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| Drafted by | Date | Submitted by | Date | Approved by | Date |
| Annagrazia Altavilla | 13/03/07 | C. Giaquinto | 13/03/07 | Objectives Coordinators | |
| Approved by | Date | Approved by | Date | Approved by | Date |
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Index

| | | |
|----|---|----|
| 1. | Authors..... | 4 |
| 2. | Abstract..... | 4 |
| 3. | Content: Recommendations on ethical issues on medicine for child..... | 6 |
| 4. | Receivers of the document..... | 17 |
| 5. | References to other documents | 17 |

1. Authors

Table 1: list of authors

| Name | Institution |
|---|-----------------------|
| Annagrazia Altavilla | AOPD |
| Mariana Catapano | CVBF |
| Adrian Georgescu, Daniela Iorgulescu, Dragos Stefanescu | Romanian Angel Appeal |
| Milena Lo Giudice | ISS |
| Maria Mellado Pena | HCIII |
| Ian Chi Kei Wong | SoP |
| Carlo Giaquinto | AOPD |
| Adriana Ceci | CVBF |
| Paola Baiardi | CVBF |

2. Abstract

These recommendations aim to integrate the "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" in the light of some international/European legal/ethical sources. For instance: the Convention on Human Rights and Biomedicine (1997), the Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (2005), the Charter of Fundamental Rights of the European Union (2000), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the International Declaration on Human Genetic Data (UNESCO, 2003).

All these sources, in fact, address ethical issues related to medicine, life sciences and associated technologies as applied to children, taking into account their social, legal and environmental dimensions, as well as the necessity to protect individuals and groups of special vulnerability (as children/minors) and to respect the personal integrity of such individuals. They aim at recognizing the importance of freedom of scientific research and the benefits derived from scientific and technological developments, while providing a universal framework of principles and procedures to guide EU and States in the formulation of their legislation, policies or other instruments in the field of bioethics. All this in order to promote respect for human dignity and protect human rights by ensuring respect for the life of human beings and fundamental freedoms, consistent with international human rights law.

Since it is a matter of fundamental rights, the respect of which constitutes, in value systems recognized in Europe, an indivisible obligation for the public authority to fulfill, the purpose is to ensure that the powers attributed to the Union by the Treaties are clearly limited by respect for the specified rights, and that each person legally implicated on Union territory may rely directly on these rights. The Union's field of competence is not affected: it is a question of ensuring that by its action the Union does not infringe on the enjoyment of fundamental rights, regardless of what they are, most of all because these international/European sources could have judicial effect, on the basis of the discretion of the courts (CJCE, CEDH and national ones) to 'refer' to its content.

In this sense, it seems important to highlight that, annually since 2001, the European Parliament has drafted a detailed report on fundamental rights in the

EU, assessing the respect for the rights laid down in the EU Charter, based on different international sources of information (United Nations, the Council of Europe, the EU institutions, ECHR and EC Court of Justice case law, Member States laws, relevant NGOs, etc) and to which citizens are allowed to have access.

On the other hand, it is important to underline that the European Court of Human Rights (CEDH) may give, without direct reference to any specific proceedings pending in a court, advisory opinions on legal questions concerning the interpretation of the Convention on Human Rights and Biomedicine.

Furthermore, the Universal Declaration on Bioethics and Human Rights (UNESCO), in the article 27, related to limitations on the application of the principles, specifies that: *"If the application of the principles of this Declaration is to be limited, it should be by law, including laws in the interests of public safety, for the investigation, detection and prosecution of criminal offences, for the protection of public health or for the protection of the rights and freedoms of others. Any such law needs to be consistent with international human rights law"*.

In the light of these considerations, special attention has been paid, among others things, to confidentiality issues and consent procedure.

In particular, with reference to privacy, it has been stressed that the confidentiality of child's personal information should be respected, that means that such information should not be used or disclosed for purposes other than those for which it was collected or consented to.

