

ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS ON MEDICINAL PRODUCTS CONDUCTED WITH THE PAEDIATRIC POPULATION

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

KEYWORDS	Ethics, Clinical trials, Child, Neonate, Minor, Adolescent, Directive, Consent, Ethics Committee, Assent
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TABLE OF CONTENTS

EXECUTIVE SUMMARY	4
1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF RECOMMENDATIONS	4
2. SCOPE	5
3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS	5
4. LEGAL CONTEXT	6
4.1 LEGAL CONTEXT	6
4.2 RELEVANT GUIDELINES	6
5. DEFINITIONS/ GLOSSARY	7
5.1 ETHICS COMMITTEE	7
5.2 PAEDIATRIC POPULATION	7
5.3 CHILD	7
5.4 MINOR	7
5.5 LEGAL REPRESENTATIVE OF THE MINOR	8
5.6 INFORMED CONSENT	8
5.7 ASSENT	8
5.8 AGE GROUPS	9
6. THE PROCESS OF INFORMED CONSENT	9
6.1 INFORMED CONSENT FROM THE LEGAL REPRESENTATIVE	9
6.2 SPECIFICS FOR INFORMED CONSENT OF THE LEGAL REPRESENTATIVE(S) IN THE VARIOUS MEMBER STATES	10
6.3 INFORMED CONSENT (AND ASSENT FOR CHILDREN) OF FAMILIES WITH DIFFERENT CULTURAL BACKGROUND	10
6.4 CONSENT (AND ASSENT) AT THE BEGINNING OF A TRIAL AND CONTINUED CONSENT AND ASSENT DURING TRIAL	10
6.5 WITHDRAWAL OF THE CONSENT	10
7. ASSENT FROM CHILDREN	11
7.1 ASSENT ACCORDING TO AGE GROUPS AND LEVEL OF MATURITY	12
7.1.1 <i>Children from birth to 3 years of age</i>	12
7.1.2 <i>Children from 3 years of age</i>	12
7.1.3 <i>Adolescents</i>	12
7.2 DIFFERENCE OF OPINION BETWEEN THE CHILD AND THE PARENTS / LEGAL REPRESENTATIVE	13
8. ETHICS COMMITTEE'S COMPOSITION IN RESPECT OF PAEDIATRIC TRIALS	13
8.1 EXAMPLES OF PAEDIATRIC EXPERTISE	13
8.2 OPINION ON THE PROTOCOL	13
9. DESIGN OF CLINICAL TRIALS CONDUCTED WITH THE PAEDIATRIC POPULATION	14
9.1 DESIGN AND ANALYSIS	14
9.2 PAEDIATRIC CONTROL GROUPS	15

9.2.1	<i>Use of placebo</i>	15
9.2.2	<i>Superiority versus non-inferiority trials</i>	16
9.2.3	<i>Controlled trials using (reference) medicinal products without a marketing authorisation in children</i>	16
9.2.4	<i>Clinical trials using medicinal products containing radio-isotopes</i>	16
10.	PAIN, DISTRESS, AND FEAR MINIMISATION	16
11.	RISK ASSESSMENT AND MONITORING	17
11.1	ASSESSMENT OF RISK	17
11.2	MONITORING THE LEVEL OF RISK	18
12.	BENEFIT AND MEASURES OF BENEFIT	18
12.1	BALANCE OF BENEFIT AND RISK	19
13.	ASSAYS IN RELATION TO AGE/BODYWEIGHT AND BLOOD SAMPLING	19
13.1	TYPE OF ASSAYS AND SAMPLE COLLECTION	19
13.2	VOLUME OF BLOOD	20
14.	TRIALS WITH NEONATES (TERM AND PRE-TERM)	20
15.	TRIALS WITH HEALTHY CHILDREN	20
16.	VACCINES	21
17.	PAEDIATRIC FORMULATIONS TO BE USED IN PAEDIATRIC TRIALS	21
18.	INDIVIDUAL DATA PROTECTION	21
19.	UNNECESSARY REPLICATION OF TRIALS	22
19.1	PUBLICATION OF PAEDIATRIC TRIALS AND RESULTS	22
19.2	INTERNATIONAL DATABASE AND AVAILABILITY TO THE PUBLIC	22
20.	ADVERSE REACTIONS AND REPORTING	22
21.	INDUCEMENTS VERSUS COMPENSATION FOR CHILDREN	22
22.	INSURANCE ISSUES	22
23.	TRIALS IN CHILDREN IN NON-EU COUNTRIES	23
24.	ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GCP	23
25.	ANNEX 1: RESPONSES TO QUESTIONNAIRE	24
26.	ANNEX 2: LIST OF ISSUES FOR A TRIAL WITH THE PAEDIATRIC POPULATION	28
27.	ANNEX 3: INFORMATION FOR INFORMED CONSENT	29
28.	ANNEX 4: EXAMPLES FOR LEVELS OF RISKS	30
29.	REFERENCES	32
29.1	GENERAL GUIDANCE	32
29.2	NATIONAL GUIDANCE ON ETHICS	32
29.3	RESEARCH AND CLINICAL TRIALS IN CHILDREN	33
29.4	CONSENT AND ASSENT	33
29.5	NEONATES IN CLINICAL TRIALS	34
29.6	PLACEBO USE	34

EXECUTIVE SUMMARY

This document has been developed by the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC¹ 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 birth up to the legal age of adulthood. This will contribute to the protection of all children who are the subject of clinical trials. As the approval of clinical trials, including ethical approval, is performed by the Member States, any recommendations on ethical aspects of clinical trials in children will also facilitate a harmonised approach to the application of the clinical trials directive across the EU, thereby facilitating the conduct of clinical trials in the EU and in whichever country the paediatric trial occurs. 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 (in the legal sense) but their assent should be sought using age appropriate information. Ethics Committees need paediatric expertise to balance the benefits and risks of research in children. The lack of legal ability to consent has implications on the design, analysis and the choice of comparators used in 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

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. 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) and in doing so lays down specific provisions 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.

