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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

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EXECUTIVE SUMMARY

This document has been developed by the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC[1] relating to good clinical practice in the conduct of clinical trials on medicinal products for human use, chaired by the European Commission. The document provides recommendations on various ethical aspects of clinical trials performed in children from 0 up to 18 years. This will contribute to the protection of children who are the subject of clinical trials in the EU. As the approval of clinical trials, including ethical approval, is primarily a competence of the Member States, any recommendations on ethical aspects of clinical trials in children will also facilitate a harmonised approach to clinical trials across the EU, thereby facilitating the conduct of clinical trials in the EU. The protection against the risks of research in such a vulnerable population is paramount whilst this should not lead to denying them the benefits of research. Children are not small adults and there is a need to carry out specific trials that cannot be performed in adults. In general, children (minors) are unable to consent but their assent should be obtained using age appropriate information. Ethics Committees need paediatric expertise to balance the benefits and risks of research in children. The lack of consent has implications on the design, analysis and the choice of comparators used in the trials, which should only be performed by trained investigators with paediatric experience. Pain, fear, distress and parental separation should be prevented and minimised when unavoidable. The neonate represents the most vulnerable of all paediatric age groups and requires even more careful review. Finally, various other aspects relating to the performance of trials in children are discussed.

1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF RECOMMENDATIONS

This document has been developed by 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, chaired by the European Commission. The document provides recommendations on various ethical aspects of clinical trials performed in children from 0 up to 18 years. This will contribute to the protection of children who are the subject of clinical trials in the EU. As the approval of clinical trials, including ethical approval, is primarily a competence of the Member States, any recommendations on ethical aspects of clinical trials in children will also facilitate a harmonised approach to clinical trials across the EU, thereby facilitating the conduct of clinical trials in the EU.

Trials are necessary and should aim at progressing the well-being and treatment, prevention and diagnosis of ill health (WHO definition) including in children. The same ethical principles apply across age ranges, from children to the elderly. However, the third recital of Directive 2001/20/EC (hereinafter the Clinical Trials Directive) in particular recognises the need for investigation of medicinal products in the vulnerable population of children (i.e., minors in the meaning of the Clinical Trials Directive) whilst ensuring their protection: “However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.” Specific protection should be defined for research performed in children, at all stages and ages.

[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.

The reasons why medicinal products need to be studied in children have been detailed in various publications. To sum up, children are not small adults. Differences in pharmacokinetics and dynamics, and in adverse reactions are common in children compared to adults. Growth and maturation processes, as well as specific diseases are not found in adults. Specific consequences of medical interventions may be seen in children and may appear long after exposure. This has been unfortunately demonstrated by previous catastrophes with the use of untested medicinal products, and most often occurred in children.

Because of the special protection they deserve, children should not be the subject of clinical trials when the research can be done in less vulnerable subjects (i.e. adults). If research in children proves necessary, the least vulnerable among them should usually be included (i.e., older children). This document proposes the application of ethical principles as they are understood currently. With time, the need for revision of this document may emerge.

2. SCOPE

This document is intended to provide guidance on various ethical aspects of the performance of interventional clinical trials falling under the provisions of Directive 2001/20/EC and its implementing texts. Medicinal products may be used with a view to treating, preventing or diagnosing a disease or condition.

The document is intended for sponsors of clinical trials, ethics committees and investigators of clinical trials performed in children of all ages (minors). This document is without prejudice to the obligations created by Directive 2001/20/EC and the need to follow EMEA guidelines (Article 4 of the same Directive).

It focuses on the specificities of paediatric clinical trials and should therefore be read in conjunction with appropriate legal texts and guidelines.

The recommendations in the document aim to contribute to the protection of the rights of children (minors) who are vulnerable and unable to give informed consent. The clinical trials performed in children should be carried out under conditions providing the best possible protection for this vulnerable population whilst recognising children have the right to benefit from research.

3. ETHICAL PRINCIPLES

Ethical principles referred to in this document are those expressed for example in the Declaration of Helsinki, the United Nations Convention on the Rights of the Child, and 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. These principles are also expressed and developed in the ICH E6 guideline on Good Clinical Practice.

These principles have been elaborated upon, for example as the “Belmont principles”. For the purpose of research three principles of beneficence, justice and respect to persons can be identified, where beneficence is defined as the ethical obligation to do good and avoid harm, and justice is a fair distribution of burden and benefits of research. These are fully applicable to clinical trials in children.

4. LEGAL CONTEXT

4.1 Legal context

- 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 (hereinafter the ‘Clinical Trials Directive’).

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.

- Directive 2005/28/EC of the European Commission of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

- Regulation of the European Parliament and the Council (EC) No xxx/200x on medicinal products for paediatric use (herein 'Paediatric Regulation').

4.2 Relevant guidelines

- Clinical Investigation of Medicinal Products in the Paediatric Population (E 11), CPMP/ICH/2711/99

- Guideline for Good Clinical Practice (E 6), CPMP/ICH/135/95

- Choice of Control Group in Clinical Trials (E 10), CPMP/ICH/364/96

- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC.

- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) (revision 1) as required by Article 11, Article 17 and Article 18 of Directive 2001/20/EC.

- Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1) as required by Article 8 of Directive 2001/20/EC.

- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 2), as required by Article 9 (8) of Directive 2001/20/EC.

- Detailed guidance on the European clinical trials database (EUDRACT Database) as required by Article 11 and Article 17 of Directive 2001/20/EC, CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset.