With reference to consent procedure and in the light of differences existing between the legal frameworks of the European countries, integrations proposed aimed to guarantee that parents/legal representatives consent and/or child assent are really free, informed and revocable at any time, for any reason without any disadvantage or prejudice for the child as well as without being subject to any liability and/or to any form of discrimination, in particular regarding his/her right to medical care. Furthermore, refusal or withdrawal of the child shall be respected, in accordance with national law.

References have been also made to the necessity to focus on the racial and ethnic groups' issues.

3. Content: Recommendations on ethical issues on medicine for child

| SPECIFIC COMMENTS ON EMEA RECOMMANDATIONS | | |
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| GUIDELINE SECTION TITLE | | |
| Para.3, line 2, line 4 | <p>Council of Europe has adopted an Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research that develops rules for the protection of individuals, especially for vulnerable people who are not able to give consent (e.g. minors). CETS No.: 195, opened to signatures the 25th of January 2005. It has not yet come into force because of lacking of conditions: five ratifications including four COE member States. As 1 January 2007 just Bulgaria, Hungary, Slovakia and Slovenia ratified it. Anyway it will come soon into force.</p> <p>Furthermore it has to be taken into account the Charter of Fundamental Rights of the European Union (2000), as well as the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), Universal Declaration of Human Rights of 1948, the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) and the International Declaration on Human Genetic Data (UNESCO, 2003)</p> | <p>ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS</p> <p>“Ethical principles and fundamental rights referred to in this document are those expressed (...) in the Declaration of Helsinki, the United Nations Convention on the Rights of the Child, in the Charter of Fundamental Rights of the European Union (2000), in the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) in the International Declaration on Human Genetic Data (UNESCO, 2003), in the Universal Declaration of Human Rights of 1948, in the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine - COE, 1997) as well as in its Additional Protocol concerning Biomedical Research (COE 2005)”.</p> <p>All these sources aim at recognizing the importance of freedom of scientific research and the benefits derived from scientific and technological developments. On the other hand, they provide a universal framework of principles and procedures to guide EU and States in the formulation of their legislation, policies or other instruments in the field of bioethics. All of that in order to promote respect for human dignity and protection of human rights, by ensuring respect for the life of human beings, and fundamental freedoms, consistent with international human rights law.</p> |
| Para. 6.1, line 6 | <p>In this sense, see Directive 2001/20/EC, as underlined in your document. The written form of consent of parent(s)/legal representative is provided for by the Additional Protocol to the Convention on Human Rights and Biomedicine on</p> | <p>Article 4(a) of the Clinical Trials Directive requires that specific and in writing informed consent of parent(s)/legal representative must be sought prior to enrolling a child in a trial.</p> |

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| | Biomedical Research (art. 15, sec.iv). For the expression “specific” see art. 16 of the Convention on Human Rights and Biomedicine and its Additional Protocol (art. 14) | |
| Para. 6.3, title | | 6.3 Informed consent (and assent for children) of immigrant families with different cultural background |
| Para. 6.4, line 2 | <p>Convention on Human Rights and Biomedicine establishes, in the art. 6 section 2, related to Protection of persons not able to consent, that: “Where, <u>according to law</u>, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with <u>the authorisation of his or her representative or an authority or a person or body provided for by law</u>.</p> <p>In the article 17 specifies that Research on a person without the capacity to consent... may be undertaken ...only “exceptionally and <u>under the protective conditions prescribed by law...</u>”</p> <p>In this sense, the International Declaration on Bioethics and Human Rights, in the article 7, related to Persons without the capacity to consent, establishes that : “ <u>In accordance with domestic law</u>, special protection is to be given to persons who do not have the capacity to consent: (a) authorization for research and medical practice should be obtained in accordance with the best interest of the person concerned and <u>in accordance with domestic law...</u>”</p> <p>See also article 15 of the Additional protocol to the Convention on Human Rights and Biomedicine and art. 2(j) of the Directive 2001/20/EC</p> | Investigators should devote sufficient time to provide information, and seek express and specific legal representative(s)’ consent as well as child’s assent, in accordance with national law. |
| Para. 6.5, line 2 | <p>For the expression “freely withdraw” please make reference to Convention on Human Rights and Biomedicine art. 16, and its Additional Protocol on Biomedical Research art. 14.</p> <p>For the necessity to make reference to the best interest of minors, please see the Convention on Human Rights and Biomedicine, art. 6 section 5, related to Protection of persons not able to consent.</p> | In all circumstances, parent(s)/legal representative should be made aware of the rights to refuse participation in a clinical trial and are entitled to freely withdraw their informed consent, without giving reasons, in the best interest of minors. |
| Para. 6.5, line 4 | Universal Declaration on Bioethics and Human Rights (Unesco , 2005), art. 6, related to consent, specifies that: “The consent should, where appropriate, be express and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice”. | ... Parent(s)/legal representatives should be reassured that the withdrawal from the trial will not cause disadvantage or prejudice to the child. |
| Para 6.5, line 6 | See considerations make above in the para.6.5 line 2 | so as to be able to freely withdraw the child from the research at any time. |