The reasons why medicinal products need to be studied in children have been detailed in various publications. In summary, children are not small adults. Differences in pharmacokinetics and pharmacodynamics, and in adverse reactions are common in children compared to adults. Growth and maturation processes, as well as certain specific diseases are unique to children. Specific consequences of medical interventions may be seen in children and may only appear long after exposure. Unfortunately this has been demonstrated by previous catastrophes with the use of medicinal products.

Because of the special protection they deserve, children should not be the subject of clinical trials when the research can be done in legally competent subjects (i.e. adults capable of informed consent).

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. OJ L 121, 1.5.2001, p. 34

If research with children proves necessary, the least vulnerable among them should usually be included (i.e. older children). If there is a necessity to subject children to a clinical trial, the choice of subsets of the paediatric population to be included should be made on the basis of the likely target population for the medicine being tested, the possibility of extrapolation, and the scientific validity of such an approach.

The recent Community Regulation on medicinal products for use in the Paediatric population (Regulation (EC) No 1901/2006) will lead to the increase in the number of clinical trials conducted in this population. The recommendations in this guideline aim to bring together ethical principles from the various documents that already exist (cf. 4.2), as they are understood currently. With time, the need for revision of this document may emerge.

2. SCOPE

This document is intended to provide recommendations 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 all persons involved in any stage of a clinical trial, including sponsors of clinical trials, ethics committees, regulatory authorities, pharmaceutical companies, insurance companies (regarding trial subjects), investigators (including all trial-related staff) of clinical trials performed in children of all ages (minors, cf. 5.4), families and patient representatives. This document is without prejudice to the obligations created by Directive 2001/20/EC and the need to follow EMEA guidelines (Article 4(f) of the same Directive). In addition, these recommendations do not distinguish between non-commercial and commercial research.

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

The recommendations in the document aim to contribute to the promotion and protection of the dignity, the well-being and the rights of children (minors) all of whom 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.

The recommendations provided here are also relevant to clinical trials conducted in non-EU countries, especially developing countries. In principle, recommendations from this guideline can be used also in trials other than clinical trials, such as non-interventional trials.

3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS

Ethical principles referred to in this document are those expressed, for example, in the Declaration of Helsinki published by the World Medical Association, the United Nations' Convention on the Rights of the Child, the Charter of Fundamental Rights of the European Union (2000), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005), the Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997), the International Declaration on Human Genetic Data (UNESCO, 2003), the Universal Declaration of Human Rights of 1948, and the Council of Europe's 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 echoed and referred to in the ICH E6 guideline on Good Clinical Practice.

For the purpose of research, three ethical principles should be adhered to: respect for persons, beneficence and justice, 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 (herein the ‘Clinical Trials Directive’), as amended.
- 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 2003/94/EC of the European Commission of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
- 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 (EC) No 1901/2006 of the European Parliament and the Council, as amended, on medicinal products for paediatric use (herein the ‘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
- 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/PhVWP/235910/2005- rev.1
- 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)
- World Health Organization, Operational Guidelines for Ethics Committees That Review Biomedical Research (Geneva, 2000)
- 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).
- Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI.
- Confederation of European Specialists in Paediatrics (CESP) guidelines.

5. DEFINITIONS/ GLOSSARY

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 *Paediatric Population*

According to Regulation (EC) No 1901/2006, the term “paediatric population” refers to the part of the population aged between birth and 18 years. This term is used throughout these recommendations to cover all paediatric age groups.

5.3 *Child*

In contrast to ICH E11 guideline which refers to children as individuals aged from 2 to 11 years, when the term “children” is used within these recommendation, it is used consistently with the recitals of the Clinical Trials Directive to mean minors.

5.4 *Minor*

Article 4 of the Clinical Trials Directive refers to children as minors. When quoting or referencing the Clinical Trials Directive in relation to legal competence, the term “minor” will be used, and it applies to all individuals from birth until the legal age of adulthood (usually 18 years and above, rarely 16 years).

5.5 *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, who consent(s) on behalf of the minor.

5.6 *Informed consent*

Article 2(j) of the Clinical Trials Directive defines informed consent as follows:

“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 not be a minor and should be formally independent of the sponsor and the investigator. There is a need to clearly record the names and sufficient details of their relationship to the child of all persons involved in informed consent.

In these recommendations, “consent” refers only to the legal definition of consent.

5.7 *Assent*

The notion of assent is not explicitly included in the Clinical Trials Directive but is recognised in the Declaration of Helsinki:

“When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.”

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 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 who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator;”

In this document, “assent” should be understood in the context of Article 4(c) of the Clinical Trials Directive as the expression of the minor'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 of a child to make voluntary, informed decisions, i.e. to assent, evolves with age, maturity and previous experience of life and illness.

The notion of “presumed will” enables the parents or legal representatives to express their duty to protect their child and the child's interests, based on their experience with the child during the child's life up to that time.

5.8 Age Groups

When referring in these recommendations to a specific subset of the paediatric population, the age range will be given for clarity. The word “child” is not limited to the age range of 2 to 11 years as defined in ICH E11. Further subsets of the paediatric population as defined in ICH E 11 are: preterm newborn infants, term newborn infants (birth to 27 days), infants from 1 to 23 months, and adolescents from the age of 12 up to but not including 18 years (see also “Child” and “Minor” above). By emancipation² or when the child reaches adulthood during the time, in which he or she is participating in the trial, an adolescent may become legally competent to make decisions and to give informed consent.

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.