- Revised Questions and Answers on Clinical Trials (Notice To Applicants, Volume 10, April 2006)

- CHMP Guideline on clinical trials in small populations. CHMP/EWP/83561/2005.

- CHMP Guideline on conduct of Pharmacovigilance for medicines used by the paediatric population (June 2006). EMEA/CHMP/235910/05.

- Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). *International Ethical Guidelines for Biomedical Research Involving Human Subjects (Geneva 2002, under revision).*
http://www.cioms.ch/frame_guidelines_nov_2002.htm

- Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI.

- Confederation of European Specialists in Paediatrics (CESP) guidelines[2].

5. DEFINITIONS/ GLOSSARY

The definitions provided below refer, when appropriate to those in Clinical Trials Directive.

5.1 Ethics committee

Article 2(k) of the Clinical Trials Directive defines:

> "An independent body in a Member State, consisting of healthcare professionals and non medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent."

5.2 Legal representative of the minor

The Clinical Trials Directive does not provide for a definition of legal representative, as this varies according to the Member State's legislation. See Annex 1 for details of each Member State. In most clinical trials performed in children, the legal representative will be one or both parents.

In this document the notion of legal representative should be understood as the parent(s), or legal representative(s), as defined in Member States' national laws.

5.3 Minor

The articles of the Clinical Trials Directive refer to minors rather than children. The definition of a minor may differ according to Member States' legislation. It generally refers to a person who has not reached the legal age of adulthood (usually 18 and above, rarely 16). ICH E11 guideline defines children as being individuals aged from 0 up to 18. For the sake of these recommendations, the term minors is understood to mean children from 0 to 18 years.

5.4 Informed consent

Article 2(j) of the Clinical Trials Directive defines:

> "A decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation."

The witness referred to in this definition should be independent of the sponsor and the investigator.

5.5 Assent

For clinical trials performed in minors, the Clinical Trials Directive requires the informed consent of the legal representative. Article 4 of the Clinical Trials Directive states "In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if: (a) the informed consent of

[2] See references Section 27

the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor; (b) the minor has received information according to its capacity of understanding, from staff of experience with minors, regarding the trial, the risks and the benefits; (c) the explicit wish of a minor is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator;

The notion of assent is not explicitly included in the Clinical Trials Directive but is recognised in the Declaration of Helsinki. In this document, 'assent' should be understood as the child's will to participate in a clinical trial. Some authors use 'knowing agreement' to reflect the outcome of the process of providing age appropriate information, obtaining assent, and whenever possible obtaining written confirmation from the child. The capacity to make voluntary, informed decisions for a child, i.e., to assent, evolves with age, maturity and previous life experience.

5.6 Age Groups

Age groups used in this document follow ICH E 11 guideline groups: i.e., neonates from 0 to 27 days, infants from 1 to 23 months, children from the age of 2 to 11 years and adolescents from the age of 12 up to but not including 18 years (see also Minor). It should be noted that these age groups poorly correlate with maturation especially from the developmental point of view and trials may be performed across age groups, with consequences for ethical aspects of their conduct.

In this document, the word 'child' generally encompasses all age groups.

6. Informed consent

6.1 Informed consent from the legal representative

As the child (minor) is unable to provide legally binding consent, the parent(s)/ legal representative are entitled to give informed consent (see definition above) on his behalf. Informed consent and legal representative are generally further defined in national laws. If an adolescent aged 16 to 18 is no longer a minor, or is emancipated, then written informed consent is required as for any adult capable of giving consent.

Article 4(a) of the Clinical Trials Directive requires that the informed consent of parent(s)/legal representative must be sought prior to enrolling a child in a trial.

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

The investigator when seeking informed consent should not put undue pressure on the parent(s)/legal representative. For example:

- According to Article 4(d) of the Clinical Trials Directive there must not be financial inducement to enroll the child in the trial; no financial incentive should be offered (other than compensation of expenses and time spent),

- Parent(s)/legal representative should be informed of the possibility to revoke informed consent even though it was made in writing, in line with Article 4(d) of the Clinical Trials Directive.

- Parent(s)/legal representative should be reassured that the child's treatment will not be prejudiced by withdrawal from the trial, in line with Article 4(d) of the Clinical Trials Directive..

- Consent should be obtained from the parent(s)/legal representative before assent is sought from the child, in line with Article 4 (a), (b) and (c) of the Clinical Trials Directive.

6.2 Requirements for informed consent of the legal representative in the various Member States

See Annex 1

6.3 Informed consent (and assent for children) of families with different cultural background

Where appropriate, a cultural mediator independent from the sponsor and investigator, experienced in the language, social habits, culture, traditions, religion and particular ethnic problems should assist in the process of obtaining informed consent and assent.

6.4 Consent (and assent) at the beginning of a trial and continued consent and assent during trial

Investigators should devote sufficient time to providing information, seek the legal representative(s)' consent and the child's assent.

Consent or assent is a dynamic, continuous process. It should be sought at the beginning, and should be maintained during the trial. This is part of the ongoing dialogue between children, parents and investigators. In long term trials during which the child maturation may change, it is particularly important to check assent.

In the case of a change in legal representative during the trial, informed consent should be sought again as soon as possible.

6.5 Withdrawal of the informed consent

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 withdraw informed consent, without giving reasons. Parent(s)/legal representatives should be reassured that the withdrawal from the trial will not prejudice the child. Legal representatives who gave informed consent for a child to participate in clinical trials should have the opportunity to follow research as it proceeds (unless clinically inappropriate, e.g., during an operation under general anaesthesia), so as to be able to withdraw the child from the research at any time.

