Consultation document

Ethical considerations for clinical trials on medicinal products conducted with minors

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

Note for Public consultation

The main objective of updating these recommendations is to align them with the requirements of the Clinical Trials Regulation (EU) No 536/2014 and with the latest (scientific) insights on research with children.

Main changes were made on the following:

- More emphasis on the evolving maturity of children, underlying the requirement of the Regulation to respect the explicit wish of a minor to refuse participation in, or to withdraw from, a clinical trial at any time;
- Recommendations on the requirement of participation of the minor in the informed consent process;
- Introduction of the term 'agreement', equivalent to the term 'assent' in medical literature, since the Regulation reserves the term 'assent' to have legal value in some Member States;
- More emphasis on informed consent as a continual process;
- More emphasis on burden, next to risk, its subjective nature and the importance to involve children in the assessment and minimisation of burden;
- Assessment of the relationship between benefit, risk and burden, in particular when there is no direct benefit for the participant, only benefit for the population, and the risk and burden should be minimal in comparison to the standard treatment;
- Additional recommendations for emergency situations;
- Addition of the latest insights on trial designs and sampling methods;
- Additional recommendations on trials with female adolescents;
- Updates on data protection;
- Updates on GCP compliance.

Specific feedback on the following topics would be highly appreciated:

Q1: The table of Annex 3 (previously Annex 4) has not been changed. Is the proposed categorisation of these procedures still adequate?

Q2: Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

F1: General feedback on clinical trials in minors in emergency situations (within the meaning of article 35 of the clinical trials Regulation) is welcome.

F2: If you are aware of any other relevant references you are invited to put them forward.

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EXECUTIVE SUMMARY

This document has been revised by the European Commission expert group on Clinical Trials in preparation for the implementation of **Regulation (EU) No 536/2014**[1] on clinical trials on medicinal products for human use. The objective of the revision is to update these recommendations to bring them in line with the changed legal context of the new regulation. The document provides recommendations on various ethical aspects of clinical trials performed in minors from birth up to the legal age of competence to provide informed consent. This will contribute to the protection of all minors who participate in clinical trials. 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, both from participation in clinical trials and from access to the resulting evidence based medicinal products (recital 8). As the authorisation of clinical trials, including ethical approval, is performed by the Member States, any recommendations on ethical aspects of clinical trials in minors will also facilitate a harmonised approach to the application of the clinical trials Regulation across the EU, thereby facilitating the conduct of clinical trials across the EU, in whichever country the clinical trial in minors occurs.

Minors are not small adults and there is a need to carry out specific trials that cannot be performed in adults in order to obtain evidence specifically attuned to the needs of children. By definition, children (minors) are unable to consent (in the legal sense), but they should be involved in the process of informed consent as much as is possible, using age appropriate information. In the ethical review, paediatric expertise is required to balance the benefits, risks and burden of research in minors. The difference between minors and adults as research participants has implications on the design, conduct and analysis of trials, which should also include paediatric expertise. Pain, fear, discomfort 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

Off label use of medicinal products in children without proper evidence poses an ethical problem. That is why the need for clinical trials with children has now been widely recognised and is stimulated by European legislation, e.g. by requiring Paediatric Investigation Plans[2]. At the same time, children are a vulnerable population, relatively incapable of protecting their own interests, and therefore they deserve protection against the risks and burden of research. It is the duty of all involved in paediatric research to minimise and mitigate any risks and burden while doing research with children. That is why in Regulation (EU) No 536/2014 (hereinafter the Clinical Trials Regulation) an appropriate balance is sought between protecting children (i.e. minors in the meaning of the Clinical Trials Regulation) and enabling research that provides evidence for good medical care. Trials are necessary and should aim at progressing the wellbeing and treatment, prevention and diagnosis of ill health of patients, including children. Furthermore, clinical trials facilitate the development of appropriate drug dosage forms. Although the same ethical principles apply across age ranges, from children to the elderly, additional protection should be defined for research performed in minors, at all stages and ages.

[1] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (Text with EEA relevance)

[2] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use

The reasons why medicinal products need to be studied in minors have been detailed in various publications. In summary, minors are not small adults. Data on effectiveness and safety cannot reliably be derived from data in adults. Major changes in pharmacokinetics and pharmacodynamics occur with increasing age, due to changes in body composition, drug metabolism and transport and renal function. Growth and maturation processes, as well as certain specific diseases are unique to children. Specific consequences of medical interventions may be seen in minors if no appropriate clinical trials are conducted and may only appear long after exposure. Unfortunately this has been demonstrated by previous calamities with the use of medicinal products. Trials are therefore necessary in the paediatric population to develop a better knowledge of drugs' effects in children (safety and efficacy).

Because of the special protection they deserve, minors 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). If research with minors proves necessary, in line with Article 32(1e) of the Clinical Trials Regulation, the least vulnerable among them should usually be included. However, a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended. Such an approach will ultimately result in prolonged off-label use for the younger age groups (especially neonates) and the impossibility of conducting any trial to provide age specific evidence for these groups. If there is a necessity to subject minors to a clinical trial, the choice of subsets of the paediatric population to be included should be made on the basis of the likely real-life target population for the medicine being tested, the possibility of extrapolation, and the scientific validity of such an approach.

The recommendations in this document aim to bring together ethical principles from the various documents that already exist (cf. section 4.2), as they are understood currently. In addition, the European Network of Paediatric Research (Enpr-EMA) has recognised expertise in performing clinical studies with children and has the main objective to foster high-quality, ethical research on the quality, safety and efficacy of medicines for use in children. Over time, with changing legislation or progressing insights, e.g. by Enpr-EMA, the need for further revision of this document may emerge.

2. SCOPE

This document is intended to provide recommendations on various ethical aspects related to the conduct of interventional clinical trials and studies falling under the provisions of the Clinical Trials Regulation on medicinal products for human use.

The document is intended as recommendations for all persons involved in any stage of a clinical trial, including sponsors of clinical trials, assessors, 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. section 5.8), families, and participants. This document is without prejudice to the obligations created by the Clinical Trials Regulation and other European and Member State legislation.

This document focuses on the ethical specificities of clinical trials with minors and should therefore be read in conjunction with the relevant legal texts and guidelines. In particular, the specific legislation of the Member States may differ. These recommendations do not distinguish between non-commercial and commercial research.

3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS

The Clinical Trials Regulation and these underlying recommendations should be applied in line with the Charter of Fundamental Rights of the European Union (2012). In particular Article 24 on the rights of the child is relevant in this context (see also recital 83 of the Clinical Trials Regulation).

In addition, ethical principles referred to in this document are those expressed, for example, in the Declaration of Helsinki published by the World Medical Association (2008)[3], the International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO (Geneva 2002), the United Nations' Convention on the Rights of the Child, 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 and its additional protocol concerning biomedical research. These principles are also echoed and referred to in the ICH E6 guideline on Good Clinical Practice and in the ICH E11 guideline on the Clinical Investigation of Medicinal Products in the Paediatric Population.

Although the above mentioned documents might differ and emphasize specific ethical requirements, they share a common ground. They all build on four important ethical principles that should be adhered to when performing research with children: Beneficence, non-maleficence, respect for persons and justice. Beneficence is defined as the ethical obligation to secure/promote well-being and non-maleficence is the obligation to avoid harm. Respect for persons is defined as the obligation to treat individuals as autonomous agents and protect those with diminished autonomy. Justice is defined as a fair distribution of risk, burden and benefits of research. These are fully applicable to clinical trials in children.

The Clinical Trials Regulation underlines the importance of taking account of the wishes of children with regard to their participation in clinical trials. The Regulation requires their full engagement with the aim to treat children as developing autonomous beings, whose maturity gradually evolves with age and experience, and whose will should be taken seriously. Although it is acknowledged that children form a vulnerable group, the focus should be on their capacities and the shared goal of enabling them to participate in decision making processes.

4. LEGAL CONTEXT

4.1 Legal context

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (herein the 'Clinical Trials Regulation').
- 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.
- 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

[3] This version of the Declaration of Helsinki is referenced in the Clinical Trials Regulation.

for human use and investigational medicinal products for human use. [Note: this will be repealed – reference to the new legislation will be included after the public consultation]

– 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.

– Regulation (EC) No 1901/2006 of the European Parliament and the Council, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (herein the 'Paediatric Regulation').

4.2 Relevant guidelines

– Clinical Investigation of Medicinal Products in the Paediatric Population (E 11), CPMP/ICH/2711/99 (addendum E11(R1) under preparation)

– Concept paper on the involvement of children and young people at the Paediatric Committee (EMA/PDCO/388684/2012)

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

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

– Guideline on clinical trials in small populations, CHMP/EWP/83561/05, CHMP

– Guideline on conduct of Pharmacovigilance for medicines used by the paediatric population (June 2006) EMA/CHMP/PhVWP/235910/2005- rev.1, CHMP

– Guidelines on Good pharmacovigilance practices (GVP)[4], EMA

– Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (EudraVigilance – Clinical Trial Module) ENTR/F2/BL D(2003) [note: this reference will be updated].