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| <p>Para 6.6, line 8</p> | <p>Freedom of consent implies that consent may be withdrawn at any time and that the decision of the person concerned shall be respected once he or she has been fully informed of the consequences. This principle is laid out in sentence 2 of paragraph 1 of the Art. 14. <u>Paragraph 2 adds that such a decision shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care. The participant cannot be held liable for any consequences of withdrawal, particularly of a financial nature. The participant should not be required to give a reason for withdrawal. Any obligation arising out of the mere fact of withdrawal would be contrary to the right to withdraw consent.</u> In this sense, please see the of art. 14 section 2 of the Additional Protocol on Biomedical Research to the Convention on Human Rights and Biomedicine and the section 80 of its Explanatory report .</p> | <p>(A child should not incur any disadvantages in medical care if consent is withdrawn - <u>this phrase is to be deleted and substituted by the following</u>)</p> <p>Refusal to give consent or withdrawal of consent to participation in research shall not lead to any liability and/or to any form of discrimination against the person concerned, in particular regarding the right to medical care. The same level of care and information should be maintained during treatment or investigations.</p> |
| <p>Para. 6.6, after line 7</p> | <p>For research on persons in emergency clinical situations, please make reference to the Convention on Human Rights and Biomedicine art. 8 and its Additional Protocol on Biomedical Research art.19, that refer back to national law providing with some conditions. The Additional Protocol on Biomedical Research to the Convention on Human Rights and Biomedicine, in this art.19, related to research on persons in emergency clinical situations, establishes that: “The law shall determine whether, and under which protective additional conditions, research in emergency situations may take place, for the benefit of the health of the person concerned, when: i. a person is not in a state to give assent, and ii. because of the urgency of the situation, it is impossible to obtain in a sufficiently timely manner, consent from his or her representative or an authority or a person or body which would in the absence of an emergency situation be called upon to give authorisation. The law shall include the following specific conditions: i. <u>research of comparable effectiveness cannot be carried out on persons in non-emergency situations;</u> ii. <u>the research project may only be undertaken if it has been approved specifically for emergency situations by the competent body;</u> <u>iii. any relevant previously expressed objections of the person known to the</u></p> | <p>to be gathered in children.....</p> <p>In emergency situations, retrospective informed consent from the parent(s)/legal representative shall be obtained as soon as possible. Assent of minors should be obtained once consent has been granted.</p> |