When the legal representative's consent is withdrawn during the trial, this should be respected.

A child should not incur any disadvantages in medical care if consent is withdrawn. The same level of care and information should be maintained during treatment or investigations.

6.6 Informed consent in emergency trials

The Clinical Trials Directive does not include provisions for entering patients in trials without prior informed consent. In emergency situations (e.g status epilepticus) it may not be possible to obtain prior informed consent from the legal representative(s). Including a child into a trial without prior consent of the legal representative(s) would be a major concern. As for non-emergency situations however, it would be unethical to deny children the benefit of research in these situations. Some conditions / diseases may only (or mostly) be observed in children and therefore data will have to be gathered in children.

In these situations, consent should be obtained according to national law. It has been suggested to obtain consent from one or several designated individuals, aware of the research purpose, but fully

independent of the research team when the national law allows it. Ethics committee should assess the protection provided in such trials.

Retrospective informed consent from the parent(s)/legal representative should be obtained as soon as possible. Assent should be obtained once consent has been granted.

7. Assent from children

Involving children in discussions and decision-making process respects their emerging maturity. This process should be conducted only after obtaining consent from the parent(s) or the legal representative, as, where appropriate, the central role of parents should be recognised. The Clinical Trials Directive only requires that the minor's will be 'considered', however, although not a legal requirement (see section 5.5 for relevant provisions from the Clinical Trials Directive), it is recommended that the investigator obtain assent (age permitting) in addition to informed consent of the legal representative. If the child's assent is not collected, this should be recorded in the consent form signed by the parents/legal representative and investigator, with the reasons. The child's assent is not sufficient to allow participating in research unless supplemented by informed consent of the legal representative.

Separate information sheets and consent and assent forms should be used in order to provide age appropriate information. Informed assent form should be age appropriate and should include providing information on purpose of the trial, and benefits and harms. This information should be given in language and wording appropriate to age, psychological and intellectual maturity.

Assent, like consent, is a continuous process and should be sought during the trial as well. Objections raised by a child at any time during a trial should be considered. The child's will should be respected provided it is not considered detrimental to his/her health. The child should not be forced to provide reasons. The legal representative's consent should be checked. The child should be informed of the possibility to withdraw from the trial.

7.1 Assent according to age groups

7.1.1 Neonates (preterm and term),infants and pre-school children

In this age group, it is not possible to obtain assent and the understanding of research is not expected. Where the child has some capacity of understanding (pre-school children), age-appropriate information is still needed despite the fact that it will not be possible to obtain assent.

7.1.2 Children of school age (from about 6 years old)

Within this age group there is the emergent capacity to agree.

Research on cognition shows that younger children have significant ability to provide assent. It is recognised that children from the age of 3-4 can understand some expression of altruism. From the age of 9, children may be able to understand benefits and risks of research but are less able to understand conflicting or abstract information. This should be taken into consideration when writing the information form aimed at children. Most children are unlikely to understand randomisation, as indeed are some parents. However, it has been shown that children with chronic illness may have been challenged to develop increased capacity to make independent judgements based on previous life experience.

In any case, it is of major importance to inform the child, obtain assent as described above, preferably in writing when the child is of 'school age', i.e., able to read and write as in the ICH E6 guideline (about 6 or 7 years old), and then keeping track of such assent.

7.1.3 Consent and assent in adolescents

The ability to conduct research in this group remains difficult although many threats to adolescent health continue to be evident. Adolescents belong to the paediatric age group, although they have the capacity to make adult decisions in many other areas of life. Seeking consent should put in balance the emerging capacity of an adolescent for independent decision-making with the need for continued special protection as provided by parents or other parental figures. Most guidelines and publications recognise that adolescents are, under certain circumstances, able to make independent judgements, i.e. they have the emerging capacity to provide informed consent and this should be respected. The individual capacity is also linked to developing cognition and previous life experiences.

Whether the consent of an adolescent is sought or not, the Clinical Trials Directive requires the consent of the parents or legal representatives (see Article 4(a)).

An additional issue of trials in adolescents is the protection of confidentiality, especially for research on socially sensitive issues such as illicit drugs, sexuality, and violence. As the Clinical trials Directive does not require an adolescent's independent consent obtaining assent becomes ever more important.

In some Member States, discretion and professional secrecy vis-à-vis parents when dealing with adolescents may bind health professionals. The specific aspects of disclosure to parents of information concerning adolescents should therefore be taken into consideration for clinical trials in this age group, as well as emancipation status, and age to consent to medical care.

In addition to the requirement for the consent of parents or the legal representative, emancipated adolescents can provide additional informed consent to participate in clinical trials (when in accordance with national law). When consent is sought from an adolescent who is also a parent of a child to be included in a trial (particularly preterm neonates), precautions should be taken to ensure that information provided is sufficiently understood.

When an adolescent ceases to be a minor, informed consent should be sought.

7.2 Assent in emergency trials

See Section 6.6 on Consent in emergency trials. It is recommended to obtain assent once consent has been obtained according to national law and as soon as possible.

7.3 Difference of opinion between the child and the legal representative

Every effort should be made to understand and respect differences of opinion between the child and his/her legal representative. National legal provisions, relating to this situation should be followed, where they exist.