– The rules governing medicinal products in the European Union. Volume 10 – Guidance documents applying to clinical trials. Questions & Answers, Version 11.0 [note: update of this document is ongoing].

– Standards and operational guidance for ethics review of health-related research with human participants,World Health Organization (WHO)_(Geneva, 2011)

– International Ethical Guidelines for Biomedical Research Involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). (Geneva 2002).

– Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI, Council for International Organizations of Medical Sciences (CIOMS)

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c

5. DEFINITIONS/ GLOSSARY

5.1 Age groups

When referring in these recommendations to a specific subset of the paediatric population, the age range will be given for clarity. This age range is meant to provide guidance regarding the proper involvement of minors of different ages in the informed consent process. With the exception of the age range of 2 to 11 years, subsets of the paediatric population as defined in ICH E11 are adopted, and the age group of 2 to 11 years is redefined. This leads to the following age groups: preterm newborn infants (gestational age less than 37 weeks, post-natal age up to one month), term newborn infants (gestational age 37 weeks or more, post-natal age up to one month), infants (1-23 months), preschoolers (2-5 years), schoolers (6-9 years) and adolescents (from the age of 10 up to but not including 18 years). Of note, in some Member States not all adolescents are regarded as minors (see section 5.8)

It should be noted that these age groups only partly correlate with maturation especially from the developmental point of view. Where it is necessary to set some boundaries, the definition of the different age groups should be viewed as a practical instrument. Maturity rather than age should be the starting point for the way a trial is discussed with children. Each individual child should be involved in a way that matches his or her maturity and ability to take part in the decision making process. Although this may be difficult, as 'maturity' is not a clear-cut criterion in contrast to age, such an approach will foster more attention to differences between children and will support that they are properly involved in decisions that concern them.

It is important to distinguish the above mentioned age groups from 'physiological or metabolic' definitions of age groups, which will be used for other purposes, for example to define dose, or to establish inclusion criteria.

5.2 Assent

The term assent in the context of the Clinical Trials Regulation has a different meaning from that in medical literature and therefore also in this document, since it has legal value depending on Member State law (cf. Section 5.3).

The notion of assent is explicitly included in article 29(8) of the Clinical Trials Regulation:

> "This Regulation is without prejudice to national law requiring that, in addition to the informed consent given by the legally designated representative, a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial."

In this document, "assent" should be understood as a legally required expression of the minor's will to participate in a clinical trial, dependent on Member State law. Usually the legal requirement of assent only applies to minors of a certain age. Assent is a statement of will with legal value, required at the same time as the consent of the parents/legally designated representative. The minor's assent is not sufficient to allow participation in research unless supplemented by informed consent of the parents/legally designated representative.

5.3 Agreement

The Clinical Trials Regulation provides a number of conditions for participation of minors in clinical trials, one of which is for investigators to respect the explicit wish of a minor, who is capable of forming an opinion and assessing information, to refuse participation in, or to withdraw from, the clinical trial at any time.

Agreement in this document is used in accordance with the term "assent" in the medical literature. It means the expression of the minor's will to participate in a clinical trial. This document supports a systematic request for agreement, and recommends that the investigator obtains agreement from the child in addition to informed consent of the parents/legally designated representative, even when this agreement is not mandatory by law.

The way in which the minor participates in the informed consent process, leading to the potential agreement, depends on his or her maturity. So agreement is not age-dependent, in contrast to legally required assent. In addition, whereas lack of legal assent mostly means the minor's refusal to participate (depending on Member State law), lack of agreement does not necessarily mean the child will not participate, since it may be evaluated that the child is not mature enough to express agreement.

Dissent however, meaning the expression of the minor's will not to participate, should be respected, in line with Article 32(1c) of the Clinical Trials Regulation on condition that the minor is capable of forming an opinion and assessing the information given.

The Clinical Trials Regulation requires the following involvement of the minor in the informed consent procedure (Article 32):

> "1(b) the minors have received the information referred to in Article 29(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
> 1(c) the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator;
> 2. The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity."

The notion of agreement recognises the evolving autonomy of minors. The capacity of a minor to make voluntary, informed decisions i.e. to agree to participate in a clinical trial, evolves with age, maturity and previous experience of life and illness.

The recommendations provided in this document refers both to (legally-required) assent and to agreement, which were covered by the term "assent" in the previous version of this document as referred to in the Declaration of Helsinki (2008).

5.4 Child

When the term "children" is used within these recommendations, it is used consistently with the provisions of the Clinical Trials Regulation to mean minors, in contrast to ICH E11 guideline which refers to children as individuals aged from 2 to 11 years.

5.5 Ethical review

The ethical review shall be performed in accordance with the Clinical Trials Regulation and the law of the Member State concerned. Member State law will define the body performing the ethical review. In the case of paediatric clinical trials, there is a requirement to include paediatric expertise during the assessment of applications for the authorisation of clinical trials.

5.6 Informed consent

Article 2(2.21) of the Clinical Trials Regulation defines:

> "Informed consent means a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of

> all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial."

Articles 29 and 32 of the Clinical Trials Regulation provide additional requirements related to informed consent. In this document, "consent" refers to the legal definition of informed consent, as stated above. The Clinical Trials Regulation states that the child should be involved in the process of informed consent.

Some Member States use the concept of assent, meaning that minors of a certain age are required to assent, in addition to the consent given by the parents/legally designated representative.

5.7 Legally designated representative of the minor

Article 2(2.20) of the Clinical Trials Regulation defines a legally designated representative as

> "a natural or legal person, authority or body which, according to the law of the Members State concerned, is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor."

For most minors, the legally designated representative will be one or both parents, depending on national law. Although national law may allow written consent from only one parent, both parents should be encouraged to participate in the informed consent process. Legally designated representatives may be other family members, guardians or local authorities. Parents/legally designated representative have the duty to protect their child, the child's interests, and the child's point of view based on their knowledge of the child during the child's life up to that time.

5.8 Minor

Article 2(2.18) of the Clinical Trials Regulation defines:

> "Minor means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent."

Of note, in the case of multinational trials the age of legal competence may differ across Member States.

5.9 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. Exposure to medicinal products may occur before birth in the context of clinical trials with pregnant women; this topic is not covered in this document.

6. The process of informed consent

6.1 Informed consent from the legally designated representative

As the child (minor) is unable to provide legal consent, informed consent must be sought from the parents/legally designated representative (see definition above) on the child's behalf. Articles 29 and 32 of the Clinical Trials Regulation require that the specific and written informed consent of parents/legally designated representative must be sought prior to enrolling a child in a trial.

The person providing the information – usually the investigator or his adequately trained delegate – should be experienced in providing such information and in working with children. The information should be given to each parent, or the legally designated representative, both in oral and written form. Article 29.2(a) describes the information that should be provided. The parents/legally designated representative should be given sufficient time and necessary information to consider their decision to endorse participation of their child. 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.

Regarding the information given to the parents/legally designated representative, items for review by the ethics committee are proposed in Annex 1.

When seeking informed consent, the investigator should not put undue pressure on the parents/legally designated representative. In particular:

- Parents/legally designated representative should be explicitly informed of their right to refuse to have the child participate and the right to withdraw their child from the clinical trial at any time without any resulting detriment for the child and without having to provide any justification, in line with Article 29(2aii) of the Clinical Trials Regulation.
- According to Article 32(1d) of the Clinical Trials Regulation there must not be financial inducement to enrol the child in the trial; no financial incentive should be offered except compensation for expenses and loss of earnings of the parents directly related to the participation in the clinical trial.

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 perceived obligations and emotional subordination on the side of the parents. Moreover, this may not be perceived by either party. Therefore, the investigator should not put undue pressure or be the one to make the decision on participation, 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 a continual process.

If an adolescent is no longer a minor as defined by the Clinical Trials Regulation, or is an "emancipated minor"[5], 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/legally designated representative. As soon as a minor becomes legally competent to give informed consent during the course of the trial, no trial-related procedures may be performed until informed consent is provided.

Considering that the age when a person is considered to be an adult is highly variable across Member States, a multi-state trial may include at the same time minors of the same age who are still minors in one Member State and "adults" i.e. those able to consent in another Member State. Adolescents may still have some elements of vulnerability, even though they are legally allowed to provide their own consent. In practice, the adolescent with the legal capacity to consent may decide to involve his or her parents in the informed consent process. The information given to adolescents should therefore recognize the potential situation of vulnerability.

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

6.2 Participation of the child in the informed consent process

Consent in line with Article 29 of the Clinical Trials Regulation should be obtained from the parents/legal representative and, in line with Article 32, the child should be involved throughout this process and receive the information adapted to their age and mental maturity. Participation of minors is addressed in section 7.

6.3 Informed consent of families with different cultural background

It is important that the language skills of the child and consenting parents/legal representative are sufficient for them to understand the provided information. Also cultural differences may lead to misunderstandings. Where appropriate, a translator and/or a cultural mediator, familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent. A translated informed consent form could also be an appropriate way to provide trial related information adapted to the specific needs of families with a different cultural background.