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| | <p><u>researcher shall be respected:</u> iv. where the research has not the potential to produce results of direct benefit to the health of the person concerned, it 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 category or afflicted with the same disease or disorder or having the same condition, and entails only minimal risk and minimal burden. Persons participating in the emergency research project or, if applicable, their representatives shall be provided with all the relevant information concerning their participation in the research project as soon as possible. Consent or authorisation for continued participation shall be requested as soon as reasonably.</p> | |
| <p>Para. 6.6, after line 7</p> | <p>As above indicated, the regulation related to emergency clinical situations, provided into the Convention on Human Rights and its additional Protocol on Biomedical Research, establishing some conditions, refers back to national law. It seems, thus, necessary to modify following paragraphs in order to assure that, given the lack of specific provisions in the Directive 2001/20, emergency situations shall be effectively regulated in accordance with national laws, only where existing.</p> | <p>In emergency situations, thus, consent should be obtained according to national law. It should be suggested to obtain consent from one or several designated individuals, aware of the research purpose, but fully independent of the research team, only when the national law allows it. Ethics committees (should – to delete) shall assess the protection provided in such trials, in accordance with the national law.</p> <p>(Retrospective informed consent from the parent(s)/legal representative shall be obtained as soon as possible. Assent should be obtained once consent has been granted). <u>To be put before ...see above.</u></p> |
| <p>Para.7, line 10</p> | <p>For instance, Finnish legislation specifies that written consent of a minor, that reached the age of 15 and, in view of his/her age and maturity and the type of illness and research, is capable of understanding the importance of the research procedure, shall be sufficient to be involved in a research if the research is likely to be of direct benefit to the minor's health. See art. article 8 section 3, Medical Research Act 295/2004. Thus, it is necessary to make reference to specific national laws, where existing. To know other examples of specific values attributed to the minor assent please refer back to TEDDY report "Altavilla. A, Giaquinto C., Ceci A., <i>European survey on ethical and legal framework of clinical trials in paediatrics: results and perspective</i>".</p> | <p>The child's assent is not sufficient to allow participating in research unless supplemented by informed consent of the legal representative, only if in accordance with national laws providing for specific regulations.</p> |

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| <p>Para.7, line 13</p> | <p>In order to guarantee the transparency of clinical trial development as well as to be sure that children assent be “really informed”, it seems important to better specifies conditions of information, according to <u>Convention on Human Rights and Biomedicine (art.5), and its Additional protocol on biomedical research (art.13, 16 section 3 and 15 section 1, related to protection of persons not able to consent to research).</u> <u>IMPORTANT:</u> <u>The same rules should be adopted for the information process of parent(s)/legal representative.</u></p> | <p>Informed assent form should be age appropriate and should include appropriate information on the purpose and nature of the trial, as well as on its consequences, benefits and harms. The informed assent form shall include the opinion of the competent ethics committee. Before being asked to assent to participate in a research project, the child concerned shall be specifically informed, according to the nature and purpose of the research: i. of the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project; ii. of available preventive, diagnostic and therapeutic procedures; iii. of the arrangements for responding to adverse events or the concerns of research participants; iv. of arrangements to ensure respect for private life and ensure the confidentiality of personal data; v. of arrangements for access to information relevant to the participant arising from the research and to its overall results; vi. of the arrangements for fair compensation in the case of damage; vii. of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials; viii. of the source of funding of the research project. The child undergoing research has to be informed of his/her rights and safeguards prescribed by law for his/her protection, unless he/she is not in a state to receive the information This information should be given in language and wording appropriate to age, psychological and intellectual maturity.</p> |
| <p>Para. 7, line 18</p> | <p>Integrations proposed according to remarks taken above for para. 6.5 line 2, para.6.5 line4, para.6.5 line 6 and 6.6 line 8, in the light of principles set out in the ethical/legal sources above mentioned.</p> | <p>The child should be informed of the possibility to freely withdraw from the trial at any time for any reason without any disadvantage or prejudice. In addition, the child being asked to participate in a research project shall be informed of the rights and safeguards prescribed by law for his/her protection, and specifically of his/her right to refuse or to withdraw from the trial, without being subject to any liability and/or to any form of discrimination, in particular regarding his/her right to medical care.</p> |