8. Ethics Committee's composition in respect of paediatric trials

In its Article 4(h), the Clinical Trials Directive includes the need for appropriate expertise in the Ethics Committee when providing opinion on a clinical trial to be performed in children of any age group. "The Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol;" The expert(s) may be permanent members of the Ethics committee, or experts providing advice and consulted on an *ad-hoc* basis. Paediatric experts should be independent of the sponsor, the investigator and the research proposed.

Ethics Committee's paediatric expertise should be available when reviewing the initial protocol as well as any subsequent significant amendments.

8.1.1 Examples of Paediatric expertise

Paediatric expertise goes beyond having dealt with children and could be defined on the basis of education and experience on the various aspects of child development, ethics and psychosocial aspects. Therefore, this would include i) physicians with paediatric qualification; ii) paediatric ethicists; iii) qualified paediatric nurses or psychologists, etc. In addition to qualification, it is recommended that the experts demonstrate at least some years of experience in paediatric care, and direct experience of clinical trials, for example as an investigator in several trials performed in children of a similar age groups.

If this cannot be found in one individual, two or more experts could combine the expertise needed.

Expertise used should be documented and recorded by the Ethics Committee.

8.1.2 Opinion on the protocol

Considering the need for additional protection of children involved in trials and with a view to providing an opinion on the protocol, the Ethics Committee should also check the content of the protocol with respect to paediatric protection. If the Ethics Committee is not in charge of scientific review according to national law, it should however check that the competent scientific body has confirmed that the research is scientifically sound. This is achieved by national Competent Authorities in the process of authorising the clinical trial. In particular, the following points should be checked:

- Protection of children is ensured (including minimisation of risks, fear, pain and distress) and appropriate paediatric expertise is available at all trial sites.

- A justification is provided for the inclusion of children to achieve the objectives and of the choice of age groups.

- Appropriate non-clinical data are available before the use of the product in children. Such data are defined, for example, in the ICH E11guideline. This may include data from juvenile animals studies, modelling or other predictive studies.

- Exhaustive review of available evidence (including relevant publications) and experimental work on the investigational medicinal product should be available and reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit, and the age ranges of children to be included. The difference expected versus comparators should be described. Replication of similar trials based on identical hypothesis should be avoided.

- The quality of the performance of the trial is such that it is likely that the results will be interpretable; monitoring, audit and quality assurance are described.

- The trial uses age appropriate formulations of the medicinal product(s).

- An independent Data and Safety Monitoring Board with appropriate expertise in the conduct of clinical trials in children is identified in the protocol, unless otherwise justified.

- There are provisions in the protocol for systematic independent publications of results, within a reasonable timeframe, including when results are unfavourable.

- The protocol includes provision of the medicinal products to patients involved in trials after the completion of the trial where appropriate, unless the benefit to risk balance of the medicinal product tested proves negative.

- The Ethics Committee and the Competent Authorities should ensure that the sponsor permanently monitors the balance of risk and benefits of the research so that the health and well being of the children enrolled are safeguarded.

- For randomised trials, in particular those using a placebo, there should be equipoise (genuine uncertainty) at the beginning of the trial and no participants should receive care known to be inferior to existing treatments.

To help Ethics Committees in reviewing paediatric trials, Annex 2 is a list of the aspects to be taken into consideration when reviewing a clinical trial to be performed in children.

9. Paediatric clinical trial designs

9.1 Design and analysis

The clinical trial design depends on the objective(s) of the trial and the scientific question(s) to be answered. If the trial is conducted with a view to provide data for regulatory purposes, reference should be made to scientific guidelines for drug development in children, in particular EMEA guidelines.

To ensure feasibility of trials to be performed in older children or adolescents, the trial design can be set up following consultation of the patients from age groups to be involved in the trial.

As is the case for trials in adults, all measures to avoid bias should be included in trials performed in children. For example, open and/or uncontrolled trials are subject to increased bias and should be avoided whenever possible.

- When unavoidable (e.g., when differences in product mode of administration are impossible to mask), open trials should include provisions for blinding of assessment. Assessment in many cases will be based on the clinical evaluation of parents, or other carers. Whenever possible the child's evaluation should be obtained.

- Uncontrolled trials (refer to ICH E6) should be avoided in principle for demonstration of efficacy. They have limited usefulness for the demonstration of safety, unless they are used prospectively for follow up and cohorts, in predefined subgroups. Trials performed in children affected by rare diseases should follow the same methodological standards as those performed in more common diseases. Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they should be agreed with competent authorities when used with a view to provide regulatory data.

- The size of the trial conducted in children should be as small as possible to demonstrate the appropriate efficacy with sufficient statistical power. Adaptative, Bayesian or other designs may be used to minimise the size of the clinical trial.

9.2 Paediatric control groups

9.2.1 Use of placebo

Use of placebo in children is more restricted than in adults, because children cannot consent. Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions. However, the use of placebo is often needed for scientific reasons, including in paediatric trials. Placebo may be warranted in children as in adults when evidence is lacking. As the level of evidence increases, the ethical need for placebo decreases. Placebo use is not equivalent to absence of treatment, for example placebo should be used on top of standard care. In all cases, its use should be assorted with measures to minimise exposure and avoid irreversible harm, especially in

serious or rapidly evolving diseases. As appropriate, rescue[3] treatment and escape procedures[4] should be set up. Other trial designs should be considered if appropriate. Active-control trials may be more difficult to interpret than placebo-controlled ones but may provide useful information on comparative benefit/risk balance. Reference is made to the ICH E6 guideline, and other relevant guidelines. The CPMP statement[5] on placebo-controlled trials in relation to the revised Declaration of Helsinki can also be consulted.

