recommendations as it does not consider any of these and instead, adopts the formulation of the Directive 2001/20/EC almost word for word⁷⁸. One amendment had been suggested, emphasising the need of paediatric expertise of the EC when the trial involves children⁷⁹, but was not adopted in the final version. This is unfortunate and surprising, as a survey involving ECs in Europe demonstrates ECs' lack of knowledge on both legal and ethical aspects of paediatric research, and the need of training and education of ECs in paediatrics⁸⁰.

4.2 Collaboration of European Research Ethics Committees in Paediatrics

An EU-wide study identified networking among ECs as a fundamental tool for enhancing collaboration, experience and information exchange⁸¹, especially on ethical issues including procedures and principles of ethical assessment. The need of a network or platform organized at the European level was suggested at multiple times^{82 83 84}. Two amendments, submitted in 2013 for an organisation at the European level of a network of ECs, argue that it is the role of the Commission to set up a European Platform to bring consistency in ethical reviews by encouraging

⁷³ The Part II data sent through the EU portal does not appear to include approval of ethical aspects by the EC, although it specifically concerns ethical aspects. Petrini C., "Regulation (EU) n° 536/2014 on clinical trials on medicinal products for human use : An overview", *Ann Ist Super Sanita*, Vol. 50, n°4, 2014, p. 320.

⁷⁴ Directive 2001/20/EC, Article 4.h.

⁷⁵ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §8.

⁷⁶ The rest of the recommendation gives examples of paediatric expertise: "Therefore, this would include i) physicians with paediatric qualification; ii) paediatric ethicists; iii) a paediatric pharmacologist, iv) qualified paediatric nurses or psychologists, etc", the experts also have to demonstrate and document their experience with children in addition to expertise. *Ibid.*, §8.1.

⁷⁷ *Ibid.*, §8.

⁷⁸ Regulation 536/2014, Recital 19 and Article 10.1.

⁷⁹ "In cases of clinical trials involving minors, the ethics committee shall include at least one healthcare professional with paediatric expertise". Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*, Amendment 64, §2, 10a (new).

⁸⁰ Altavilla A. *et al.*, "Impact of the new European paediatric regulatory framework on ethics committees: Overview and perspectives", *Acta Paediatrica*, Vol. 101, n°1, 2012, p. 5.

⁸¹ *Ibid.*, p. 5.

⁸² European Commission, Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC. Summary of the responses to the public consultation paper, SANCO/C/8/SF/dn D(2010) 380240, 2010, p. 6.

⁸³ European Commission, Revision of the "Clinical Trials Directive" 2001/20/EC. Summary of the replies to the public consultation on the "Concept Paper", SANCO/D/3/PB/SF/ddg1.d.3(2011)816084, 2011, §38, p. 5.

⁸⁴ A quality and accreditation system could be established for all Ethics Committees so that all trials are reviewed by "competent" bodies playing a key role also in the "risk-benefit assessment". Westra A.E. *et. al.*, "New EU clinical trials regulation needs a few tweaks before implementation", *op. cit.*

cooperation and sharing of best practices among ECs⁸⁵. This proposal is particularly important if we consider that ethical and legal disparities among Member States are still a major concern, possibly leading to so-called "ethics shopping", as highlighted by different stakeholders and by the European Group of Ethics⁸⁶. Unfortunately, none of those potentially helpful suggestions has been adopted during the legislative process of the new EU Regulation on clinical trials.

Actually a network (EUREC) bringing together national Research Ethics Committees (REC) associations, networks or comparable initiatives on the European level exist. It aims at promoting awareness of specific working practices of RECs across Europe, enhancing the shared knowledge base of European RECs⁸⁷. Nevertheless, as clinical trials in children shows very distinct particularities and challenges, there is still a need for a specific network among ECs involved in paediatric research. To promote and foster their cooperation and improve their expertise, best practice models of ethical evaluation of paediatric trials should be developed. A quality and accreditation system could be established for these Committees so that all trials are reviewed by "competent" bodies playing a key role also in the "risk-benefit assessment"⁸⁸ particularly complex for children.