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| | | The same level of care and information should be maintained during treatment or investigations. |
| Para. 7, line 18 after having add parts above indicated | <p>The Universal Declaration of Bioethics and Human Rights (UNESCO) – in the art. 7 (b), related to persons without the capacity to consent, - establishes that “Refusal of such persons to take part in research should be respected”.</p> <p>The Convention on Human Rights and Biomedicine (art. 17 section 1 -V.) and its Addition Protocol on Biomedical research (art. 15 section 1 –V.) provides that: “Research on a person without the capacity to consent may be undertaken only if all the following conditions are met:....V. the person concerned does not object”.</p> <p>In this sense, French law provides that minors consent prevails and it is impossible to pass over their refusal or the withdrawal of their consent (see art. L.1122-2 of Public Health Code). Finnish legislation establishes that, taking account of minor age and maturity, his/her opinion opposing a research or a research measure shall be complied with. For a more in depth analysis, please refer to TEDDY article (above mentioned) herewith enclosed.</p> <p><u>It seems important to clearly specify the value to attribute to child’s refusal/withdrawal, according to national law and international instruments.</u></p> | Refusal or withdrawal of the child shall be respected, in accordance with national law. |
| Para 7.1.3., Line 5 | | ...as provided by parents or other (to delete parental) legal representative figures |
| Para 7.1.3. Line 13 | Relating the importance to attribute to adolescent assent please refer to remarks above mentioned for the para.7 line 10. To analyse some European countries laws, please refer to TEDDY report (above mentioned). | ..obtaining assent becomes even more important, in accordance to national law. |
| Para. 7.3, line 3 | According to remarks done for Para 7 line 18, it <u>seems important to clearly specify the value to attribute to the child’s refusal/withdrawal.</u> | Anyway, refusal or withdrawal of the child shall be respected, in accordance with national law. |
| Para 8.1.1., line 9 | To know different approaches existing in Europe concerning paediatric expertise please refer to TEDDY report (above mentioned). | Expertise used (to delete should) shall be documented and recorded by Ethics Committees, in accordance with national law. |
| Para. 8.1.2, Line 6 | | ...In particular, the following (points to delete) conditions should be (checked to delete) examined: |
| Para. 8.1.2., Line 7 | Integrations proposed according to Convention on Human Rights and Biomedicine Additional Protocol on Biomedical research (art.21) | Protection and safety of children is ensured (by including minimisation of risks, fear, pain and distress measures) and appropriate paediatric expertise is |

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| | | available at all trial sites. |
| Para. 8.1.2 Line 30 | Integrations proposed according to Convention on Human Rights and Biomedicine Additional Protocol on Biomedical research (art.24) | Ethics Committees and Competent Authorities should ensure that the sponsor permanently monitors and re-examines the balance of risk and benefits of the research so that the health and well being of the children enrolled are safeguarded, taking into account scientific developments or events arising in the course of research. |
| Para. 8.1.2 Add after the last paragraph | Integrations proposed according to Convention on Human Rights and Biomedicine Additional Protocol on Biomedical research (art.11, 13 and its appendix) and some national legislations, given important differences existing across Europe concerning consent procedures. The integration proposed respond to the necessity to avoid distortions in the legal frame at European level in the current situations related to clinical trials. For an in-depth analysis, please refer to TEDDY article (above mentioned) herewith enclosed. | <ul style="list-style-type: none"> ▪ Loyal, comprehensive, understandable informed consent and Information sheets for legal representative, in accordance with national law, even in the international multicentre studies. ▪ Loyal, understandable, age specific Informed assent and Information sheets for children, in accordance with national law, even in the international multicentre studies. |
| Para. 8.1.2 Add after the last paragraph | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedicine (art.25, 26, 27, related to confidentiality, right to information and duty of care). Please make reference also to the Directive 95/46/EC, on the protection of individuals with regard to the processing of personal data and on the free movement of such data, as implemented in the different Member states | <ul style="list-style-type: none"> ▪ Anonymity of data as well as confidentiality of personal information related to the child involved in the research and to his/her family, have been respected in accordance with national law and international law, in particular international human rights law. |
| Para.8.1.2 Add after the last paragraph | Integrations proposed according to Convention on Human Rights and Biomedicine (art.21 related to Prohibition of financial gain) and its Additional Protocol on Biomedical research (art.12 related to undue influence) | <ul style="list-style-type: none"> ▪ No undue influence, including that of a financial nature, will be exerted on child or his/her legal representative to participate in research. |
| Para. 8.1.2 After the last paragraph, line 4 (actually at pag.14) | In order to attribute importance to the evaluation of the aspects listed in the annexe2, it seems necessary to modify the sentence. | To assure child protection and with the aim of helping Ethics Committees in reviewing paediatric trials, aspects listed in the ANNEXE 2 have to be taken into consideration when reviewing a clinical trial to be performed in children. |
| Para. 9.2.1, Line 6 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.23 section 3) | ...on top of standard care. Placebo is permissible only where there are no methods of proven effectiveness and safety, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden. |