Therefore it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for paediatric clinical trials.

9.2.2 Superiority versus non inferiority trials

Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins, may raise issues as any decrease in quality of the trial performance blurs the difference between treatments, increasing the probability of concluding that products have equivalence when this is not the case.

Please refer to existing guidelines on methodology issues and/or specific EMEA guidelines per therapeutic area.

9.2.3 Controlled trials using reference medicinal products devoid of marketing authorisation in children

As many medicines used in children have not been fully assessed and authorised, the choice of active control products should be discussed thoroughly. Unauthorised products may be considered suitable as controls if they represent evidence-based standard of care.

9.2.4 Clinical trials using medicinal products containing radio-isotopes

The use of stable isotopes should be considered to avoid irradiation.

10. Pain, distress, and fear minimisation

Pain should be prevented as much as possible, and effectively treated when unavoidable. This requires that pain intensity is assessed and regularly monitored according to guidelines and age and condition-appropriate validated scales. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly on the basis of the assessments performed. Patient-controlled analgesia may be used where appropriate, i.e., in children of sufficient understanding. Pain may be due to the disease or condition itself, and directly or indirectly to the medical interventions. Painful procedures should be minimised. This may be achieved for example by using indwelling catheters introduced under topical anaesthesia if repeated blood sampling is necessary. Non-invasive procedures should be preferred if validated. Population approaches for pharmacokinetic data may reduce the number of blood samples in each child.

The parents/legal representative should be informed of which procedure is part of the usual care and which is performed in relation to the trial. Examples of painful procedures include but are not limited to physical discomfort (exposure to cold, heat or light, noise), positioning and immobilisation,

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[3] Rescue refers to treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level

[4] Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level in a trial

[5] http://www.emea.eu.int/pdfs/human/press/pos/1742401en.pdf

invasive procedures such as blood sampling (capillary, venous and especially arterial) and vascular access, biopsies, lumbar puncture, sampling, repeat examination of injured or traumatised limbs or part of the body, endotracheal intubations and airways clearance, oral or nasal tubing.

In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedure(s) should be maintained.

Facilities should be appropriate to childcare and the personnel should be trained to look after children and supervised by experienced personnel. Staff should be trained to communicate with both parents (or legal representative) and children. Children in a trial should be hosted in a familiar environment, including appropriate furniture, toys, activities, and where appropriate, school attendance.

Fear should be prevented if possible, or if not, minimised; the need of the child for comfort and reassurance should always be kept in mind. Age appropriate information should be given to the child and his representatives prior to any investigations or procedures. Changes in the procedures should be announced to the child. Separation of the child from parents or familiar persons should be avoided whenever possible.

The variability of response to pain, distress and fear between children should be taken into consideration. Different reactions may be expected, when children are affected by a chronic or acute disease. Tolerance of pain increases with age and maturation when medical procedures are not considered any more as ‘punitive’.

In all situations, investigations should be limited to a minimum and performed using size/age-appropriate material and devices.

11. Assessment of the level of risk and its monitoring

11.1 Assessement of risk

Risk assessment is a crucial step in assessing a protocol (and conducting the trial). Risk is defined as potential harm (real or theoretical) or potential consequence of an action. It may be physical, psychological, or social, and may be immediate or delayed. It may vary according to age groups. Risk should be assessed in terms of probability, magnitude and duration.

Risk assessment includes the evaluation of the risk of the medicinal product tested or the control, the risk of withholding active treatment in some cases, the risk of the disease itself. Potential harms would include invasiveness, intrusiveness of research, the severity as well as seriousness of potential harms, the reversibility of adverse effects and reactions, and preventability. The accumulation of research projects in the same population (over-studied population) is another aspect.

The timing of paediatric studies in relation to the information obtained from preclinical data and in adults may also be related to the level of risk, either when studies are performed ‘too early’ or when a delay to study potentially effective medicinal products in children is linked to obtaining adult data.

The unavailability of age-appropriate paediatric formulations may also incur a level of risk.

It should be noted that for example a pre-symptomatic diagnosis (e.g., genetic diagnosis) might incur a level of risk, such as decrease in opportunities and freedom of choice. Similarly, violation of privacy is considered as potential harm.

In case of emerging issues during a trial with potential conflict between the children’s interest and research interest, the protocol should envisage the management of such issues, e.g., harm in giving versus harm in withholding treatment. The child’s interest should always prevail over that of research (as is required under Article 4(i) of the Clinical Trials Directive).

In addition to the risk inherent to the trial, there is a need for evaluation of external risks, for example linked to the centres involved with variable level of expertise or experience.

Risk assessment is difficult in practice as probability is unknown; the elements that influence the risks should be identified in the protocol.

Finally, any identified risk should be associated to measures to prevent, minimise and monitor such risks.

Determination of the levels of risk involved in a clinical trial is proposed in some Member States guidance. The following examples of guidance are informative:

- Risk management proposed in a UK guideline

Risks should be i) minimised and ii) reasonable in relation to the expected benefit (including knowledge gained). Analysis should take into consideration risks of short term as well as long-term risks including delayed occurrence of such risks.

- Risk management in the French law

  - Either there is expected direct benefit which justifies the known risks

  - Or there is expected benefit for other minors, and then the foreseeable risks and inconveniences should be minimal.

- Examples of risk levels in the US regulations `

  - No more than minimal risk

  - More than minimal but potential for direct benefit

  - Minor increase over minimal risk without direct benefit, but research is likely to yield generalisable knowledge about subject's disorder or condition

  - Not otherwise approvable, but presents an opportunity to understand, prevent or alleviate a serious problem affecting health or welfare of children.