6. The process of informed consent

6.1 Informed consent from the legal representative

As the child (minor) is unable to provide legally binding consent, informed consent must be sought from the parents/ legal representative (see definition above) on the child’s behalf. Article 4(a) of the Clinical Trials Directive requires that the specific and written informed consent of parent/legal representative must be sought prior to enrolling a child in a trial. Information should be given by an experienced investigator, or his adequately trained delegate, to each parent, or the legal representative, on the purpose of the trial and its nature, the potential benefits and risks, and the name of investigator(s) who are responsible for conducting the trial with background professional information (such as education, work experience) and direct contact details (telephone and e-mail) for further information regarding the trial. The parent/legal representative should be given sufficient time and necessary information to consider the benefits and risks of involving the child in the clinical trial. When providing such information, it is important to take into consideration the fear and uncertainty of parents, especially when they are inexperienced with respect to the child’s condition. However, the parents/legal representative might need more detailed and explicit information, and hence more time, to also reflect on the implications of consenting, especially since they bear the full responsibility for the child, unlike in adult trial where one takes the responsibility for oneself.

Regarding the information given to the parents and legal representatives, items for review by the Ethics Committee are proposed in Annex 2.

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 enrol the child in the trial; no financial incentive should be offered except compensation and expenses.
- 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(a) of the Clinical Trials Directive.
- Parent(s)/legal representative should be reassured that the child’s treatment will not be prejudiced by declining to participate, or by withdrawing from the trial, in line with Article 4(a) of the Clinical Trials Directive.

² This is a legal term and applies under exceptional conditions: Minors can become emancipated through certain actions, such as marriage.

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

In the complex relationship between parents and physician(s), especially in case of chronic diseases and of rare diseases, but also in acute serious illnesses, or in the situation of less educated parents, there is a risk of unrealised obligations and emotional subordination on the side of the parents. Moreover, this may not be perceived by either party. However, the investigator should not take part in the decision making, but should ensure that the information has been understood and that there has been enough time allowed to come to a decision. Provision of information is also a continuous process.

If an adolescent aged 16 to 18 is no longer a minor as defined in national law, or is an “emancipated minor”, then written informed consent is required from these individuals as for any adult capable of giving consent. Under these conditions, informed consent is no longer required from the parents/legal representative, although an adolescent is still vulnerable and may require additional discussions and explanations.

6.2 *Specifics for informed consent of the legal representative(s) in the various Member States*

See Annex 1.

6.3 *Informed consent of families with different cultural background*

Where appropriate, a cultural mediator, familiar with medical terminology, independent from the sponsor and investigator, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent.

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

As discussed above, investigators should devote sufficient time to provide information and seek the legal representative(s)’ consent as well as the child’s assent, in accordance with legislation.

It is important to realise that consent is a dynamic, continuous process, and should therefore not only be obtained prior to enrolling a child in a trial but should be maintained during the trial on a continuous basis. This could be done for example, by a brief discussion during each repeat visit. It is recommended to document this process in the medical records or equivalent. The discussion is part of the ongoing dialogue between children, parents and investigators and should focus on all aspects of the trial but in particular on any new information that arises in relation to the trial and that might affect the willingness of the parent and child to continue.

Especially in long-term trials, the investigator should check the progressing maturation of the child and its ability for assent.

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

6.5 *Withdrawal of the consent*

In all circumstances, parent/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. Parent/legal representatives should be reassured that the withdrawal from the trial will not prejudice the child, will not result in any detriment and will not affect treatment. In addition, refusal to give consent or withdrawal of consent to participation in research must not lead to any liability or discrimination (e.g., with regard to insurance or employment) against the person concerned.

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 decide whether to withdraw the child from the research at any time. In the event of withdrawal from a blinded trial, if the parents/legal representative wishes to continue to follow the progress of the trial, information should be given that the actual data will not be available until the trial has ended.

When consent is withdrawn during a procedure, for example, during anaesthesia, it may not always be possible to stop the procedure immediately, as this might jeopardize the health of the child.

It must be emphasised that after a child withdraws from a trial, the investigator is still responsible for reporting trial-related events. In addition, the investigator needs to assure appropriate treatment and follow-up.

7. Assent from children

Whenever appropriate, the child should participate in the (informed) consent process together with the parents. Involving children in discussions and the decision-making process respects their emerging maturity. This process should be conducted with enough time and at the same time as obtaining consent from the parent(s) or the legal representative, so that the informed consent reflects the presumed will of the minor, in accordance with Article 4(a) of the Clinical Trial Directive. The central role of parents in the protection of their child should be recognised. The parents might also wish to discuss with the child on their own, after having been informed on the trial, and before meeting with the investigator.

The evaluation of whether or not a child can give assent should not solely be based on chronological age, but should also depend on other factors such as developmental stage, intellectual capacities (especially in children with special needs and/or learning difficulties), life / disease experience, etc. This needs to be made after discussion of the parents / legal representative with the investigator, but the parents will normally know the child best and hence are usually in a position to decide on whether the child has understood the information as much as is possible.

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), this document recommends that the investigator obtains assent in addition to informed consent of the legal representative. If the child's assent is not obtained, it is recommended that this be documented with justification in the consent form which is signed by the parents/legal representative and investigator. The minor's assent is not sufficient to allow participation in research unless supplemented by informed consent of the legal representative.

Separate information sheets for adults and children, and separate consent and assent forms should be used in order to provide age appropriate information, in language and wording appropriate to age, psychological and intellectual maturity. The assent information sheets and assent forms should be age appropriate and should include provision of information on the purpose of the trial, and potential benefits and harms, in terms that are honest, but not frightening. See also Annex 3 for recommended contents.

As discussed above, assent, like consent, is a continuous process and should be sought during the trial as well, e.g. during repeat trial visits. Objections raised by a child at any time during a trial should be considered. The child's will should be respected. The child should not be forced to provide reasons. 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 (cf. section 6.5).

The processes for informing the child and seeking assent should be clearly defined in advance of the research and documented for each child. While assent may not be possible in all age groups (e.g., neonates) or in all research conditions (e.g., research in emergency situations), the information process provided to the child and the child's response should be documented.

7.1 Assent according to age groups and level of maturity

7.1.1 Children from birth to 3 years of age

In this age group, it is not possible to obtain assent and understanding of research is not expected.