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| | | In all cases, the use of placebo should be recommended only in the context of well designed clinical trials |
| Para.11.1 Line 1 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.6, related to risks and benefits, as well as art. 15 section 2, related o protection of persons not able to consent to research) | Research shall not involve risks and burdens to the child disproportionate to its potential benefits. 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 child concerned, such research may be authorised subject to the following additional conditions: the research entails only minimal risk and minimal burden for the individual concerned; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden. Risk assessment, thus , is a crucial step in assessing a protocol ... |
| Para. 11.2, Line 9, pag 17 | Integrations proposed according to Convention on Human Rights and Biomedecine Additional Protocol on Biomedical research (art.24) | ...In this report the sponsor should perform a specific analysis of the subjects' safety in the paediatric population enrolled in the clinical trial, and provide an update of the risk-benefit evaluation for the paediatric population, in the light of scientific developments or events arising in the course of the research. All of that with the purpose also to establish whether: the research needs to be discontinued or if changes to the research project are necessary for the research to continue; research participants (child), if applicable, or their representatives, need to be informed of the developments or events; additional consent or authorisation for participation is required. Any new information relevant to their participation shall be conveyed to the research participants (child), or, if applicable, to their representatives, in a timely manner. The competent body and Ethics Committees shall be informed of the reasons for any premature termination of a research project. |
| Para. 12.2, Line 10, pag.18 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art. 15 section 2, related o protection of persons not able to consent to research) | At the end of the paragraph 12 add: Any consideration of additional potential benefits of the research shall not be used to justify an increased level |

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| | The Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine, in the art. 15 section 2, related to protection of persons not able to consent to research, specifies that any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden | of risk or burden. |
| Para. 18, line 4, p.20 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.25, 26, 27, related to confidentiality, right to information and duty of care) and the art. Art. 12 of Convention on Human rights and biomedicine related to predictive genetic tests. See also International Declaration on Human Genetic Data (UNESCO on 16 October 2003). See also Charter of fundamental rights of the EU, art. 8 related to protection of personal data. Furthermore, see the Convention for the Protection of Individuals with regard to Automatic Processing of Personal data (COE of 28 January 1981) | ... After the first paragraph it should be added: Any information of a personal nature collected during biomedical research shall be considered as confidential and treated according to the rules relating to the protection of private life. Children participant in research shall be entitled to know any information collected on their health. Other personal information collected for a research project will be accessible to them in conformity with the national law on the protection of individuals with regard to processing of personal data. If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of health care or specific counselling, most of all in the case of predictive genetic tests. In communication of such information, due care must be taken in order to protect confidentiality and to respect any wish of the child (and/or his/her legal representative) participant not to receive such information, in accordance with national law. |
| Para. 18, line 10, p.20 | Integrations proposed according to Universal Declaration on Bioethics and Human Rights (UNESCO) –Art. 9 related to Privacy and confidentiality | The privacy of the children concerned and the confidentiality of their personal information should be respected. Such information should not be used or disclosed for purposes other than those for which it was collected or consented to. Where personal information on a child is collected, stored, accessed, used, or disposed of, a researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject and/or the collectivity are respected in accordance with national law and international law, in particular international human rights law. |