  Minimal risk is defined as "probability of harm or discomfort not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

11.2 Monitor the level of risks

The level of risk may evolve over time, during the trial and with evolving knowledge. It should be continuously monitored. For this purpose the use of Data and Safety Monitoring Board is recommended. Stopping rules should be included in the protocol if interim analyses are planned.

The sponsor of the clinical trial should identify and assess the risks (real and theoretical) and harms induced by the investigational medicinal products in the safety report submitted once a year throughout the clinical trial, or on request, to the Competent Authority and the Ethics Committee of the concerned Member States. 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.

12. Measures of Benefit

12.1 Direct benefit

Benefit can be defined as progress in treatment, diagnosis, or prevention for the group of children affected. It is a tangible outcome that may be experienced by the subject. This may be obtained through either increased efficacy or safety resulting in better risk-benefit balance, or through the provision of an alternative to existing treatment with at least similar expected benefit to risk. Benefit can also be obtained through contribution to patient care (for example, better route of administration, decreased frequency of dosing). Benefit, either direct or indirect, should be expected in any trial performed in children.

The potential benefit may seem easier to determine than the risks. The benefit of research should be assessed in particular to determine whether or not there will be potential direct benefit for the children included in the trial.

In addition, a fair distribution of the benefits of research should involve checking that gender and ethnic groups are balanced and minorities or children from certain cultural backgrounds are not excluded from clinical trials.

12.2 Direct benefit for the group

The European Convention on Human Rights and Biomedicine states in its article 17.2 “Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions:

1. The research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;

2. The research entails only minimal risk and minimal burden for the individual concerned.”

In terms of legal requirements, Article 4(e) of the Clinical Trials Directive states “some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;” and Article 4(i) states “the interests of the patient always prevail over those of science and society”.

Benefit for the group, i.e., children affected by the same disease, or a disease which shares similar features and for which the medicinal product could be of benefit, could be defined by increased knowledge of the condition and/or treatment, which would eventually result in better diagnosis, treatment or prevention.

Measures of such benefit would include the importance of knowledge gained, severity of the issue to be addressed, commonality of the issue, likelihood of obtaining results from proposed research, and usefulness of benefits obtained.

13. Assays in relation to age/bodyweight - Blood sampling

Assays, investigations and blood sampling volumes should be described in the protocol.

13.1 Type of assays

The number and type of assays and investigations should take into consideration the age and/or bodyweight (body surface area if appropriate) of the children to be included in the trial. Specific facilities and material should be used. Sampling should be performed by trained staff. For blood and tissue assays, micro-volumes and micro-assays should be used, whenever possible. Local or general anaesthesia should be used as appropriate for planned painful and/or invasive procedures.

13.2 Volume of blood

- Preterm and term neonates have very limited blood volume, are often anaemic due to age and frequent sampling related to pathological conditions. Per trial, blood loss should not exceed 3 per cent of the total blood volume, which is estimated at 80 ml/kg body weight, and should not exceed 1% at any single time. This should be taken into consideration when defining blood or tissue sampling volume and timing.

- Timing of sampling should be co-ordinated as far as possible to avoid repeat procedures in order to minimise pain and distress, and the risk of iatrogenic complications.

Monitoring of actual blood loss is required in preterm and term neonates.

14. Studies in neonates (term and pre-term)

Neonates, be they preterm or term, represent the most vulnerable of the paediatric populations. When affected by serious diseases, they are multi-drug users with potential interactions to be taken into consideration. Trial protocols in this population should take into account the complexity of the situation and potential for long-term, including developmental effects. Particularly thorough scrutiny from ethics committee and investigators is therefore required.

15. Healthy children/ ‘volunteers’ studies

In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable. Studies should not be performed in children when they can be performed in adults. In some situations however, studies have to be performed in healthy children. Prevention trials or paediatric vaccine trials, including immunogenicity studies, may fall into this category are an example of such trials. Whenever possible the older age groups should be considered for inclusion before the younger ones.

Proof of concept should be obtained in relevant animal models and/or in adults whenever possible. Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible, i.e., the one affected by the disease, although it is recognised that data obtained in affected children may have increased variability. Vaccines trials are performed in healthy children, but who represent the intended population.

16. Vaccines

Immune response should be studied in the target population taking into consideration immune system maturation. See also Section 15.

17. Paediatric formulations to be used in paediatric trials

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. 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.

When they exist, paediatric formulations should be used. If extemporaneous preparations are used for lack of appropriate formulation, the conditions for preparing it and the dose should be indicated and should follow Good Manufacturing Principles, as expressed in Commission Directive 2005/28/EC. Excipients used for the formulation should take into consideration the age of the children included in the trial (e.g., benzyl alcohol is contraindicated in neonates). Conditions to avoid bacterial contamination and degradation of the medicinal product should be specified in the protocol. Refer to Commission guideline on excipients and the Reflection Paper on Formulations of choice in the paediatric population.

18. Individual Data protection

The specificity of data protection in children relates to future (unknown) use of data obtained in children. Biobank samples retention and the need for consenting to such use should be discussed in the protocol. The trial documents should be archived for a duration that takes into consideration the potential need for long-term review of trials performed in children (long-term safety).

Children are less likely to challenge records about themselves. Therefore there is additional duty from researchers to protect confidentiality and access to data.