4.3 Interactions with the Paediatric Committee (PDCO)

However, at the European institutional level, the new Regulation confirms the importance of the role of the Paediatric Committee (PDCO) by expressly requiring the opinions of the latter to be taken into account in the assessment of anticipated therapeutic and public health benefits⁸⁹.

Still there remain uncertainties about the roles of ECs and their interactions with the RMS authorities and PDCO. Coordination between competent authorities and ECs will need to be carefully established, particularly when Part I and II are presented together and the two assessments are processed in parallel within the same national timetable⁹⁰. What happens when the PDCO gives the approval to the Paediatric Investigation Plan but the RMS and/or the EC does not approve the protocol of the same trial? The decision of the EC will entail more than balancing risk/benefit because it takes into account the whole protocol. On the contrary, the protocol was not yet designed at the time of the PDCO's decision, which only concern the PIP. Nevertheless as you would expect, the PDCO has a paediatric expertise that the EC and the national authorities in charge of the protocols evaluation does not necessarily have. Whose decision should prevail over the other? Further clarification would be helpful regarding interaction with authorities involved in the protocol review, ethical review conducted at a national level, evaluation of PIPs

⁸⁵ "Currently, the ethical review procedure varies greatly between Member States, often with various bodies at national, regional and local levels, and multiple procedures leading to divergent assessments. This is a source of delays and fragmentation. In the interests of European patients and public health, the procedures and principles of ethical review should be better harmonised through the sharing of best practices between ethics committees. To this end the Commission should facilitate the cooperation of ethics committees". Willmott G. (ENVI), Report on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*, Amendment 27, Recital 14b (new); See also: "The Commission shall facilitate cooperation of ethics committees and the sharing of best practices on ethical issues including the procedures and principles of ethical assessment". *Ibid.*, Amendment 79, Article 4a (new) 2.

⁸⁶ EGE, Statement on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, *op. cit.*

⁸⁷ EUREC is connected with the EURECNET Project that is a consortium of twenty European research facilities which has been established in March 2011 and is being funded by the European Commission under Framework Program 7 (FP7). It is coordinated by the German Reference Centre for Ethics in the Life Sciences (DRZE). Following already existing efforts, especially efforts within a previous project (EUREC), one of its primary objectives is to foster a sustainable infrastructure for European RECs. <http://www.eurecnet.org/index.html>.

⁸⁸ Westra A.E. *et. al.*, "New EU clinical trials regulation needs a few tweaks before implementation", *op. cit.*

⁸⁹ Regulation 536/2014, Article 6.1.b.i.

⁹⁰ Petrini C., "Regulation (EU) n° 536/2014 on clinical trials on medicinal products for human use : An overview", *op. cit.*

by the paediatric experts of PDCO, as well as detailed criteria and ethical guidelines for systematic use in the assessment of protocols and PIPs⁹¹.

5 Secondary Use of Data in Children

One novelty of the Regulation 536/2014 is the introduction of secondary use of data collected in children: "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 or her legally designated representative at the time when the subject or the legally designated representative gives his or her informed consent to participate in the clinical trial to consent to the use of his or her data outside the protocol of the clinical trial exclusively for scientific purposes. That consent may be withdrawn at any time by the subject or his or her legally designated representative"⁹².

This new provision seems to be helpful to avoid unnecessary replications of trials and develop useful epidemiological studies, especially for generating data on children⁹³. However, this "broad consent", given in advance, will never be as precise and informed as a repeated informed consent procedure. Even if doing so proves to avoid additional risks to children, because the samples are already obtained, a broad parental consent deprives the child of the opportunity to exercise autonomy, by not allowing his/her ratification of the parental consent at a later date. This problem could be particularly relevant in longitudinal studies that imply a potentially lengthy period of involvement of children. Moreover, if the minor keeps the right to withdraw his/her consent, notably when becoming legally competent, he/she has to be able to exercise this right. This means that he/she has to be informed of the existence of a new study. Thus it implies that re-identification of his/her data must be possible.