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| Para. 22, line 3 after first paragraph p.21 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.31 related to compensation for damage) | The person who has suffered damage as a result of participation in research shall be entitled to fair compensation according to the conditions and procedures prescribed by national law. |
| Annexe 2 para. 26, line 2, p.29 | In order to attribute importance to the evaluation of the aspects listed in the annexe2, it seems necessary to modify the sentence. | List of issues that have to be taken into consideration for planning a paediatric study: ... |
| Annexe 2 para. 26, line 10, p.29 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.21 section 2) | The competence of the responsible study investigator and his/her team and the infrastructure of the institution or primary care practice that (should be experienced <u>NO</u>) should possess the necessary qualification and experience in paediatric research in general and in particular in the field of the applied project. |
| Annexe 2 para. 26, line 16, p.29 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.23 section 3) | Use of active control or placebo, that is permissible only where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden. In all cases, the use of placebo should be recommended only in the context of well designed clinical trials |
| Annexe 2, line 27, p.29 | Integrations proposed according to Additional Protocol on Biomedical research of Convention on Human Rights and Biomedecine (art.25, 26, 27, related to confidentiality, right to information and duty of care). | List of issues that have to be taken into consideration for planning a pediatric study.... - Anonymity and confidentiality of personal data related to the child involved in the research and to his/her family, |
| | | |
| P13. 8.1.1 | Paediatric expertise goes beyond having dealt with children and could be defined education and experience on the various aspects of child development, ethics aspects. Therefore, this would include i) physicians with paediatric qualification; ii) ethicists; iii) qualified paediatric nurses or psychologists, etc. In addition recommended that the experts demonstrate at least some years of experience direct experience of clinical trials, for example as an investigator in several children of a similar age groups. If this cannot be found in one individual, two or more experts could combine the Expertise used should be documented and recorded by the Ethics Committee. | Therefore, this would include i) physicians with paediatric qualification; ii) ethicists; iii) qualified paediatric nurses or psychologists, a paediatric pharmacist or external formulation expert, etc. |
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|----------|--|---|
| P19 | <p>In order to minimise the risks incurred by children included in trials, formulations used should be described in the protocol. Recent data show that formulations used in paediatric clinical trials are not reported in publications *..</p> <p>*Standing JF, Khaki ZF, Wong ICK. Poor formulation information in published paediatric drug trials. <i>Pediatrics</i> 2005;116(4):e559-62.</p> | <p>Age-appropriate formulations should be used to avoid the risk of adverse reactions (for example young children choking on tablets), the risk of dosing errors or inaccuracy</p> |
| 7 | <p>The minor assent is stated in the same Order no. 615/21.05.2004 updated by Internal Norm no.0/25.07.06, published in M.O. no. 671/04.08.2006, updated by Internal Norm no.0/25.07.06.</p> <p>It is not mentioned neither the age from which the child assent must be required, nor the fact that this assent should be oral or written.</p> | <p>We appreciate a questionnaire could be used for adolescent assent according to the following form:</p> <p>Give an answer to the following questions. Encircle the right answer.</p> <p>Information regarding these clinical trial was explained to you ----- Yes/No Did you receive and read a copy of written information prepared for the subject----- -----Yes/No Did you have the opportunity to ask or to discuss about this clinical trial?---Yes/No Who is the person that gave you information? Name _____</p> <p>Did you understand you are free to go out of these clinical trials? - At any moment of it?----- -----Yes/no - Not being compulsory a reason?----- Yes/no - Without any negative consequences for your further care?- ----- Yes/no - Do you agree to participate at these clinical trials----- Yes/no</p> <p>Subject signature, date, Witness signature, date</p> |
| 07/01/03 | <p>According to the above order mentioned, it is not enough just the adolescent assent even if he is able to take mature decisions.</p> <p>The consent of the parents / legal representative is compulsory.</p> | |

4. Receivers of the document

This document has been sent to the European Commission, DG Enterprise and Industry, for the Consultation on the draft document on "Ethical Considerations for Clinical Trials Performed in Children".

5. References to other documents

- 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;
- Universal Declaration of Human Rights of 1948;
- Convention on Human Rights and Biomedicine (1997);
- The Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997);
- The Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (2005);
- The Charter of Fundamental Rights of the European Union (2000);
- The International Declaration on Human Genetic Data (UNESCO, 2003);
- The Universal Declaration on Bioethics and Human Rights (UNESCO, 2005) .