Protocols should specify the level of protection of educational records when studies are performed in schools (access, amendments and disclosure), and the information given to parents or legal representative. This is particularly important when trials include adolescents and address issues of sexuality, illicit drug use or violence.

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.

19. Unnecessary Replication of trials

It is considered unethical to replicate unnecessarily trials in children. This can only be avoided by ensuring that information gained in any trial is made available to researchers and the public, as is provided for in Article 41 of Regulation (EC) No xxx/2006 on medicinal products for paediatric use (see below).

19.1 Publication of trials and of results

Systematic registration of paediatric clinical trials and publication of results including unfavourable ones, and thorough analysis of the literature should allow detecting similar trials, with similar aims.

Trials in phase 2, 3 and 4 should be published. Phase 1 trials should be published as they contribute to general knowledge, in particular with respect to safety. Ethics Committees should not accept paediatric protocols limiting the possibility of independent publications by the investigator.

The Paediatric Regulation includes a derogation to Article 11 of the Clinical Trials Directive ensuring that part of the information concerning clinical trials performed with a view to developing medicinal products for paediatric use are made public (Article 41 of Regulation (EC) No xxx/2006 on medicinal products for paediatric use).

19.2 International database and availability to the public

There is an ethical duty to check whether existing knowledge is susceptible to modify the initial hypothesis for the trial. Public access to ongoing and completed trials through existing databases will facilitate avoiding replicating unnecessarily trials in children.

20. Adverse reactions and reporting

Rules and obligations are identical to those of adult trials, in particular the notification of serious adverse reactions observed in clinical trials is applicable to paediatric clinical trials (article 17 of Clinical Trials Directive).

As adult data are poorly predictive of safety in children, reporting may cover target organs and types or severity of reactions differing from that expected in adults. A specific assessment of the adverse reactions associated with the administration of the investigational medicinal product in children should be performed in the annual safety report.

Parents/legal representative and carers should be encouraged to report adverse reactions and events to the investigators. Young children may not be able to identify adverse reactions.

21. Inducements versus compensation for children

Article 4(d) of the Clinical trials Directive requires that there must be no inducement to enter a trial, either for the parents, legal representatives or children. Parents/legal representative can only be compensated for their time and expenses.

22. Insurance issues

Insurance is mandatory according to the Clinical Trials Directive (Article 3(f)). Obtaining insurance for trials performed in children, in particular those in neonates, may be difficult as insurance companies often invoke issues of long-term liability. Ethics Committees should pay careful attention to waivers of liability in the insurance contract, in particular with respect to long term effects on development. However, unrecognised congenital defects are generally excluded.

23. Trials in children in non-EU countries

According to Directive 2004/27/EC, amending Directive 2001/83/EC, clinical trials submitted in a marketing authorisation in the EU performed in third countries (non EU countries) should be conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of that Directive and should comply with good manufacturing practices of EU countries. CIOMS guidelines[6] state that ethical standards should be no less exacting than they would be for research carried out in a EU member state. The trial should ensure that it responds to the public health needs and priorities of the hosting country. It is the responsibility of all involved parties to ensure that this is respected and that the paediatric specificities, including assent are obtained for children.

24. Ethical violations, and non compliance with GCP

Although not specific to paediatric trials ethical violations and non compliance with GCP is particularly important as children are a vulnerable population. There is a role for Ethics Committees and Competent Authorities in case of violation, and non-compliance with GCP. The preferred option to avoid such violations is education and counselling. Failing this, Ethics Committees should liaise with Competent Authorities if they are informed of such violation or non-compliance.

Compliance with GCP should be explicit in publications, and results of studies conducted unethically should be refused for publication. Similarly, data submitted in support of applications for marketing authorisation, which have been obtained unethically (violation of, or non compliance with GCP) may be considered as fraudulent and validity of the marketing authorisation application and the study

[6] see Section 4.2

results should be scrutinised. Sensitivity analysis with and without non-GCP data should be performed. Overall reliability of the trial should be questioned. Subsequent measures should be taken in accordance with national legislation, if appropriate.

25. ANNEX 1 (responses to questionnaire)

Content of the questionnaire:

1) **National provisions for consent**[7] (legal representative) in the Member States

Do you have a law covering consent in clinical trials?

Do you have a legal definition of 'legal representative'?

Do you have national guidelines[8] covering consent in clinical trials?

Do you have national guidelines defining 'legal representative'?

What is the requirement from at national level:

Consent should be obtained from one parent?

Consent should be obtained from both parents?

In case of disagreement between the 2 parents, do you have specific provisions (law or guidelines) to deal with such disagreement?

What are these provisions?

2) Specific national provisions for child' s assent

Do you have a law, addressing assent from a child participating in a trial?

Do you have national guidelines addressing assent from a child participating in a trial?

[7] Consent refers to legal representatives, as opposed to assent which refers to minors

[8] Guideline means implemented at national level, excludes local recommendations.

Is assent required?

If yes, from which age?

In relation to development milestone (eg, from school age)?

Is there a need for written child's assent?

If yes, from which age?

3) Neonates

Do you have laws or national guidelines to confer additional protection to neonates?

4) Adolescents

Do you have a law stating that adolescents can consent independently?

Do you have a national guideline stating that adolescents can consent independently?

If yes, from which age?

Is there a possibility for adolescents to overrule their parents's decisions (or legal representatives's decision)

Is the investigator obliged to follow the parent(s)'s decision?

Is the investigator obliged to follow the adolescent's decision?