Furthermore, different legislations have adopted different definitions to guarantee the confidentiality of personal data⁹⁴. Terms such as "anonymization", "pseudonymisation", "codification", and "de-identification" are indiscriminately used in guidelines and legal texts to indicate similar concepts as different requirements and level of confidentiality protection have been identified taking into account the notion of "reversibility" within the data processing procedures⁹⁵. That's why it is important to have clear definitions and frameworks, so that parents and minors know exactly what they consent to when they are told that their child's information will be coded or anonymized. Finally, specific requirements must be established with reference to specific data, such as genetic data, which can raise concerns in terms of equity and discrimination especially for children. Precise definitions and provisions need to be developed, guaranteeing transparency to minors and legal representatives, and assuring legal certainty. Perhaps the forthcoming reform of the EU data protection legal framework will bring some answers to these questions⁹⁶.

⁹¹ Enpr-EMA has set up a Working Group to gather examples of "good practice when ECs consider trials related to children and young people" and to develop proposals to disseminate those examples. Enpr-EMA, Mandate of the Enpr-EMA working Groups, EMA/493016/2013Rev.1, 2014, p. 4.

⁹² Regulation 536/2014, Article 28.2.

⁹³ Regulation 1901/2006, Article 41; Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §19.

⁹⁴ Canadian guidelines differentiate between directly identifying information, indirectly identifying information, coded information, anonymized information and anonymous information. For more details: Centre of Genomics and Policy (CGP), Maternal Infant Child and Youth Research Network (MICYRN), Best Practices for Health Research Involving Children and Adolescents, 2012, p. 92.

⁹⁵ Global Research in Paediatrics (GRiP), Report on ethical and governance issues related to processing of healthcare data, D.2.04, 2015.

⁹⁶ European Commission Website, http://ec.europa.eu/justice/data-protection/review/index_en.htm.

6 Other Relevant Ethical Standards Impacting Paediatric Research

There are other issues that require attention towards paediatric research. All of these are included in the EU Ethical Recommendations, and often correspond to internationally recognised ethical and methodological standards. Here we address those issues that require specific mention within the framework of the new EU Regulation.

6.1 Assent/Dissent and Compensation: a step forward with need of clarification

The notion of assent, introduced by the Declaration of Helsinki⁹⁷ and mentioned in the WHO-CIOMS⁹⁸ and ICH-E11 guidelines⁹⁹, was introduced into the EU legal framework only with Regulation 536/2014¹⁰⁰. Nevertheless, Member States still have a large margin within which to manoeuvre in applying this principle, again possibly leading to some disparities, especially with multinational trials.

The new Regulation is significantly progressive with respect to "dissent" of the child. While Directive 2001/20/EC notes that dissent of the child has to be "considered"¹⁰¹, the new Regulation now expects it to be "respected": "the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator"¹⁰².

Best-practice guidelines that take into account national legislations and are based on a well-sustained methodological approach should be developed. Specific requirements to obtain the child's assent, adapted to different age-ranges, provided in the EU Ethical Recommendations¹⁰³, as well as international provision related to the respect of refusal¹⁰⁴ could be an important starting point for the implementation of these guidelines. Regarding compensation, the new Regulation changes the provision applicable in the EU, stating that "no incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in the clinical trial"¹⁰⁵.

This provision is quite progressive compared to the Directive 2001/20/EC, which forbade financial incentives but allowed "compensation" without further detail on the nature and extent of this compensation¹⁰⁶. The new Regulation implements and supplements the EU Ethical

⁹⁷ Declaration of Helsinki, §29.

⁹⁸ 2002 CIOMS Guidelines, Guideline 14.

⁹⁹ ICH E11, §2.6.3, p. 11.

¹⁰⁰ EU Member States may foresee, in their national law, that the «minor who is capable of forming an opinion and assessing the information given to him or her, should himself or herself assent in order to participate in a clinical trial». Regulation 536/2014, Recital 32 and Article 29.8.