7.1.2 Children from 3 years of age

Within this age group there is the emergent capacity to agree. Where the child has some capacity of understanding (pre-school children), age- and maturity-appropriate information is still needed even if after giving information, assent is evaluated not to be obtainable.

Research on cognition shows that younger children have significant ability to provide assent. It is recognised that children from the age of 3-4 years 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 information forms 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 and obtain assent as described above, preferably in writing, when the child is of 'school age' (about 6 or 7 years old), i.e. able to read and write, and to then keep track of such assent.

7.1.3 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 assent 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 legal representatives. Most guidelines and publications recognise that adolescents are, under certain circumstances, able to make independent judgements, and this should be respected in the context of Article 4 of the Clinical Trials Directive. As in the younger age groups, the individual capacity is also linked to developing cognition and previous life/disease experiences.

Assent from an adolescent who is a minor should be sought, and, where possible respected. In any event, the Clinical Trials Directive requires the consent of the parents or legal representatives (see Article 4(a)). The information about the clinical trial needs to be provided to the adolescent according to their level of understanding and maturity.

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 and should be transparent to the adolescent concerned, as well as emancipation status, and age to consent to medical care.

When an adolescent is legally emancipated, i.e. ceases to be a minor, informed consent must be sought directly from the individual and as soon as possible. Precautions should be taken to ensure that information provided is sufficiently understood.

7.2 *Difference of opinion between the child and the parents / legal representative*

Every effort should be made to understand and respect differences of opinion between the child and his/her parents or legal representative. Strong and definitive objections from the child should be respected.

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

The Clinical Trials Directive includes the need for appropriate expertise in the Ethics Committee when providing an opinion on a clinical trial to be performed in children of any age group (Article 4(h)) "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. All members of the ethics committee including paediatric experts consulted on an ad hoc basis should be independent of the sponsor, the investigator and the research proposed. The qualifications and expertise of the experts used and the members of the Ethics Committee should be documented and annexed to its opinion.

Ethics Committee's paediatric expertise should be available when reviewing the initial protocol as well as any subsequent substantial amendments. Ethics Committees specialised in paediatrics could be considered for the evaluation of trial protocols that are complex or in serious paediatric diseases. Ethics Committees normally also include lay persons, some of whom may be parents.

8.1 *Examples of Paediatric expertise*

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

If this cannot be found in one individual, two or more paediatric experts could contribute to the expertise needed. Expertise used should be documented and recorded by the Ethics Committee.

8.2 *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 protocol has had adequate peer-review by experts in the field or the competent scientific body has confirmed that the research is scientifically sound. This is assessed by national Competent Authorities in the process of authorising the clinical trial.

In particular, the following points should be examined:

- Whether the trial replicates similar trials based on an identical hypothesis (which should be avoided)
- Protection and safety 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 trial objectives, for the choice of age groups. Depending on age groups, inclusion/exclusion criteria may need to include the outcome of a pregnancy test.
- Appropriate non-clinical data are available before the use of the product in children. Such data are defined, for example, in the ICH E11 guideline. This may include data from juvenile animals studies, modelling or other predictive studies.
- Extensive and comprehensive 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.
- 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 (DSMB) 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 regularly monitors and re-examines the balance of risk and benefit of the research so that the health and well being of the children enrolled are safeguarded.
- For randomised trials there should be equipoise (“genuine uncertainty within the expert medical community [...] about the preferred treatment”) 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 provides a list of the aspects to be taken into consideration when reviewing a clinical trial to be performed in children.

9. Design of clinical trials conducted with the paediatric population

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, including EMEA guidelines.

To ensure feasibility of trials to be performed, it is recommended that the trial design be set up following consultation of the patients from age groups to be involved in the trial (in older children or adolescents) or from patient representatives.

In addition to the selection of the age group(s) of children to be included in the trial (cf. sections 1 and 8.2), particular attention should be paid to the inclusion (and possibly detection) of certain ethnic subgroups, or subgroups with certain genetic characteristics (e.g. G6PDH deficiency). Genetic variations may produce significant differences in drug metabolism, in clinical response to drugs, and in adverse reactions that are to be expected.

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

Whenever possible (e.g., when differences in product mode of administration are impossible to mask), open trials should include provisions for blinding of assessment. Assessment, i.e., a systematic evaluation and documentation, in many cases will be based on the assessment by parents, or other carers. Whenever possible, the evaluation by the child should additionally be obtained.

Uncontrolled trials for demonstration of efficacy (refer to ICH E6) should be avoided in principle. They have limited usefulness for the demonstration of safety, unless they are used prospectively for longitudinal studies or 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 data for regulatory purposes.

The size of the trial conducted in children should be as small as possible but large enough to demonstrate the appropriate efficacy with sufficient statistical power. In conjunction with the analysis of risks and benefit, trials involving fewer children should be weighed against trials involving more children but using less invasive procedures. Adaptive, Bayesian or other designs may be used to minimise the size of the clinical trial.

9.2 Paediatric control groups

The use of control groups, including the use of placebo, should be based on equipoise, should be appropriate to the condition(s) under investigation in the trial, and should be justified scientifically.

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. The use of placebo is often needed for scientific reasons, including in paediatric trials. The use of placebo may be warranted in children as in adults when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain, hay fever). As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases.

Placebo use is not equivalent to absence of treatment, for example placebo could be used on top of standard care. In all cases, its use should be associated with measures to minimise exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases. As appropriate, rescue³ treatment and escape procedures⁴ should be set up. Other situations where the use of placebo should be scrutinised and challenged include run-in periods where a protocol requires active treatment to be withheld.

Situations in which placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the investigational medicinal product is the first one that may modify the course of the disease process, or, when the commonly used therapy for the condition is of questionable efficacy or carries with it a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.