Do they have the right to privacy vis-à-vis parents (or legal representatives) in a clinical trial (e.g., for contraceptive use, Sexually Transmitted Diseases)?

5) Emergency trials

Do you have a law on consent in emergency trials?

Do you have a guideline on consent in emergency trials?

Do you have specific provisions for consent in paediatric emergency trials?

6) Other questions:

Can parents contact directly Ethics Committees to obtain information?

Is there a role for national authorities when there is disagreement between parents and investigators?

Is an investigator required to provide information to parents in case of a negative opinion of Ethics Committee during trial?

MS	AT	BE	BG	CY	CZ	DK	ES	FI	FR	GE	GR	HU	IS	IE	IT	LV	LT	LU	MA	NO	PL	PT	RO	SL	SP	SW	NL	UK	CH
Law on consent					Y	Y	Y	Y	Y	Y		Y				Y	Y		Y		Y				Y	Y		Y	
Legal Repres. legal Definition					N	Y	Y	Y	Y	Y		Y				Y	Y		Y		Y				Y	N		Y	
Guidelines on consent					Y	Y	Y	Y	Y	Y		Y				N	Y		Y		N				N	Y		Y	
Guideline on Legal Repres.					Y	Y	-	Y	Y	N		Y				Y	Y		N		N				N	N		Y	
One parent consent					Y	N	Y	Y[9]	Y[10]	Y		Y				Y	N		-		Y				Y	N		Y	

[9] Special conditions (trial characteristics) for consent from only one parent

[10] Special conditions for consent from only one parent

2 parents consents					-	Y	-	Y	Y	N		N				N	Y		Y		- Y?				-	Y		N	
Disagreement between parents GL					-	N	N	Y	N	N		N				Y	N		Y court		Y court				Y	Y		Court	
Law Child assent					Y	Y	Y	Y	Y	Y		Y				Y	N		Y		Y				Y	Y		Y	
GL child assent					N	Y	N	Y	Y	N		Y				N	Y		Y		N				-	Y		Y	
Assent required					Y	Y	Y	Y	Y	Y		Y				Y	Y		N		Y				Y	Y		Y	
From age					NS	NS	7	15	NS	NS		NS				7	NS		NS		16				12	NS		NS	
Written assent					Y	N	Y	Y	N	Y		N				Y	Y		N		Y				Y	Y		Y	
From age					NS	-	7	15	-	NS		-				7	NS		-		16				12	NS		NS	
Neonates provisions					N	N	N	Y	N	N		N				N	N		N		N				Y[11]	N		N	
Law Adolescent consent					N	Y	N	Y	N	Y		N				N	N		N		N				-	N		N	
GL adolescent					N	Y	N	Y	N	N		N				N	N		N		N				-	N		Y	

[11] For breast feeding mothers

consent																												
From age					-	15	-	15	-	-		-				-	-		-		-				-	-		-/16	
Adolescent overrule parents					Y	+/-	N	Y	N	N		-				N	N		Y court		N				-	Y		N	
Investigator follows parents					N	-	Y	Y[12]	Y	-		-				Y	N		Y		Y				N	Y		N	
Investigator follows Adolescent[13]					Y	Y	N	Y	Y	-		-				Y	N		Y		Y				Y	Y		N	
Privacy right for adolescents vz parents					Y	Y	N	Y	N	N		N				N	N		N		N				-	Y		N	
Law on consent in emergency T					Y	Y	Y	Y	Y	Y		N				N	N		N		Y/N				Y	Y		N	
GL on consent emergency					N	Y	N	Y	Y	N		N				N	N		N		N				-	N		N	

[12] Agreement between parents and adolescents should be reached if parents negative and adolescent positive

[13] This was understood in most cases as respect of refusal from adolescent to participate (and not the possibility for an adolescent to consent when parents don't)

T																												
Consent in paed emergency T					N	N	N	Y	N	Y		N				N	N		N		N				N	N		N	
Contact parents EC					Y	-	Y	Y	N	N		Y				Y	Y		Y		Y				-	Y		N	
NCA and disagreement parents/ investig					Y insp	N	Y	N	N	N		Y				Y	N		Y court		N				N	N		N	
Negative opinion EC to parents					Y	-	Y	Y	Y	Y		Y				Y	Y		Y		Y				Y	Y		N	

Y: yes; N: no; NS: not stated

26. ANNEX 2

List of issues to be taken into consideration for planning a paediatric study:

- Identification and scientific validity of the study question to be answered
- Justification of the study to be performed in children and in the proposed age groups
- Evidence of direct benefit for the child, or benefit for the group
- The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial. The balance of risks versus expected benefits should be positive for the clinical trial.
- 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 in paediatric research in general and in particular in the field of the applied project.
- The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a paediatric clinical trial
- The clinical results of adult studies (literature, investigator's brochure), if any.
- Type and phase of the study
- Use of placebo or active control
- Age-appropriate scales or measures of end-points (e.g., pain scale)
- Study design and biometric planning in relation to the trial question
- Inclusion and exclusion criteria
- Statistical methods
- Criteria for the termination of the study
- Safety measures
- Study risks, pain, fear and discomfort
- Comprehensive, understandable Informed Consent and Information sheets for legal representatives
- Understandable age specific Informed Assent and Information sheet for children
- Anonymity of the data
- Appropriate pharmacovigilance procedures are put in place by the sponsor
- Insurance of child participants, in the relevant country
- If available, opinions of other ethics committees for international multicentre studies
- Publication of study results
- Continuation of trial medication where appropriate

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