¹⁰¹ Directive 2001/20/EC, Article 4.c.

¹⁰² Regulation 536/2014, Article 32.1.c

¹⁰³ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §5.7, §6.1, §6.4 and §7.

¹⁰⁴ Oviedo convention, Article 17.1.v; United Nations Commission on Human Rights (UNCHR), Convention on the Rights of the Child of 20 November 1989, Article 12.1.

¹⁰⁵ Regulation 536/2014, Article 32.1.d).

¹⁰⁶ Directive 2001/20/EC, Article 4.d.

Recommendations¹⁰⁷. The EU framework on clinical trials might now be stricter than the Council of Europe Conventions¹⁰⁸ and U.S. legislation¹⁰⁹.

However, questions remain concerning the definitions of "inducement" or "incentive"¹¹⁰. It is not clear what the two terms in the new Regulation really entail. Therefore, it is also not clear which exact elements ECs should examine when reviewing payments. What constitutes an undue influence can be very different depending on the age of the minor, familial background and his/her financial or social situation¹¹¹.

6.2 Measures to Minimize Pain, Risk Monitoring and Use of Placebos: Missed Chances for Improvement

Directive 2001/20/EC required trials with minors and incapacitated adults to be "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"¹¹². With the new EU Regulation, this is now a general provision for all participants and not only children and incapacitated persons¹¹³.

Yet the EU Ethical Recommendations give thoroughly detailed guidelines on how to minimise pain, distress and fear in children, taking into account age and condition-appropriate validated scales. Furthermore, the document underlines the requirement to limit investigations/interventions to the minimum necessary for obtaining valid data (e.g., using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling). Surprisingly, the new EU Regulation does not mention any of these recommendations or even the fact that children deserve specific attention and care to prevent physical and emotional pain and distress.

Furthermore, whereas the EU Ethical Recommendations expressly recommend to monitor the level of risk especially for paediatric populations¹¹⁴ and to use a Data and Safety Monitoring Board (DSMB), the new EU Regulation only requires investigators to monitor three elements¹¹⁵, including risks but only indirectly¹¹⁶. Using a DSMB for paediatric research is not mentioned.

¹⁰⁷ The EU Ethical Recommendations are stating that this ban of financial incentives should concern not only the child but also the parents / legal representatives, and that compensation was only related to the time and expenses of the latter. Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §21.

¹⁰⁸ The Oviedo Convention only forbids in its Additional Protocol on Biomedical Research «undue influence, including that of financial nature» on the potential participant. Additional Protocol, Article 12.

¹⁰⁹ The CFR provides that the IRBs is responsible of assessing «the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence». 21 CFR 50.20

¹¹⁰ Canadian guidelines give precise and clearly distinguished definitions of reimbursement, compensation, appreciation and incentive. According to those, reimbursement would concern transportation, parking, meals, lodging or babysitting whereas compensation would rather be for time and inconvenience. Appreciation could be toys, gift certificate, books, movie coupons etc. and finally incentive could take the form of a draw, lottery or community service credit. CGP & MICYRN, Best Practices for Health Research Involving Children and Adolescents, *op. cit.*, p. 114.

¹¹¹ Since an increasing proportion of clinical trials are conducted in developing countries, the prohibition of (hidden) remuneration is particularly important for the protection of participants, *i.e.* with socially and financially disadvantaged populations who hope either for health care or for payment when they take part in a clinical trial. Regulation 536/2014; A Altavilla A., "Ethical standards for clinical trials conducted in third countries: The new strategy of the European Medicines Agency", *European Journal of Health Law*, Vol. 18, 2011, pp. 65-75.

¹¹² Directive 2001/20/EC, Article 4.

¹¹³ Regulation 536/2014, Article 28.

¹¹⁴ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §9.

¹¹⁵ Monitoring of the objective and methodology, monitoring of low-intervention trials, and monitoring of the degree of deviation from normal clinical practice. Regulation 536/2014, Article 48.