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

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 statement⁵ on placebo-controlled trials in relation to paragraph 29 of 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 in relation to sample sizes feasible in the paediatric population, raise several issues, and should be fully justified when used instead of superiority trials. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non-inferiority trials. Existing guidelines on methodology issues and/or specific EMEA guidelines per therapeutic area should be consulted.

9.2.3 *Controlled trials using (reference) medicinal products without a 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. Medicinal products not having a marketing authorisation may be considered suitable as controls if they represent evidence-based standard of care. Definitions of standard of care may vary, which should be respected in trial design and analysis.

9.2.4 *Clinical trials using medicinal products containing radio-isotopes*

Except when radio-isotopes are required for therapy, the use of stable isotopes should be considered to avoid irradiation.

10. Pain, distress, and fear minimisation

Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and distress intensity is assessed and regularly monitored according to guidelines and age and condition-appropriate validated scales, particularly in preterm, newborn and other children who cannot express it. 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 and sparse sampling 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. Age-appropriate explanation should be given to the child prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might also lead to humiliation (therefore causing emotional pain) of the child (such as undressing) should be avoided or explained. Examples of painful procedures include but are not limited to physical discomfort (exposure to cold, heat or light, noise), positioning and immobilisation, invasive procedures such as blood sampling (capillary, venous and

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

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.

In order to minimise pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. 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, and their concerns should be addressed by skilled personnel.

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. Changes in the procedures should be announced to the child. Separation of the child from parents or familiar persons should be avoided whenever possible. If unavoidable, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent the procedure should be stopped; a short pause to allow the child to feel in control, further explanation and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure.

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/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.

11. Risk assessment and monitoring

The child's interest should always prevail over that of science and society. This is paramount when assessing and monitoring risks. Risks are to be viewed in balance to the benefit (section 12).

11.1 Assessment of risk

Risk assessment is a crucial step in evaluating 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. Paediatric trials should be analysed for potential risks, including those that may not usually be of concern in adults because medicines or procedures may cause adverse effects in children that have not been identified in adults. It is the responsibility of the investigator to make a thorough analysis of the risks in the trial and to describe this in the protocol in order for the ethics committee to be able to conclude on the approvability.

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

The timing of paediatric studies in relation to the information obtained from preclinical data and in adults may also be related to the levels 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 risk. Disclosure of a risk for an incurable disease following a pre-symptomatic diagnosis (e.g., genetic diagnosis) might also incur a 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. 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 and / or experience.

Risk assessment is difficult in practice as probabilities are 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 as much as possible.

The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. The following distinct risk levels are proposed as a means to decide on the ethical acceptability of trials.

- Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
- Minor increase over minimal risk
- Greater than minor increase over minimal risk

Practical examples for these risk categories are presented in Annex 4.

11.2 Monitoring the level of risk

The level of risk may evolve over time, during the trial and with evolving knowledge. Risk should be continuously monitored and pre-specified in the protocol. Stopping rules should be included in the protocol, especially for unscheduled or scheduled analyses in relation to safety or non-compliance. The use of a Data and Safety Monitoring Board (DSMB) is recommended. The DSMB should include paediatric experts. If a DSMB is not used, for example in certain pharmacokinetic studies, this should be justified. .

In line with the Clinical Trials Directive, 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, in the light of scientific developments or events arising in the course of the research.

12. Benefit and measures of benefit

Direct benefit refers to benefit for the individual and / or benefit for the group. For the purpose of this document, the term "indirect benefit" is not used.

Benefit can be defined as progress in treatment, diagnosis, or prevention for the child or 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 a better risk-benefit balance, or through the provision of an alternative to existing treatment with at least similar expected benefit risk balance. Benefit can also be obtained through contribution to patient care (for example, better route of

administration, decreased frequency of dosing, improvement in relation to potential medication errors or compliance, reduced treatment duration, or a clinically relevant age-appropriate formulation).

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 possibly 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 the proposed research, and usefulness of benefits obtained.

12.1 Balance of benefit and risk

The determination of the levels of risk and the associated benefits are the basis for ethical approvability. The risk levels should be presented by the sponsor and assessed by the ethics committee. As the assessment of the risk and the benefit may be based on probabilities and assumptions, respectively, this should also be balanced with the severity of the condition or diseases to be studied and the risk and benefit of alternative treatments.

In the following examples, levels of risk are considered to be in balance with the benefit for a trial with the paediatric population:

- Minimal risk with benefit for the individual or benefit for the group
- Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favourable as that of available alternative approaches.
- Greater than minor increase over minimal risk with benefit for the individual that is especially favourable in relation to available alternative approaches for the individual's condition.

With regard to benefit for the group, it is also emphasised in the European Convention on Human Rights and Biomedicine which 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 [...]” if:

“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; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden”.

13. Assays in relation to age/bodyweight and blood sampling

Assays, investigations and blood sampling volumes related to the trial should be described and justified in the protocol.

13.1 Type of assays and sample collection

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: appropriate facilities and material should be used. Alternative sampling (e.g. urine or saliva sampling) for pharmacokinetic studies should be preferred when possible. For blood and tissue assays, micro-volumes and micro-assays should be used, whenever possible. In principle, general and / or local anaesthesia should be used as appropriate for painful and/or invasive procedures.

Timing of sampling should be co-ordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimise pain and distress, and the risk of iatrogenic complications. Sampling should be performed by trained staff. The number of attempts for sampling should be limited. Timing of sampling and number of sampling attempts should be defined in the protocol. For example, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure.

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. The fact that children, especially in this age group, receive blood transfusions (or iron or erythropoietin supplementation) should not be used as a convenience for increased volume or frequency for blood sampling.

The following blood volume limits for sampling are recommended (although are not evidence-based). If an investigator decides to deviate from these, this should be justified. Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight.

Monitoring of actual blood loss is routinely required in preterm and term neonates. Expected blood loss should be detailed in any trial protocol, and should be detailed also in the patient information sheet.

14. Trials with 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. This paediatric subset may also differ pharmacologically from older ones. 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 committees and investigators is therefore required.