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

As discussed above, investigators should devote sufficient time to provide information and seek the parents'/legally designated representative's consent as well as the child's assent/agreement prior to trial enrolment. It is important to realise that consent is a dynamic, continual 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 continual basis. The child should be involved in this (cf. Section 7). 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 parents and child to continue.

During the progress of the trial, especially in long-term trials, the investigator should check the progressing maturity of the child and his or her ability for assent/agreement. This should be documented.

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

6.5 Withdrawal of the consent

In all circumstances, parents/legally designated representative should be made aware of the right to refuse participation in a clinical trial and are entitled to freely withdraw their informed consent at any time, without giving reasons. Parents/legally designated representative should be reassured that the withdrawal from the trial will not prejudice the child, will not result in any detriment and will not affect the provision of normal clinical practice[6]. 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. The parents/legally designated representative need to be informed about the risks that premature termination of the trial would present to the subject's health, if applicable.

[6] Normal clinical practice is defined by the Clinical Trials Regulation as the treatment regime typically followed to treat, prevent, or diagnose a disease or disorder.

Parents/legally designated representative who give informed consent for a child to participate in clinical trials should have the opportunity to follow the research as it proceeds (unless clinically inappropriate, e.g., during an operation under general anaesthesia), so as to be able to decide on whether to withdraw the child from the research at any time. In the event of withdrawal from a blinded trial, if the parents/legally designated representative wish to continue to follow the progress of the trial, and it should be stated that the summary of the results, including a summary that is understandable to a layperson, will be available in the EU database.

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. If this possibility can be envisaged beforehand, due to the trial design or a specific intervention, this should be clearly explained as part of the initial consent process, to manage expectations before the situation arises.

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.

6.6 Consent, assent and agreement in emergency situations

Research involving children in rapidly evolving, life-threatening situations is necessary to advance outcomes and treatments. Emergency situation trials may concern children with various conditions, including some that are specific, or relatively frequent, in children (e.g. initial manifestations of metabolic diseases, status epilepticus, acute trauma). In some emergency situations, consciousness may be altered and/or treatment or intervention is required within minutes, thus the parents/legally designated representative may not be available to provide prior informed consent and children cannot be informed, nor express assent or agreement.

Article 35 of the Regulation provides for derogation from prior informed consent requirement, including for paediatric trials in emergency situations, with some restrictions. However, in all cases, informed consent should be sought as soon as possible after the decision to include the child into the trial or after the first intervention (sometimes called deferred consent). Of note, there is no derogation for such clinical trials from the requirement to respect the child’s explicit wish to refusal to participate.

Recruitment and inclusion procedures for such trials should be scrutinised from the ethical perspective, in particular the time lag until consent is obtained, how and by whom the decision to include the child in the trial will be taken, information given to the legally designated representative, highlighting the right to object to the use of the data obtained in these circumstances, and the assent or agreement process.

Various approaches to obtain informed consent in particular situations have been used or should be considered according to national law. It is sometimes possible to identify participants before the emergency situation arises (known risk of worsening, for example, sepsis in immune-compromised children). This provides opportunities to inform parents, and even early informed consent and assent/agreement (pre-consent). In other cases, awareness of a trial recruiting within a community can be ensured through schools, medias, or outpatient

clinics.[7] Emergency situations described in this paragraph are not to be confused with those referred to under article 35 of the Clinical Trials Regulation.

Some Member States recommend that a third party is involved (if available in such a timeframe, a healthcare provider knowing the child) with the responsibility to protect the child's best interest. Conversely, other Member States prohibit to ask third parties (for example teachers) to substitute for the legally designated representative.

Feedback requested:

General feedback on clinical trials in minors in emergency situations (within the meaning of article 35 of the Clinical Trials Regulation (EU) No 536/2014) is welcome.

7. Participation of minors in the informed consent process and agreement

The child should participate in the informed consent process together with the parents (article 32(2)), in a way that is appropriate to his or her age and maturity (Article 32(1b) of the Clinical Trials Regulation). The aim is to treat children as persons who, in the context of their own family and social environments, have the potential from an early age to play an active role in determining their own lives and in engaging with others. 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 parents/legally designated representative, so that the child is optimally involved in the informed consent process and the minor has the opportunity to dissent (in line with Articles 32(2) and 32(1c) of the Regulation). 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 and consenting to participation of their child.

This document supports a systematic request for agreement, and recommends that the investigator obtains agreement from the child in addition to informed consent of the parents/legally designated representative, even when this agreement is not mandatory by law. If the child's agreement is not obtained, it is recommended that this be documented with justification in the consent form which is signed by the parents/legally designated representative and investigator.

The evaluation to what extent a child is able to provide agreement 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. The contribution of these other factors to the child's maturity and the extent to which the child is able to participate in the informed consent process need to be established after discussions between the investigator, the parents/legally designated representative, and the child.

[7] Wellcome Trust, MRC Hubs for Trials Methodology Research: Research without Prior Consent (Deferred Consent) in Trials Investigating the Emergency Treatment of Critically Ill Children: CONNECT Study Guidance. Version 2 July 2015, available at https://www.liverpool.ac.uk/psychology-health-and-society/research/connect/

Refusal of a minor to participate, i.e. dissent, should be respected, in line with Article 32(1.c) of the Clinical Trials Regulation, stating:

> "the explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 29(2) to refuse participation in, or to withdraw from, the clinical trial at any time, is respected by the investigator".

It is important to note that "forming an opinion" should not be understood to only apply to children that have reached a certain age or level of maturity, as even young children are able to form and express their opinion in one way or another. Therefore, any objections raised by a child at any time during a trial should be analysed, including those of very young children. The child's will should be respected. The child does not have 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). This also means that investigators should be able to recognize signs of resistance in children. They should evaluate whether these signs are part of the anticipated burden (e.g. distress or fear), consult with the parents/legally designated representative, and appropriately respond to the child's worries, e.g. by trying to decrease the burden. This behaviour may lead to the understanding that the child dissents, and that therefore the child should not be enrolled in or should be withdrawn from the trial.

Separate information material for adults and children should be used in order to provide age appropriate information, in visuals, language and wording appropriate to age and psychological and intellectual maturity. The information material should be ethically approved by the Member State concerned. The information material should have been tested in the relevant population, and should include provision of information on all the relevant aspects of the trial, in terms that are honest, but not frightening, using visual such as drawings, cartoons etc. See also Annex 2 for recommended contents. In addition, separate consent and agreement forms (where applicable, cf. Section 7.2) should be used, satisfying the above mentioned criteria for the information material.

Agreement, like consent, is a continual process and should be sought during the trial as well, e.g. during repeat trial visits. The processes for informing the child and seeking agreement should be clearly defined in advance of the research and documented for each child. While agreement may not be possible in all age groups (e.g., neonates), the information process provided to the child and the child's response should be documented. In any case, the investigator should report on the agreement procedure in writing, even if the agreement could not be given in writing.

7.1 Assent

Some Member States have a legal requirement to obtain assent. Any specific requirements for assent are defined by national law, recognised by Article 29(8) of the Clinical Trials Regulation. Recommendations on participation of the minor in the informed consent process, leading to the possible assent, are given in this section. The recommendations provided for various age groups (section 7.2) to seek agreement to participate in a clinical trial should be in accordance with national law.

7.2 Participation and agreement according to age groups and level of maturity

7.2.1 Newborns and infants (from birth to 2 years of age)

In this age group, it is not possible to obtain agreement, and understanding of research is not expected. Providing information to the child is mostly aimed at preparing the child for the procedures to come. Although these children are not able to raise verbal objections, any signs

of resistance or protest should be identified and lead to a discussion with the parents/legally designated representative.

7.2.2 Pre-schoolers (2-5 years of age)

Within this age group there is the emergent capacity to provide agreement. Where the child has some capacity of understanding, age- and maturity-appropriate information is still needed even if after giving information, agreement is evaluated not to be obtainable. Since information in text is not helpful for most of these children, other ways of providing visual information should be sought, e.g. videos, pictograms, cartoons or drawings, which can be taken home and discussed with the parents/legally designated representative, in order to ensure that the child is properly informed.

Research on cognition shows that younger children have significant ability to provide agreement. It is recognised that children from the age of 3-4 years can express altruism and have an emerging capacity to form an opinion. At the same time, these children have significant ability to express fundamental resistance and protest, beyond the usual signs of discomfort during or after unpleasant procedures. These expressions should be taken seriously and discussed with both the child and the parents/legally designated representative. When it is evaluated that these are expressions of dissent, this should be respected.

7.2.3 Schoolers (6-9 years of age)

Within this age group there is a growing capacity to provide agreement, and this group is known to be able to express altruism. From the age of 7, children may be able to understand benefits and risks of research and start to understand conflicting or abstract information. This should be taken into consideration when developing information material and agreement forms (if applicable) aimed at children. Most children and parents are not familiar with the concept of randomisation, making it a complex notion to understand. However, it has been shown that children with chronic illness may have developed an increased capacity to make independent judgements based on previous life experience. These judgments and the child's point of view should be taken into account. The dissent should be respected, as these children are capable of forming an opinion of their own.