¹¹⁶ The monitoring of the "objective and methodology" does not necessarily include the monitoring of the risks. As for the other elements, one of them only concerns the monitoring of low-intervention trials, and only the last element

However, it would be useful to expressly address monitoring of risks, instead of leaving it up to the sponsor to decide the extent and nature of that. It would also be useful to mention that monitoring of risks should be specific to vulnerable groups, including children. The constant update of risk/benefit evaluation, in light of scientific developments during research, should be particularly important for the paediatric population, particularly if we take into account the fact that children are constantly developing themselves.

Finally, regarding control groups and placebos, although Directive 2001/20/EC does not contain specific requirements, the EU Ethical Recommendations give precise guidelines on the use of placebos and paediatric control groups¹¹⁷. Placebo is not acceptable when it implies that an effective and available treatment be withheld, especially for life-threatening conditions. There might be some occasions where its use is permissible but must be discussed, and then harm and exposure to harm should be avoided or minimised as much as possible, and 'rescue treatments and escape procedures' organised. However, none of these recommendations were included or mentioned in the new Regulation, not even in a general manner, despite the fact that various institutions, like the EMA¹¹⁸, and guidelines, such as the WHO-CIOMS guidelines¹¹⁹ or the Declaration of Helsinki¹²⁰ require as much¹²¹.

6.3 Provisions for Trials Carried Out outside the EU: Inadequate Implementation for Paediatrics

The new Regulation, which confirms existing rules adopted at the international¹²² and European¹²³ level, introduces an equivalence criterion and specifies that clinical trials conducted outside the EU shall be conducted in accordance with principles equivalent to those in the Regulation, with regard to the rights and safety of a subject and the reliability and robustness of data¹²⁴. As with any type of clinical trial, paediatric trials performed in non-EU countries should be conducted in accordance to the laws and regulations of the country of conduct, most

could lead to monitoring the risks: "degree of deviation of the intervention from normal clinical practice". Regulation 536/2014, Article 48.

¹¹⁷ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §9.2.1.

¹¹⁸ The EMA warned against the danger to justify the use of placebos when the standard treatment is not available in the country where the trial is conducted. EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU regulatory authorities, EMA/121340/2011, London, 2012, §4.6, p. 26-27.

¹¹⁹ By principle, the use of placebo is forbidden, and only acceptable by exception: "- when there is no established effective intervention; - when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; - when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects". 2002 CIOMS Guidelines, Guideline 11.

¹²⁰ The Declaration of Helsinki only allows the use of placebo when there is no proven intervention available, when it is indispensable to assess the safety and efficacy of the trial, or when the use of placebo does not expose the participant "to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention". Declaration of Helsinki, §33.

¹²¹ Regulation 536/2014, Recital 80.

¹²² 2002 CIOMS Guidelines, Guideline 3.

¹²³ Directive 2001/83/EC, as amended by Directive 2004/27/EC, established that clinical trials performed in third countries (non-EU countries) and submitted in a Marketing Authorisation application in the EU should be conducted in accordance with the principles of Good Clinical Practice and the ethical requirements equivalent to the provisions of Clinical Trials Directive and should comply with Good Manufacturing Practices of EU countries. In this sense, the EMA Reflexion Paper, released in 2012, proposed that EU competent authorities should refuse to consider data obtained that is not in accordance with ethical standards. EMA, Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA, *op. cit.*

¹²⁴ Regulation 536/2014, Article 25.5.

importantly, in accordance to all ethical standards and good clinical practice applicable in the European Union, regardless of any goal for obtaining a Marketing Authorization¹²⁵.

Nevertheless, as demonstrated, many aspects especially related to ethical and methodological standards for paediatric research are not clear and harmonised in Europe. Hence, the criterion of equivalence could be interpreted in various and broad ways leading to an increasing shift of paediatric trials outside Europe, especially in low-income and emerging countries that, as many reports show, are particularly attractive for sponsors¹²⁶.