15. Trials with healthy children

In principle, healthy children should not be enrolled as healthy volunteers, because they cannot consent and are vulnerable like children with a disease or condition. Studies should not be performed in children when they can be performed in adults. Exceptions could be where healthy children participate in palatability testing such as swill and spit taste testing for a new flavoured medicine.

In some situations, studies need to be performed in children who are healthy at the time of the trial. Prevention trials or paediatric vaccine trials, including immunogenicity studies, will fall into this category but include the target population likely to benefit. Trials in children with intermittent diseases (e.g., flare-ups or seizures) are acceptable because even in the “healthy” phase the children are affected. Whenever possible the older age groups should be considered for inclusion before the younger ones.

Proof of concept should first 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.

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

Formulations used in a trial should be described in the protocol, as recommended by ICH E6, section 6.4.4. Additionally, formulations used in paediatric clinical trials should be 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 as a consequence of a lack of appropriate formulation, the conditions for preparing them and the dose should be indicated and should follow Good Manufacturing Principles, as required by Commission Directives 2003/94/EC⁶ and 2005/28/EC⁷.

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).⁸ Conditions to avoid bacterial contamination and degradation of the medicinal product should be specified in the protocol.

18. Individual Data protection

The specificity of data protection in children also 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 longer-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 performance records contained in trial documents when studies are performed in schools (access, amendments and disclosure), and the information given to parents or legal representative. This is also 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 the community are respected. Children participating in a trial are entitled to know any information collected on their health. Other personal information collected for a research project will need to be made accessible to them in conformity with national laws on the protection of individual data. Disclosure of genetic findings, which may be risks in clinical trials, requires expert counselling in an adequate setting.

⁶ Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

⁷ Commission Directive 2005/28/EC 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

⁸ Commission guideline on excipients, the Final Concept Paper Good Pharmaceutical Practices for extemporaneous dispensing, and the Reflection Paper on Formulations of choice in the paediatric population

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 1901/2006 on medicinal products for paediatric use (see below).

19.1 Publication of paediatric trials and results

Article 41 of Regulation (EC) No 1901/2006 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 is made public. This will cover both the descriptions of interventional clinical trials and their results.

Systematic registration of paediatric clinical trials and publication of results including unfavourable ones, together with a thorough analysis of the literature should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in children.

Ethics Committees should not accept paediatric protocols that prevent independent publication by investigators, and the timeline for publication should be specified in the respective protocols.

19.2 International database and availability to the public

There is an ethical duty to check whether existing knowledge is available 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 for adverse reactions reporting in paediatric trials are identical to those in adults, in particular, but not exclusively, the notification of serious adverse reactions observed in 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 strongly encouraged and carefully instructed to report adverse reactions and events to the investigators in a timely manner. This is particularly important in young children, who 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, for example, because of different insurance regulations in Member States, or because insurance companies invoke issues of long-term liability. Insurance companies' contracts should not waive liabilities regarding long-term effects, or limit the liability period, and Ethics Committees should pay careful attention to the

insurance contract regarding this issue, in particular with respect to long-term effects on development. Unrecognised congenital defects are generally excluded. Suspected unexpected serious adverse reactions that can be related to these unrecognized congenital defects should be covered in insurance contracts.

Medical records should be protected by the privacy requirements of the applicable national laws in order not to pose a risk of labelling individuals with pre-existing conditions by insurance companies.

23. Trials in children in non-EU countries

According to Directive 2001/83/EC as amended by Directive 2004/27/EC, clinical trials submitted in a marketing authorisation application in the EU, which were 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 Clinical Trials Directive and should comply with good manufacturing practices of EU countries. These principles should also apply for paediatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation.

The Council for International Organizations of Medical Sciences states in section 3 of its guideline that ethical standards should be no less exacting than they would be for research carried out in EU, countries and that the trial protocol should be submitted for ethical and scientific review in the EU Member State in which the sponsor or its legal representative resides.

The trial should ensure that it responds to the public health needs and priorities of the country in which it is carried out. 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.

The recommendations in this document should be followed by EU researchers and sponsors carrying out trials in third countries, as well as by ethics committees reviewing such trials or their results. In addition, the laws and regulations of the countries in which the trials are carried out should be respected.

24. Ethical violations and non-compliance with GCP

GCP compliance of clinical trials is required. 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. Violations fall into critical, major and minor issues according to whether and to which extent patient safety and scientific value are compromised. The preferred option to avoid such violations is education, training and counselling. 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 made public with a clear warning specifying the unethical aspects. Information on such trials is needed to avoid unnecessary repetition of the trials and to protect future trial subjects.

If non GCP-compliant data are submitted as part of a marketing authorisation application, the quality of the data, the study results, and consequently the validity of the marketing authorisation application should be scrutinised. Sensitivity analysis should be performed within the GCP-compliant full data set, and in some cases also in comparison with all GCP-non compliant data. The overall reliability of the trial should be questioned. Subsequent measures (including initial review) should be taken in accordance with national legislation, if appropriate.

25. ANNEX 1: Responses to questionnaire

Refer to end of table for legend and explanations. Spaces are left blank when information has not been provided.