In any case, it is of major importance to inform the child and obtain agreement as described above, preferably in writing, and to keep track of the procedures to seek agreement as well as of such agreement. Even though the child is of 'school age', i.e. able to read and write, proper understanding can be enhanced by making use of visuals such as videos, pictograms, cartoons and drawings.

7.2.4 Adolescents (10-18 years of age)

In some Member States a subgroup of adolescents are no longer minors, since they have the legal right to give informed consent. This section therefore does not apply to that particular subgroup. In addition, in some Member States (part of) this group is legally required to assent.

Conducting 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 may have the capacity to make adult decisions in many other areas of life. Seeking agreement should put in balance the emerging capacity of an adolescent for independent decision-making with the need for continued special protection as provided by the parents/legally designated representative. Most guidelines and publications recognise that adolescents are, under certain circumstances, able to make independent judgements, and this should be respected according to Article 32 of the Clinical Trials Regulation. As in the younger age

groups, the individual maturity and capacity to understand and agree is also linked to developing cognition and previous life/disease experiences.

Agreement from an adolescent who is a minor should be sought and respected, but does not suppress the need for informed consent from the parents or legally designated representative (see Article 32(1.a)). The information about the clinical trial needs to be provided to the adolescent according to their level of understanding and maturity. If the adolescent dissents, this should be respected.

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. 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.

7.3 Difference of opinion between the child and the parents/legally designated representative

Every effort should be made to understand and respect differences of opinion between the child and his/her parents/legally designated representative. Objections from the child should be respected, as was clarified in section 7.2. A different situation arises if a child wishes to participate while the parents//legally designated representative oppose. In any case, the will and motives of the minor should be taken seriously. This means that the investigator should aim to reconcile the differences of opinion, in order to do justice to the (growing) capacity of children to make adult-like decisions. If the child and parents/legally designated representative are not able to come to a consensus, the dissent of either party is decisive. A minor's agreement is not sufficient to allow participation, as it should always be supplemented by the informed consent of the parents/legally designated representative.

8. Expertise required for assessment

8.1 Paediatric expertise

The Clinical Trials Regulation includes the need for appropriate expertise in the assessment of a clinical trial to be performed in children of any age group (Article 10(1)).

The expert(s) may be permanent members of the assessment body (e.g. an ethics committee), or experts providing advice and consulted on an *ad-hoc* basis. All members participating in the ethical review, including paediatric experts consulted on an ad hoc basis, should be independent of the sponsor, the investigator and the research proposed (Article 9 of the Clinical Trials Regulation). The qualifications and expertise of the experts used should be documented and annexed to its opinion.

The paediatric expertise should be available for the assessment of the application dossier, as well as for any subsequent substantial amendments. Ethics committees specialised in paediatrics could be considered for the evaluation of application dossiers that are complex or in serious paediatric diseases. As required by the Clinical Trials Regulation, lay persons should participate in the assessment of the applications for the authorisation of clinical trials, some of whom may be parents.

Paediatric expertise goes beyond having professionally worked with children and could be defined on the basis of a combination of education, training and experience on the various aspects of child development, ethics and psychosocial aspects. Paediatric expertise is preferably provided by a paediatrician with at least some years of experience in paediatric care, some years of direct experience of clinical trials with children in similar age groups,

expertise in clinical pharmacology and expertise in ethics. If this cannot be found in one individual, two or more paediatric experts could contribute to the expertise needed. In addition, other types of expertise may be provided by nurses, health practitioners, paediatric clinical pharmacologists, and bio-statistical experts. Expertise used should be documented.

8.2 Methodological expertise

In paediatric trials minimising the number of subjects and the level of risk and burden is especially important. This may require smart trial designs, advanced statistical methods, and assays (cf. Sections 9.1 and 13.1). To guarantee that these designs and assays are of sufficient quality, contribute to valid and significant outcomes, and meet all relevant scientific requirements (e.g. regarding the use of placebo), methodological expertise is required in the scientific and ethical review processes.

8.3 Opinion on the application dossier

Considering the need for additional protection of children involved in trials and with a view to providing an opinion on the application dossier, the content of the dossier should be carefully checked with respect to protection of minors. All requirements are specified in the Clinical Trials Regulation.

Moreover, for paediatric trials, 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 description is provided of the way procedures are explained to the child during the conduct of the trial, including ways to comfort the child in case of distress.
- A justification is provided for the inclusion of children and the choice of age groups to achieve the trial objectives. Depending on age groups, inclusion/exclusion criteria may need to include the use of contraception and the outcome of a pregnancy test. Explanation of this should be clear in the information provided, including appropriate contraceptive advice.
- 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 animal studies, modelling or other predictive studies.
- Appropriate evidence is available to provide sufficient scientific ground to expect either direct benefit for the minor concerned, or benefit for the population represented by the minor according to article 32(1)(g) of the clinical trials Regulation.
- Extensive and comprehensive review of available evidence (including relevant publications) and experimental work on the investigational medicinal product should be available and should be reviewed to justify the initial hypothesis, the safety and the evaluation of expected benefit, and the age ranges of children to be included.
- The protocol has been designed with and reviewed by parents and patients (if applicable, based on age and level of understanding).
- The quality of the performance of the trial is such that it is likely that the results will be interpretable and robust; monitoring, audit and quality assurance are described in the dossier.

- The trial uses age-appropriate forms and 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, if appropriate.
- There are provisions in the protocol for systematic independent publications of results, within the timeframe required by both the Clinical Trials Regulation and the Paediatric Regulation, including when results are unfavourable.
- The protocol may include a provision for the medicinal products to be given 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 protocol should justify the duration of follow up in the given paediatric population. Follow up must include assessment of physical development (e.g. Tanner staging) where appropriate.
- The Member States should ensure that the sponsor regularly monitors and re-examines the balance of risk and benefit of the research so that the health and wellbeing 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 assessors in reviewing paediatric trials, Annex 1 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. Reference should be made to scientific guidelines for drug development in children, including EU and EMA guidelines.

To ensure feasibility of trials to be performed, the investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition) and of families in the development of information material, and where feasible also in the design, analysis and conduct of the trial. Exceptions to this recommendation should be justified.

The trial should be designed to minimise risk and burden for subjects. 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 and to provide a robust safety database. 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 or advanced data analysis methods.

To this end, it is in any case suggested to use "smart" trial designs, and advanced statistical techniques for analysis of paediatric data. Examples of designs are adaptive designs and proof of concept in combination with a randomized controlled trial (seamless approach). Advanced data analysis methods, for instance pharmacometric techniques such as population pharmacokinetic/pharmacodynamic (PK/PD) modelling and/or physiologically based pharmacokinetic (PBPK) modelling may be used to predict the behaviour of a medicinal product in children, and should be used to design the study, select the doses and analyse the data. Investigators should strive to use improved trial designs and statistical techniques that optimally protect children's interests while also ensuring scientific quality and validity.

Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they are agreed with competent authorities when used with a view to provide data for regulatory purposes.

In addition to the selection of the age group(s) of children to be included in the trial, 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) or syndromes. Like in adults, genetic variations may produce significant and informative differences in medicines metabolism, in clinical response to drugs, and in adverse reactions that are to be expected. One should therefore be alert to prevent harm. However, minorities should not be systematically excluded, leading to lack of evidence for their treatments.

Adequate dose rationale should be included in the protocol. A scientific justification has to be provided for the dose and dose regimen proposed 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, 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. Most aspects of assessment, i.e. a systematic evaluation and documentation, are usually carried out by professionals, to ensure accuracy, precision, standardisation etc. of measurements. Ideally, these professionals should also be blinded to allocation. Reporting adverse events 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. Patient-reported outcomes (PROs) are important to understand health status and changes with an intervention. Instruments to document PROs and health-related quality of life in children are increasingly available.

Trials performed in children affected by rare diseases should aim to follow the same methodological standards as those performed in more common diseases, although this will not always be feasible (for example, the power of a controlled trial in a rare disease may be reduced). These trials are generally based on increased uncertainty: for example less-known mechanism of disease, lack of validated endpoints. In addition, they have more complex logistical issues, as participants are fewer and more dispersed (this is a higher burden to children and their families), and require often more trial sites.

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

Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions. However, 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 weakens. Long-term use (beyond 3-6 months) of placebo is known to create difficulties in acceptance of the trial by participants and to increase drop-out rates.

Placebo use is not equivalent to absence of treatment, for example placebo could be used on top of standard care. In the placebo arm, participants are protected against the (potential) harms of the test product.

In all cases, placebo use should be associated with measures to minimise exposure and avoid irreversible harm from the disease, especially in serious or rapidly evolving diseases. As appropriate, rescue[8] treatment and escape procedures[9] should be set up (ICH E10). 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 only 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.

Other trial designs should be considered if appropriate. Active-control trials without a placebo arm 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 2011 EMA "Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available" can also be consulted.[10]

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 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. Some equivalence and non-inferiority trials may be acceptable. For example, new dosing regimens using drugs with a longer half-life with dosing intervals of once per day versus three times per day may offer an advantage, if side effects are comparable. Existing guidelines on methodology issues and/or specific EMA guidelines per therapeutic area should be consulted and regulatory advice should be obtained.