7 Conclusion

Regulating paediatric research in the European Union and implementing the Regulation 536/2014 represent a particularly difficult challenge that requires clarity, transparency and legal certainty. As underlined, many notions actually need to be clarified because current discrepancies will lead to uncertainties in the assessment of paediatric protocols, especially in multicentre trials and trials conducted outside of the EU. Particular clarity is needed for the concepts of minimal risk and low-intervention trials, but also for issues concerning the role and paediatric expertise of ECs and their interaction with the Paediatric Committee (PDCO), as well as the conditions for processing paediatric data (especially in the case of secondary use of data in children) and compliance with other internationally recognized ethical standards.

Furthermore, current uncertainties and disparities in the EU Regulation are not tempered by any reference to international ethical guidelines that could provide a basis for greater harmonisation. It is unclear as to what is the current status of the EU Ethical Recommendations for paediatric research since they were not repealed, but might still be obsolete because of their strong link to the provisions of Directive 2001/20/EC. All the relevant guidelines and recommendations are expected to be revised and updated so as to be in line with the changes and requirements of the Clinical Trials Regulation, but since ethical aspects are not adequately addressed in the Regulation and are instead left to national provisions, clarifications of those issues are necessary in order to ensure equal treatment of children across Europe. The Oviedo Convention and its Additional Protocol on Biomedical Research are not mentioned once in the whole text of the Regulation¹²⁷ and the legal status of the Declaration of Helsinki and the ICH guidelines is vague¹²⁸. The revision process of paediatric ICH guidelines currently continues and an addendum

¹²⁵ Recommendations of the Ad hoc group, Ethical considerations for clinical trials performed in children, *op. cit.*, §23.

¹²⁶ Low-income and emerging countries are particularly attractive for sponsors because less stringent regulation and/or weak enforcement can result in a faster approval of protocols and recruitment of subjects, for which participation in a trial may be the only option for access to medication and treatments. For more see: Koski G. and Nightingale S. L., "Research involving human subjects in developing countries", *NEJM*, Vol. 345, 2001, pp. 136-138; Hawkins J.S. and Emanuel E.J., *Exploitation and Developing Countries. The Ethics of Clinical Research*, Princeton, NJ: Princeton University Press, 2008; I. Schipper and F. Weyzig, "Ethics for drug testing in low and middle income countries, considerations for European market authorisation", *SOMO*, 2008, p. 77 .

¹²⁷ The Oviedo Convention has been ratified by 29 countries to this date, Website of the Treaty Office from the Council of Europe, <http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=23/02/2015&CL=ENG>. The Additional Protocol to the Oviedo Convention on Biomedical Research has been ratified by 9 countries to this date, Website of the Treaty Office from the Council of Europe, <http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=195&CM=8&DF=23/02/2015&CL=ENG> [15 June 2018].

¹²⁸ Their status is vague whereas their clarification was one of the claims in the responses to the public consultations as well as in literature on the proposal for the Regulation released by the European Commission. European Commission, Assessment of the functioning of the "Clinical Trials Directive" 2001/20/EC. Summary of the responses to the public consultation paper, *op. cit.*, p. 15.

GENNET É. & ALTAVILLA A., "Paediatric Research under the New EU Regulation on Clinical Trials: Old Issues New Challenges", *European Journal of Health Law*, Vol. 23, n°4, 2016, pp. 325-349.

will be developed including, among others, an enhancement of the ethical considerations in paediatric studies within a global context¹²⁹.

In the light of this analysis, we wonder if the new Regulation represents a step forward for paediatric research. Since further clarifications are needed, the implementation process of the new Regulation, carried out under supervision of the European Commission, will be a crucial step. All main stakeholders engaged in paediatric trials must play a major role in this process with the aim to facilitate and foster ethically sound paediatric research.

¹²⁹ ICH Steering Committee, Final Concept Paper E11(R1): Clinical Investigation of Medicinal Products in the Pediatric Population, 2014.