Content of the questionnaire State	#	AT	BE	BG	CY	CZ	DK	ES	FI	FR	GE
1) National provisions for consent^I (legal representative)											
Do you have a law covering <u>consent</u> in clinical trials?	1					Y	Y	Y	Y	Y	Y
Do you have a legal definition of 'legal representative'?	2					N	Y	Y	Y	Y	Y
Do you have national guidelines ^{II} covering <u>consent</u> in clinical trials?	3					Y	Y	Y	Y	Y	Y
Do you have national guidelines defining 'legal representative'?	4					Y	Y	-	N	Y	N
What is the requirement from at national level:	5										
Consent should be obtained from one parent?	6					N	N	Y	Y ^{III}	Y ^{IV}	N
Consent should be obtained from both parents?	7					Y	Y	-	Y	Y	Y
In case of disagreement between the 2 parents, do you have specific provisions (law or guidelines) to deal with such disagreement?	8					-	N	N	N	N	N
What are these provisions?	9										
2) Specific national provisions for child's assent											
Do you have a law, addressing assent from a child participating in a trial?	10					Y	Y	Y	Y	Y	Y
Do you have national guidelines addressing assent from a child participating in a trial?	11					N	Y	N	Y	Y	N
Is assent required?	12					Y	Y	Y	Y	Y	Y
If yes, from which age?	13					NS	NS	7	NS	NS	NS
In relation to development milestone (e.g., from school age)?	14										
Is there a need for <u>written</u> child's assent?	15					Y	N	Y	Y	N	Y
If yes, from which age?	16					NS	-	7	NS	-	NS
3) Specific national provisions for neonates											
Do you have laws or national guidelines to confer additional protection to neonates?	17					N	N	N	Y	N	N
4) Specific national provisions for adolescents											
Do you have a law stating that adolescents can <u>consent</u> independently?	18					N	Y	N	Y	N	Y
Do you have a national guideline stating that adolescents can <u>consent</u> independently?	19					N	Y	N	N	N	N
If yes, from which age?	20					-	15	-	15	-	-
Is there a possibility for adolescents to overrule their parents' decisions (or legal representative's decision)	21					Y	+/-	N	Y	N	N
Is the investigator obliged to follow the parent(s)'s decision?	22					N	-	Y	NS	Y	-
Is the investigator obliged to follow the adolescent's decision?	23					Y	Y	N	Y	Y	-
Do they have the right to privacy <i>vis-à-vis</i> parents (or legal representatives) in a clinical trial (e.g., for contraceptive use, sexually transmitted diseases)?	24					Y	Y	N	Y	N	N
5) Trials in emergency situations											
Do you have a law on consent in emergency trials?	25					Y	Y	Y	Y	Y	Y
Do you have a guideline on consent in emergency trials?	26					N	Y	N	N	Y	N
Do you have specific provisions for consent in paediatric emergency trials?	27					N	N	N	N	N	Y
6) Other questions											
Can parents contact directly Ethics Committees to obtain information?	28					Y	-	Y	N	N	N
Is there a role for national authorities when there is disagreement between parents and investigators?	29					Y _{insp}	N	Y	N	N	N
Is an investigator required to provide information to parents in case of a negative opinion of Ethics Committee during trial?	30					Y	-	Y	Y	Y	Y

#	GR	HU	IS	IE	IT	LV	LT	LU	MT	NO	PL	PT	RO	SL	SP	SW	NL	UK
1		Y			Y	Y	Y		Y		Y				Y	Y		Y
2		Y			Y	Y	Y		Y		Y				Y	N		Y
3		Y			Y	N	Y		Y		N				N ^{vii}	Y		Y
4		Y			N	Y	Y		N		N				N ^{viii}	N		Y
5																		
6		Y			Y ^{iv}	Y	N		-		Y				N	N		Y
7		N			Y	N	Y		Y		-Y?				Y	Y		N
8		N			N	Y	N		C		C				Y	Y		C
9																		
10		Y			Y	Y	N		Y		Y				Y	Y		Y
11		Y			Y	N	Y		Y		N				N	Y		Y
12		Y			Y	Y	Y		N		Y				Y	Y		Y
13		NS			NS	7	NS		NS		16				12	NS		NS
14					NS													
15		N			N	Y	Y		N		Y				Y	Y		Y
17		-			NS	7	NS		-		16				12	NS		NS
17		N			N	N	N		N		N	N			Y ^{vi}	N		N
18		N			N	N	N		N		N				Y ^{ix}	N		N
19		N			N	N	N		N		N				-	N		Y
20		-				-	-		-		-				16	-		-/16
21		-			Y	N	+/-		C		N				Y ^x	Y		N
22		-			Y ^v	Y	+/-		Y		Y				Y ^{xi}	Y		N
23		-			Y	Y	+/-		Y		Y				Y ^{xi}	Y		N
24		N			Y	N	N		N		N				-	Y		N
25		N			Y	N	N		N		Y/N				Y	Y		N
26		N			N	N	N		N		N				N	N		N
27		N			N	N	N		N		N				N	N		N
28		Y			N	Y	Y		Y		Y	Y			-	Y		N
29		Y			N	Y	N		C		N	N			N	N		N
30		Y			Y	Y	Y		Y		Y				-	Y		N

The above questionnaire has been sent to the (National) Competent Authorities of all EU Members States and to Iceland, Norway, Liechtenstein (EEA states), and Switzerland in 2006. Responses to this questionnaire are included in the table below as of October 2007.

Legend

Y Yes

N No

C Yes, in court

NS Not stated

–

+/- It depends

ⁱ Consent refers to legal representatives, as opposed to assent which refers to minors.

ⁱⁱ Guideline means implemented at national level, excludes local recommendations.

ⁱⁱⁱ Special conditions (trial characteristics) for consent from only one parent

^{iv} Special conditions for consent from only one parent

^{vi} For breast feeding mothers

^{vii} There is a final draft

^{viii} Defined in the Civil Law

^{ix} Regulations on emancipated adolescents

^x Without the adolescent assent the legal representative informed consent is not sufficient

^{xi} In case of adolescent's dissent parental informed consent is not sufficient for the minor to become a CT subject. In case of parental dissent the adolescent's assent is not sufficient to participate in the CT.