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

[8] Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation. As the provision of rescue treatment may undermine the efficacy measured in the trial, the number of patients receiving rescue treatment should be documented and analysed in the trial.

[9] Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level, who have a single event that treatment was intended to prevent, or who otherwise require rescue treatment (see ICH E10 for further detail).

[10] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/01/WC500100710.pdf

marketing authorisation may be considered suitable as controls if they represent evidence-based standard of care. Appropriate justification for use needs to be included in the protocol and requirements for investigational medicinal products should be followed. 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. The concept of benefit

The Clinical Trials Regulation distinguishes between trials with the prospect of direct benefit for the participating minors which outweighs the risks and burdens involved, and research with the prospect of some benefit for the population represented by the minor (Article 32(1g)). This distinction is essential because during trials that only offer the prospect of benefit for the population, the participating minors cannot expect a personal health benefit, whereas they do have to face the research risks and burdens.

Benefit can be defined as progress in treatment, diagnosis, or prevention for the children. It is a tangible outcome that may be experienced by the child or the population. This may be obtained through either increased efficacy or safety resulting in a better benefit-risk 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.

10.1 Prospect of direct benefit for the minor concerned

One may speak of a prospect of a direct benefit in cases where the clinical trial is expected to play a clinically relevant role in the treatment, diagnosis, or prevention of the disease of the participants. For example, the medicinal product changes or replaces the standard treatment, or forms an addition to normal clinical practice (or to options for care, in those cases where no standard treatment exists yet).

The estimation of whether there is a ‘prospect of direct benefit’ for the participating minors is based on a scientific hypothesis made at the inception of the trial. A controlled trial should be based on equipoise (cf. Section 9), meaning that at the outset of the trial there is genuine uncertainty in the expert medical community about the most beneficial treatment. As a consequence, it is unknown in which of the arms (intervention versus control) participants will experience the highest net benefit (in case of superiority trials: the highest efficacy; in case of equivalence trials: the least adverse events). Furthermore, at the start of a randomised controlled trial, all participants have an equal chance to be allocated to either arm. Therefore, at the outset of a trial, all participants have an equal chance to experience the highest net benefit. The same holds for trials that use a placebo control (obviously these must be superiority trials). That is why a randomised controlled trial, even when the control is a placebo, may be regarded to have a prospect of direct benefit for the minor concerned.

Therapeutic confirmatory ("phase III") drug trials are the best-known examples of research belonging to this category. However, depending on the design, early phase drug trials may also offer the prospect of direct benefit. During the benefit-risk assessment of the trial, the expected direct benefit of the intervention(s) should outweigh the risks and expected burdens.

10.2 Prospect of some benefit for the population represented by the minor

When a trial does not offer the prospect of direct benefit to the minor, there should be the prospect of some benefit for the population represented by the minor. However such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition. Benefit for the population includes increased knowledge of the medicine and/or of the condition, which is expected to result in better diagnostic tools, better prevention or better treatment strategies for the condition at stake. Examples of research falling in this category are observational studies and some PK studies.

Even though all research should produce scientific value (increased knowledge), it is important to note that the Clinical Trials Regulation requires the trial to be valuable for the population represented by the minors concerned, and that this benefit expected from the trial should be identified in the protocol. The magnitude of expected benefit for the population is determined by a variety of factors, such as the severity of the condition, its prevalence, the relevance of the data to be obtained, and the likelihood that the trial will succeed in producing these data.

10.3 Classification of trial protocols

Classification of trial protocols regarding the presence or absence of a prospect of direct benefit for the minor concerned may be a difficult task, both for investigators and for assessors. Since the level of risk and burden that may be justified in a trial depends on its classification (trial with direct benefit for the minor concerned or some benefit for the population) it is important that classification of trial protocols is consistent within and between Member States.

Whether a clinical trial provides a prospect of direct benefit for the children that participate depends on the intervention and the additional procedures that are part of it. Several factors may contribute to the decision to consider the clinical trial as providing a prospect of direct benefit for the minor concerned:

- intention of direct benefit, that is clear from the trial design (by the presence of clinical efficacy and end-points) and duration;
- existing knowledge from (pre)clinical studies with the medicinal product or comparable products in other subjects;
- indications for efficacy of the medicinal product for the condition under study or in the population under study;
- in case of existing knowledge on dosage, the plausibility that in a dose-escalating study the begin dose is effective.

However, clinical trials may consist of a combination of the two research categories described above. For example, early phase drug trials in minors often involve different aspects, including components that may be regarded as treatment options, offering direct benefit for the participants, alongside components such as PK sampling, which may or may not generate direct benefit (for example PK sampling for therapeutic drug monitoring may provide direct benefit).

11. Identifying, minimising and monitoring risks and burden

Assessment of risks and burden is a crucial step in evaluating a protocol and conducting the trial. The child’s interest should always prevail over that of science and society. This is paramount when assessing and monitoring risks and burden. Both risks and burden may be physical, psychological, or social, may be immediate or delayed, and may vary according to age groups.

Risks and burden are to be viewed in relation to the benefit (cf. Section 12). Article 28(1e) of the Clinical Trials Regulation requires that the clinical trial is designed to involve as little pain, discomfort, fear and any other foreseeable harm as possible. In other words, risk and burden should be prevented as much as possible and procedures causing risk and/or burden should be justified. Where possible within the limits of both the trial and the clinical setting, procedures should be combined, for example opportunistically taking study samples at the same time as venipunctures required for usual clinical care.

Risk is defined as the probability and magnitude of harm or discomfort anticipated in the clinical trial.

Burden is defined as the subjective load that affects a participant, parents and family, due to elements of the trial that cause pain, discomfort, fear, disturbances of their lives and personal activities, or otherwise unpleasant experiences.

11.1 Assessment of risk

To evaluate the total risk a trial carries for the minors involved, risks and harms should not only be assessed in terms of probability and magnitude, but also in terms of duration and repetition. 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. A thorough analysis of the risks in a trial should be described in the application dossier, in order to be assessed by the Member State and to be able to conclude on the approvability.

Risk assessment is difficult in practice as probabilities are unknown. Sometimes it will be difficult to pre-identify risks or harm arising in a particular clinical trial, for example if a very novel treatment is to be tested or if participants suffer from serious conditions or if standard treatment is liable to cause multiple adverse effects. Therefore, the elements that influence the risks should be identified in the application dossier. Finally, any identified risk should be associated to measures to prevent, minimise, and monitor such risks as much as possible.

Risk assessment also includes the evaluation of the invasiveness and intrusiveness of research procedures; the risks of the medicinal product tested or the control, which includes the reversibility of harm, adverse effects and reactions, and their preventability; and the risk of withholding active treatment in some cases. The accumulation of research projects in the same population (over-studied population) is another potential harm in addition to raising methodological issues. For both reasons, concurrent clinical trials using investigational medicinal products 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 the study of potentially effective medicinal products in children is delayed by obtaining irrelevant adult data.

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

Disclosure of a risk for a serious or 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 a risk.

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. In addition to the risks 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.

11.2 Assessment of burden

Burden should be assessed in terms of magnitude, duration and repetition, and is by definition determined by the experience of the person bearing the burden. It is important to realise that the burden of a clinical trial is added to the burden associated with the child's disease and routine care. Efforts should be made to avoid or minimise this additive effect. A thorough analysis of the burden in the trial (for the minors and their parents) should be described in the application dossier, in order to be assessed in the ethical review and to be able to conclude on the approvability. Since the magnitude of burden is (at least partly) a subjective experience, assessment of burden is difficult. Not only are there differences between age groups, there are also differences between individuals, due to patient age, nature and severity of the condition, previous experiences as part of the disease, experience with the intervention, and circumstantial factors. The variability of response to pain, discomfort and fear between children should be taken into consideration. Different reactions may be expected, when children are affected by a chronic or acute disease. Coping mechanisms alter with age and maturation, changing the burden experiences, for example when medical procedures are not considered any more as 'punitive'. As a consequence of its subjective nature, it seems that the assessed magnitude of burden during ethical review does not always match the burden as experienced by children. Therefore, obtaining knowledge on the burden that children experience while undergoing certain procedures is highly important and such knowledge should be used to evaluate application dossiers. In this context, also taking into consideration the burden experience of parents and families is relevant (see below).

Burden should not only be defined in terms of pain, discomfort and fear experienced by the child. It has been shown that other factors of burden provide reasons for minors and parents to withdraw from a clinical trial. For minors these are factors such as missing out on social activities, sports and even normal schooldays. For parents these are factors like finding the time to fill out questionnaires, missing work days, driving their child to appointments, collecting samples, and recording measurements or diary entries. In particular for trials without a prospect of direct benefit for the child, burden (both for the child and for parents) is an important factor for children and parents in their decision whether to enrol in a clinical trial, and also impacts their subsequent compliance. For both investigators and assessors performing the ethical review it is important to be aware that these types of burden may be crucial, and that factors such as logistics should be included in the assessment of burden of a clinical trial. Even though only the burden of the child is of importance for assessment of risk and burden in relation to benefit (Article 32 of the Clinical Trials Regulation and cf. Section 12), burden affecting compliance and participation may impact scientific soundness of the trial and as such deserves an independent assessment.

Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and discomfort 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 verbally 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 related 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 should be applied to reduce the number of blood samples required to be taken for each child. 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.

The parents/legally designated representative should be informed of which procedure is part of the usual care and which is performed in relation to the trial. In addition, they should be informed of the nature of the trial procedures, i.e. whether a direct benefit may be expected or not. 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 lead to humiliation of the child (such as undressing), therefore causing emotional pain, 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 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 (cf. Section 11.3) and the appropriate level of sedation needed for the procedure(s) should be maintained.

In order to minimise pain, discomfort, 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 the parents/legally designated representative and the 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, preferably by someone the child is already familiar with, should be attended to. Changes in the procedures should be explained 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, known to the child, who could provide reassurance. At the sign of distress and/or dissent the trial 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 and perhaps even withdraw from the trial.

11.3 Monitoring the level of risks and burden

The level of risks and burden may evolve over time, during the trial and with evolving knowledge. Risks and burden should be continuously monitored and monitoring should be pre-specified in the protocol. Burden monitoring may involve carefully observing the child and proactively checking the child's perception. It is valuable to find ways to have the child and the parents directly reporting to the investigator on the levels of burden they experience, for example through an online tool.

Stopping rules should be included in the protocol, e.g. in case of unexpected high levels of burden for (individual) children, and 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 Regulation (Articles 28.1(a) and 28.1(e)), the sponsor of the clinical trial should identify, assess and monitor the burden, risks and harms induced by the investigational medicinal products. Article 43 requires annual reporting on safety to the EMA throughout the duration of the clinical trial, or on request, for assessment by 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.

12. Assessment of the relationship between benefit, risks and burden

The determination of the benefits in relation to the levels of risks and burden are the basis for ethical approvability. As the assessment of benefit, risks, and burden may be based on probabilities and assumptions, this should also be balanced with the severity of the condition or disease to be studied and the benefit, risks, and burden of alternative treatments.

The Clinical Trials Regulation describes the following relationships between risks and burden on the one hand and benefit on the other hand (Article 32(1g)). When there are scientific grounds for expecting that participation in the clinical trial will produce:
- a direct benefit for the minor concerned: then risks and burdens should be outweighed by the benefits;
- some benefit for the population represented by the minor concerned: then the clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

12.1 Assessing trials with prospect of direct benefit for the minor concerned

For clinical trials having the prospect of direct benefit for the minor concerned, the assessment concerns the balance of benefits with risks and burden for the participants in the proposed clinical trial. In such trials, the expected benefits for the participants should always outweigh the risks and burdens of the trial (Article 32.1(g)). The crucial consideration in the ethical review is which level of benefit justifies certain levels of risk and burden.

If a clinical trial involves a prospect of direct benefit for the minor, there is a realistic possibility that their health or wellbeing will be improved by participating in the trial, including for example through additional safety monitoring. However, it is important to keep in mind that direct benefit for the minor concerned may not materialise. After all, it is a trial with an investigational medicinal product that may prove to be less effective than the standard treatment and/or may come with more adverse reactions.

12.2 Assessing trials with prospect of some benefit for the population represented by the minor

For clinical trials with a prospect of benefit for the population, there is no benefit for the trial participants. As a result, balancing benefit versus risks and burden is not appropriate because participants can only experience the risks and burden, and not any direct benefit. Directive 2001/20/EC[11] did not formulate a threshold for acceptable risks and burden for trials with "some direct benefit for the population" (i.e. without the prospect of direct benefit for the participant). As an extra protective measure, the Clinical Trials Regulation introduces a new criterion for the assessment of risks and burden, in addition to general safeguards such as ethical review, consent of the parents/legally designated representative, and subsidiarity. This new criterion demands that for trials with some expected benefit for the population represented by the minor, the risks and burden should be minimal in comparison with the

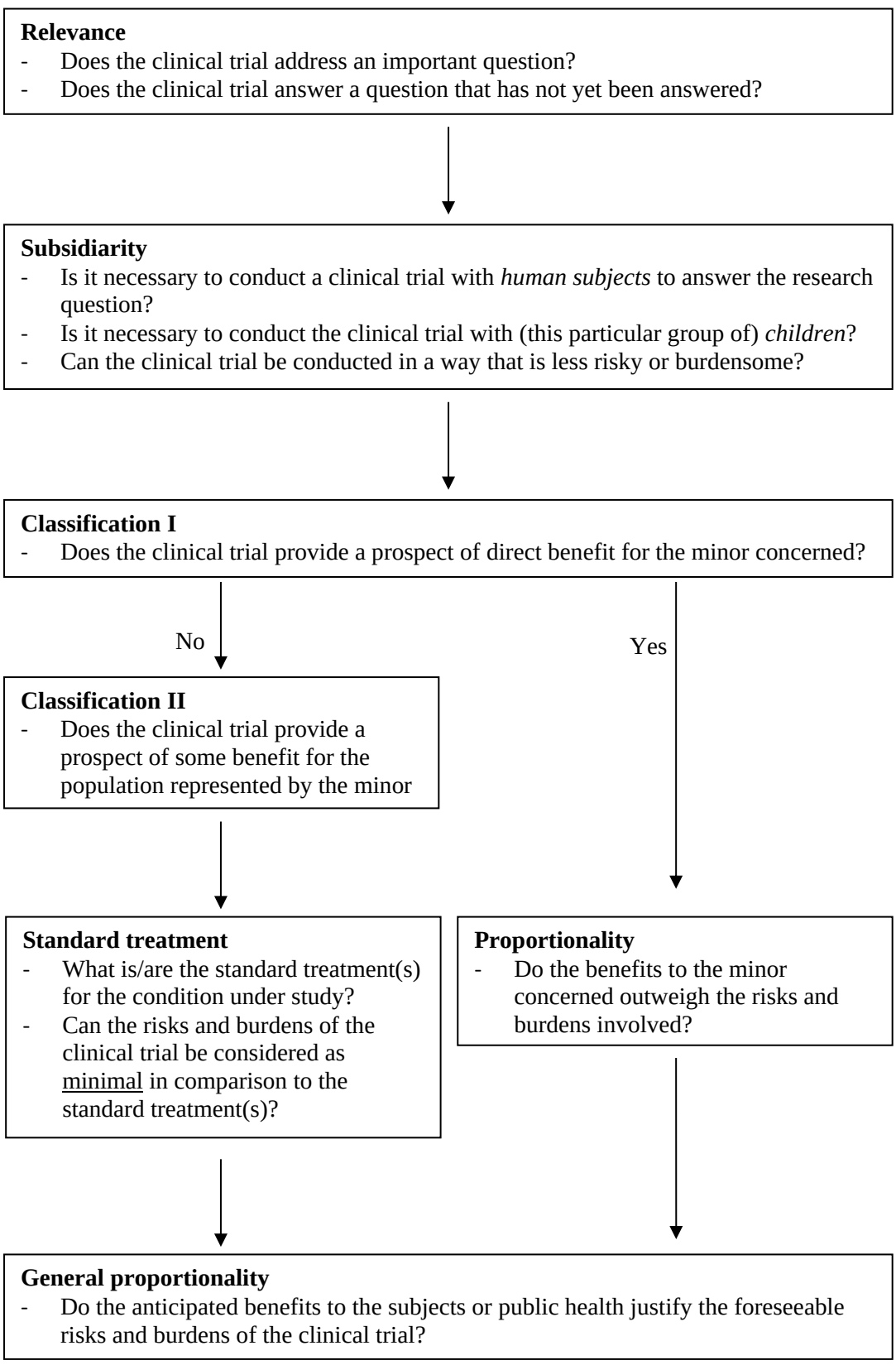
[11] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for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

standard treatment of the minor's condition. This means that in the situation where no direct benefit is expected for the trial participants, the levels of risks and burden for participants are assessed relative to that of the standard treatment they receive. In such trials the procedures are limited to those that present experiences of risk and burdens that are reasonably commensurate with those that are part of the minor's standard treatment. Overall, the level of exposure to risks and burden should be assessed with the participants' interests in mind, in line with Article 3 of the Clinical Trials Regulation.

Minimal risk can be defined as the probability and magnitude of harm or discomfort similar to risks ordinarily encountered in a child's daily life, or during the performance of routine physical or psychological examinations, or simple tests in a child. Examples of investigations, tests or procedures which could be considered minimal risk (or not) are provided in Annex 3. Given that the regulation has put 'minimal risk and burden' in direct relation to the standard treatment, there is no set definition that will apply to all clinical trials with minors without the prospect of direct benefit. As a result, in each specific trial 'minimal risk and burden' will have to be viewed in the context of the disease, health status, prior experiences and related standard treatment for the participants.