26. ANNEX 2: List of issues for a trial with the paediatric population

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

1. Identification and scientific validity of the study question to be answered
2. Justification of the study to be performed in children and in the proposed age groups
3. Evidence of direct benefit for the child, or benefit for the group
4. The competence of the responsible study investigator and his/her team
5. The infrastructure of the institution or primary care practice that should be qualified and experienced in paediatric research in general and in particular in the field of the applied project.
6. The pre-clinical safety and efficacy data (investigator's brochure, available literature) that are preconditions for a paediatric clinical trial
7. The clinical results of adult studies (literature, investigator's brochure), if any.
8. Type and phase of the study
9. Use of placebo or active control
10. Age-appropriate formulations of medicinal products
11. Age-appropriate scales or measures of end-points (e.g., pain scale)
12. Study design and biometric planning in relation to the trial question
13. Design feasibility and information sheets checked with children / patient representatives
14. Inclusion and exclusion criteria
15. Statistical methods
16. Criteria for the termination of the study
17. Safety measures including the set-up of a Data Safety and Monitoring Board (DSMB)
18. Appropriate pharmacovigilance procedures are put in place by the sponsor
19. Study risks, pain, fear and discomfort
20. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial. The balance of expected benefit versus risks should be positive for the clinical trial.
21. Comprehensive, understandable Informed Consent and Information sheets for legal representatives
22. Understandable age specific Informed Assent and Information sheet for children
23. Anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his/her family
24. Insurance of child participants, in the relevant country
25. If available, opinions of other ethics committees for international multicentre studies
26. Publication of trial results
27. Continuation of trial medication where appropriate

27. ANNEX 3: Information for informed consent

Information sheets should be separate for parents and children: they should be concise in content, precise in language (e.g., use of non-technical terms), and appropriate for the age of children (e.g., avoid abstract concepts, multiple options). The number of age-specific variations of information sheets should be kept to a minimum number required to include substantially different wording or presentation. In addition, information sheets should not cause unnecessary distress. They should possibly be designed with participants, affected children or parents.

Information sheets should be harmonised throughout sites in multi-centre trials, and address similar age groups in multinational trials.

If the primary language of the child or parents/legal representatives is not covered by that of the trial documents, the information sheets should be translated in writing, or there should be a (certified and medically) competent translator during trial-related discussions of the investigator and the parents/legal representative. These aspects also need to be documented (cf. section 7).

List of items recommended to be covered in the information sheets:

1. What is the purpose of the trial?
2. Why have I been chosen?
3. Do I have to take part?
4. What will happen to me if I take part?
5. What are the compensations?
6. What will I have to do?
7. What is the medicine that is being tested?
8. What are the alternatives for diagnosis or treatment?
9. What are the possible disadvantages and risks of taking part?
10. What are the side effects of any treatment received when taking part?
11. Is ionising radiation to be received, and which regulations are respected?
12. Is there possible harm to an unborn child?
13. What are the possible benefits of taking part?
14. What happens when the research study stops?
15. What if there is a problem?
16. Will my taking part in the trial be kept confidential?
17. What will happen if I don't want to carry on with the trial?
18. What are the options if I stop taking part in the trial?
19. How is my General Practitioner/Family doctor involved?
20. What will happen to any samples taken from my body?
21. Will any genetic tests be done?
22. What will happen to the results of the research trial?
23. Who is organising and funding the research?
24. Who has reviewed the trial and what are the results?
25. Contact details for information or complaints

Trial alert and information cards (comprising of trial essentials and especially of contact information) should be handed to the child, if appropriate, and the parents / legal representatives.

28. ANNEX 4: Examples for levels of risks

The following table provides examples of risk evaluation of measures carried out for the purpose of a trial. This evaluation is not fixed because the circumstances of child influence evaluation of risks. For example, an existing central venous line may reduce the pain and invasiveness of blood sampling, but also increases the risk of infection and of excess blood losses with line handling.

The risk evaluation of some of the measures (including, but not limited to those marked *) is very much dependent on such circumstances and on the context of its use in the trial. In addition, the risk level increases with the increase in frequency of the measures and with the susceptibility to harm of involved/exposed organs. The categorisation proposed in the table applies to single or very infrequent use of the measure. The examples presuppose that the measures are carried out to the highest professional standards.

No or minimal risk	Minor increase over minimal risk	Greater than minor increase over minimal risk
– History taking	– Urine collection via endoluminal or suprapubic catheter	– Heart catheterisation
– Clinical examination	– Arterial puncture	– Endoscopy
– Auxological measurements	– Umbilical catheter	– Biopsy
– Tanner staging	– pH metry	– Surgery or modification of standard surgical procedure carried out as part of medical treatment
– Behavioural testing	– Nasogastric tube insertion and use	– Sedation
– Psychological testing*	– Transcutaneous oxygen or carbondioxide tension monitoring	– Anaesthesia
– Quality of Life assessment	– Electrophysiological measurements (using stimulation)	– Systemic analgesia
– Venipuncture*	– Exercise testing (ergometry, spiroergometry)	– Hypoglycaemia test
– Heel prick*	– Raised volume pulmonary function testing (infants)	– Unstable isotope usage
– Finger prick*	– Peripheral venous lines	– PET scanning
– Subcutaneous injection	– Polysomnography	
– Urine collection with bag*	– Fasting (≥ 1 meal)	
– Breath condensate collection	– Spinal CSF tap	
– Collection of saliva or sputum	– Bone marrow aspiration	
– Collection of hair sample	– MRI scan	
– Collection of tissue removed from body as part of medical treatment*	– X-ray other than digitally amplified chest or limb X-ray	
– Topical analgesia*	– CT scan*	
– Stool tests	– X-ray DEXA bone density measurement	
– Bio-impedancemetry	– Use of contrast media	
– Transcutaneous oxygen saturation monitoring (pulse oxymetry)*	– Paracentesis	
– Blood pressure monitoring	– Skin punch biopsy	
– Electroencephalography	– Airways or skin hyper-reactivity challenge test	
– Electrocardiography		
– Vision or hearing testing		
– Ophthalmoscopy		
– Tympanometry		
– Lung function tests (peak flow, exhaled NO, spirometry)		
– Oral glucose tolerance test		
– Ultrasound scan		
– Digitally amplified chest or limb X-ray*		
– Stable isotope examination		

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