Ethical review needs to establish whether the level of risk and burden is minimal in comparison with the standard treatment of the minor's condition. It is important to bear in mind that even if the answer is affirmative, this does not necessarily mean that the trial, with accompanying risk and burden, is ethically acceptable. In any case, the foreseeable risks and burden should be justified by the expected benefit for the population represented by the minor and risks and burden should be minimised as much as possible (Articles 28(1a) and 28(1e) of the Clinical Trials Regulation respectively). Therefore, the sum of elements in the ethical review regarding assessment of benefit, risks and burden, schematically shown in box 1, should guarantee appropriate protection of children.

Box 1. Guide to assessing acceptable levels of risk and burden in relation to the benefit



12.2.1 Standard treatment

Where possible, standard treatments used as comparators should be evidence based. Since in paediatric medicine the level of evidence may be poor, in those cases best practices qualify as standard treatment. Importantly, the baseline of evidence will improve with every new trial that is conducted and results that are obtained. When there is no evidence based, professionally accepted standard (therapeutic) treatment available for the minor's condition, the standard treatment should be regarded as the health care delivered for the child's condition. This may include interventions to reduce pain, discomfort or fear, such as cleaning of wounds, pain medication, and oxygen therapy.

When there are multiple standard treatments, an ethics committee should assess the risks and burdens of the clinical trial in comparison to each of the different standard treatments that are common for the paediatric population under study. The risks and burden should be minimal in comparison to either standard treatment.

Furthermore, the standard treatment of the minor's disease may vary over time, depending on the condition of the minor or the phase of the disease. For instance, when the minor no longer has a prospect for cure, standard treatment is palliative care. The risks and burden that the minor is exposed to during this phase of treatment may differ substantially from the risks and burden in the previous phases. This change of standard treatment therefore has consequences for the level of risks and burden that the minor may be subjected to in the clinical trial.

12.2.2 Assessment of risks and burden for individual children

In the ethical review it is only possible to assess the context and circumstances of the population under study, not of individual minors. Therefore, investigators are responsible for assessing (advisably in consultation with a child's treating physician) whether the risks and burden of a trial are minimal for an individual child in comparison with the standard treatment the child receives for his or her condition, before enrolment in the trial. This evaluation should be carried out together with the parents/legally designated representative and where possible minorsn themselves, to ensure that the burden the child may be able to bear is taken into account in the evaluation of acceptable risk and burden. Some children who have prior experience with certain procedures know what to expect and may consider that these procedures entail minimal burden. Other children may have developed fear or distress due to the same procedures, and this will result in subjecting them to an unacceptable level of burden. These experiences should be discussed with the children and their parents/legally designated representative. Experience and knowledge of what certain procedures entail may also have a positive impact on the informed consent procedure, because parents and children understand what they agree to.

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. Alternatives to blood sampling (e.g. urine or saliva sampling) for pharmacokinetic studies should be preferred when possible.

Advanced statistical techniques such as population approaches and optimal design techniques should be applied to reduce the number of samples required. For blood and tissue assays, micro-volumes and micro-assays should be used. Not using micro-assays should be justified in the protocol. In principle, general and/or local anaesthesia should be used as appropriate for painful and/or invasive procedures in accordance with the outcome of the risk assessment.

Timing of sampling should be co-ordinated with daily activities as far as possible to avoid repeat procedures 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. For example, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure. Timing of sampling and number of sampling attempts should be defined in the protocol.

13.2 Volume of blood

Preterm and term neonates have very limited blood volume, and 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.

In addition to advanced statistical techniques, micro-methods (on dry spots and scavenged blood remnants) should be used whenever possible since they allow less trial-related blood loss. Innovative sampling methods, for example opportunistic or sparse sampling methods, methods which can be applied when population approaches are used, could also reduce the volume of blood needed and the number of times blood needs to be collected from children. The following blood volume limits for sampling are recommended (although are not evidence-based). 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. When blood sampling is also needed for normal health care, these indicated trial-related blood volumes may be too high, especially in (preterm newborn) infants. Trial-related blood sampling should always be justified.

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 group of the paediatric population. When affected by serious diseases, they are multi-drug users with potential interactions to be taken into consideration. This paediatric age group may suffer from diseases that are specific to them and also differ pharmacologically from older ones. They should be considered as a very heterogeneous group of patients (for instance weight may vary between 0.5 and 5 kg). Sponsors should take into account the complexity of the situation and the potential for long-term effects, including developmental effects when designing trial protocols in this population.

15. Trials with healthy minors

In principle, healthy minors should not be enrolled in clinical trials as healthy volunteers, because usually a trial does not benefit them or the population of healthy minors. Moreover, they cannot consent and are still considered to be a vulnerable population in the same way as 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. The desire to help others has been cited as a factor influencing the participation decisions of some children and young people. In any case, Article 32 of the Clinical Trials Regulation should be adhered to, meaning that healthy children may only be enrolled in trials when they may expect a direct benefit or when the population of healthy children may expect some benefit of the trial.

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 should include the target population likely to benefit. Trials in children with intermittent diseases (e.g., flare-ups or seizures) may be acceptable because even in the "healthy" phase the children are affected. 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. Trials with adolescent females

Young females who have developed the capacity to become pregnant should be offered the opportunity to participate in clinical trials, despite the possibility that they might become pregnant during the trial, because data are needed in this group and their access to the benefits of research should not be delayed. Therefore, inclusion with the use of contraception should be made possible by the investigator for this group of participants. There should be thorough explanation of this as part of the informed consent process.

17. Paediatric forms and formulations to be used in paediatric trials

Forms and formulations used in a trial should be described in the protocol.[12] Additionally, forms and formulations used in paediatric clinical trials should be reported in publications.

Age-appropriate forms should be used to avoid the risk of adverse reactions, invasive administration procedures (for example, intramuscular injectables or young children choking on large tablets), and the high 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 appropriate and proportionate requirements of Good Manufacturing Principles, as required by the Clinical Trials Regulation and the Commission Directive 2003/94/EC[13] [note: the reference will be updated once this is repealed]. Conditions e.g. to avoid bacterial contamination, degradation of the medicinal product, and to protect from light, should be specified in the protocol or Investigational Medicinal Product Dossier as appropriate.

[12] ICH E6, section 6.4.4

[13] 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

In addition, bridging PK data to the marketed pharmaceutical form may be required.

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).[14]

18. Individual Data protection

The processing of private data in any clinical trial, including paediatric, shall in light of Article 93 of Clinical Trial Regulation comply with the Directive 95/46/EC (as of 25 May 2018 with Regulation (EU) 2016/679 on the protection of natural persons with regard to processing of personal data and free movement of such data, repealing Directive 95/46/EC (the General Data Protection Regulation – GDPR).[15]

The specificity of data protection in children also relates to future (unknown) use of data obtained in children. The use of the data beyond the protocol, e.g. for the purpose of future research, should be subject to informed consent, and conform with Article 28(2) of the Clinical Trials Regulation. Biobank samples retention and the need for consenting to such use should be discussed in the protocol. It may be difficult to reach a minor participant of a trial after several years to obtain consent after the participant has reached the age of consent. In such cases, yearly check-ups regarding the contact data of the patient and his/her parents are advisable. The law of Member States determines how to act when the participant who has reached the age of consent, cannot be contacted, e.g. samples may have to be destroyed. The trial documents should be archived for a duration of 25 years after the end of the trial and medical files of the subjects shall be archived in accordance with national law (Article 58).

Children are less likely to challenge records about themselves. Therefore there is an additional duty for sponsors 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/legally designated 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, the investigator 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 have access to any information collected on their health. Other personal information collected for a clinical trial will have to be made accessible to them in conformity with national laws on the protection of individual data. Disclosure of genetic findings, which may be regarded as a risk in clinical trials, requires expert counselling in an adequate setting.

19. Unnecessary replication of trials

It is considered unethical to replicate trials in children unnecessarily. This can only be avoided by ensuring that information gained in any trial is made rapidly available to sponsors and the public, as is provided for in Article 41 of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Article 81 of the Clinical Trials Regulation.

[14] Commission guideline on excipients, guideline for excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006) and the guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2)

[15] OJ L 119/2016, p 1-88

19.1 Publication of paediatric trials and results

The Clinical Trials Regulation provides for public access to the data held in the EU database. In principle within 6 months from the end of the trial[16], a summary of the results is submitted to the database. The summary of the results should be accompanied by a summary of the results that is understandable by laypersons. In case of paediatric trials, the summary should be understandable by the children that have participated in the trial. The summary of the results, including a summary that is understandable to a layperson, will be available in the EU database.

The clinical trials Regulation provides for systematic registration of paediatric clinical trials and publication of results, including unfavourable ones. Together with a thorough analysis of the literature this should allow detection of similar trials, with similar aims, and thus prevent unnecessary duplication of trials in children.

Protocols that restrict independent publication by investigators should not be accepted, and the timeline for publication should be reasonable and 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 systematic reviews and databases will facilitate avoiding replicating unnecessarily trials in children. This is supported by the general provisions on transparency in the Clinical Trials Regulation and by the Paediatric Regulation, which demand that information on the results of studies in the paediatric population, as well as on the status of the paediatric investigation plans, waivers and deferrals, should be included in product information.

20. Adverse effects reporting

Rules and obligations for adverse events and adverse reactions reporting in paediatric trials are identical to the Clinical Trials Regulation requirements for adults. This includes the notification of serious adverse reactions observed in clinical trials (articles 41-43 of the Clinical Trials Regulation).

As adult data are poorly predictive of safety in children, reporting may cover target organs and types or severity of reactions differing from that known 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/legally designated representative and carers should be strongly encouraged and carefully instructed to report adverse reactions and events to the investigators in a prospective and timely manner. This is particularly important for younger children, who may not be able to identify adverse reactions.

21. Inducements versus compensation for children

Articles 28(1.h) and 32(1.d) of the Clinical Trials Regulation require that there must be no inducement to enter a trial, either for the parents, legally designated representative or children. Parents/legally designated representative can only be compensated for expenses and loss of earnings directly related to participation in the clinical trial.

[16] As provided for by the Paediatric Regulation No 1901/2006 of the European Parliament and the Council, on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, which is *lex specialis* to the clinical trial Regulation

22. Insurance issues

Coverage ensuring that damages will be compensated is mandatory according to the Clinical Trials Regulation (Article 76(1)) and Member States should ensure there is a system for damage compensation, e.g. insurance. Obtaining insurance for trials performed in children, in particular those in neonates, may be difficult, for example, 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 Member States 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 with children in non-EU countries

According to Directive 2001/83/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 (to be repealed by the Clinical Trials Regulation) and should comply with equivalent good manufacturing practices of EU countries. The same requirements apply to Paediatric Use Marketing Authorisations (PUMA), as introduced by Regulation (EC) No 1901/2006, as well as the same being applied to paediatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation.

Similarly, ethical standards should be no less exacting than they would be for research carried out in EU countries and that, in addition, the trial protocol should be submitted for ethical and scientific review in the EU Member State in which the sponsor or its legally designated 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/agreement are obtained for children.

The recommendations in this document should be followed by EU investigators 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

In order to ensure GCP compliance, the sponsor of a clinical trial and the investigator have to take appropriate account of the ICH guidelines on Good Clinical Practice. Article 52 of the Clinical Trials Regulation requires sponsors to notify the Member States concerned by the conduct of a trial about serious breaches of the Regulation or of the protocol applicable at the time when the breach occurred via the EU portal. Although this requirement is not specific to paediatric trials, monitoring and appropriate reporting of serious breaches, including ethical violations as well as GCP non-compliance are particularly important as children are a vulnerable population. The assessment of these serious breaches will be performed by the Member States.

All parties involved in protocol assessment and supervision of clinical trials in their territory should be kept informed of such violations or non-compliance. These serious breaches may fall into different categories of issues according as to whether and to which extent rights, safety and well-being of trial participants and scientific value are compromised. The preferred option to avoid such violations is education, training and implementation, and adherence to an effective quality system for clinical trials activities performed.

Compliance with GCP should be made explicit in publications. The clinical trial Regulation mandates that results of all studies, including those conducted unethically are made public. Information on such trials is needed to avoid repetition of similar errors and to protect future trial subjects. Public information with warnings on the unethical aspects also contributes to education on how to conduct paediatric trials ethically. Unethical aspects in trials are not limited to fraud and scientific misconduct. A wide range of ethical violations may occur in trials, and therefore a detailed explanation is warranted (Points to consider on GCP inspection findings and the benefit-risk balance, EMA/868942/2011).[17]

If a study is found to be non GCP-compliant during an inspection of a marketing authorisation application (MAA), or Paediatric Use Marketing Authorisation (PUMA), 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 legislation, if appropriate.

[17] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/01/WC500137945.pdf

25. ANNEX 1: List of issues to be considered in a clinical trial involving minors

List of issues to be taken into consideration for planning and assessing 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 population
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, or other design
10. Age-appropriate forms and formulations of medicinal products
11. Validated 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 trial burden checked with children / patient and family 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. The option of sperm and oocyte cryopreservation if the child’s fertility has the potential to be affected by participation in the trial
19. Appropriate pharmacovigilance procedures are put in place by the sponsor
20. Identification of benefits in trials without a prospect of benefit for participants.
21. Identification of benefits in trials with a prospect of benefit for participants.
22. Study risk for participants
23. Study burden for participants (including pain, fear discomfort, time investment and logistical aspects)
24. Study burden for parents and siblings (including time investment and logistical aspects)
25. The potential risks and burden have been weighed against the expected benefits for the children enrolled in the clinical trial with prospect of direct benefit. The balance of expected benefit versus risks and burden should be positive for the clinical trial.

26. Comprehensive, understandable Informed Consent and Information sheets for parents/legally designated representatives (as appropriate)
27. Consent, assent/agreement and information sheets: illustrated and understandable age-specific for children
28. Anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his/her family
29. The system for damage compensation in place in the relevant country
30. If available, opinions of other ethics committees for international multicentre studies
31. Publication of trial results and timelines, and informing participants and their families
32. Continuation of trial medication for participants, beyond the end of the trial, where appropriate

26. ANNEX 2: Information for informed consent

Information material should be specific for parents and children: It 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)[18]. Separating the information sheet in 2 parts (one with a summary, and the other with more detailed information) may help to prevent providing children and their parents/legally designated representative with an overload of information. Based on reading the first part, they can decide whether they are interested in the study and read the full information sheet. In addition, splitting the information into smaller chunks increases attractiveness of the information and ease of reading. The use of visual help is encouraged (drawings, pictures, cartoons), but also other media and formats (such as DVD's, computer programmes) may be used, for example to provide general information explaining what research is.

The number of age-specific variations of sets of information material 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 be designed with input from participants, affected children or parents.

Information material 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/legally designated representative 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/legally designated 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. How long is the trial going to take?
3. Will I have the same doctor or investigator from start to finish?
4. Why have I been chosen?
5. Do I have to take part?
6. What will happen to me if I take part?
7. What are the compensations?
8. What will I have to do? What will my parents have to do?
9. What is the medicine that is being tested?
10. What are the alternatives for diagnosis or treatment?
11. What are the possible disadvantages and risks of taking part?
12. What are the side effects of any treatment received when taking part?
13. Is ionising radiation to be received, and which regulations are respected?
14. Is there possible harm to an unborn child?
15. What are the possible benefits of taking part?

[18] For examples of age-specific variations in information material, see http://www.hra-decisiontools.org.uk/consent/examples.html. For an example of age-specific assent forms, see http://www.finpedmed.fi/index.php?page=1255&lang=2

16. What happens when the research study stops?
17. What if there is a problem?
18. Will my taking part in the trial be kept confidential?
19. What will happen if I don't want to carry on with the trial?
20. What are the options if I stop taking part in the trial?
21. How is my General Practitioner/Family doctor involved?
22. What will happen to any samples taken from my body?
23. Will any genetic tests be done?
24. What will happen to the results of the research trial?
25. Who is organising and funding the research?
26. Who has reviewed the trial and what are the results?
27. 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/ legally designated representative.

27. ANNEX 3: Examples for levels of risks and burden

The following table provides examples of risk and burden evaluation of procedures carried out for the purpose of a trial. This evaluation is not fixed, because the circumstances of the child influence the evaluation of risks and burden. 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 evaluation of some of the procedures (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 level of risks and burden increases with the increase in frequency of the procedures and with susceptibility to harm of involved/exposed organs. The categorisation proposed in the table applies to single or very infrequent use of the procedure. The examples presuppose that the procedures are carried out to the highest professional standards.

It must be noted that the table should function as the starting point for the evaluation of risks and burden: It should not be used dogmatically, and critical and careful assessment in the ethical review is always necessary. In addition, new or changing scientific insights into how children experience certain procedures may lead to further revision of the table.

The three categories of procedures present an increase in evaluated risks and burden.

For trials with expected direct benefit for the minor involved, the benefit should outweigh the risk and burden. Therefore, trials that involved procedures in category 2 should provide a prospect of direct benefit greater than trials only containing procedures in category 1, and so on for trials containing procedures in category 3.

For trials with some benefit for the population, the risks and burden should be minimal in comparison with the standard treatment. In general, minimal risks and burden can be defined as the probability and magnitude of harm or discomfort similar to risks and burden ordinarily encountered in daily life. By consequence, minimal risk and burden for children with a disease or disorder, who undergo routine examinations, tests and treatments, may be different from minimal risk and burden for healthy children. The procedures presented in category 1 may in general be considered as minimal in risk and burden (for example also for healthy children). Trials with only such procedures can therefore often be regarded as minimal in risk and burden (unless there are many of those procedures in the trial and/or these are frequently applied, see above). Risks and burden of procedures in category 2 might be regarded as minimal, only if the standard treatment of the child involves these or comparable procedures and the child perceives them as sufficiently minimal in burden. In addition, ethical review should determine whether in such situations the sum of risks and burden can indeed be regarded as minimal for the particular group of children involved. Trials with procedures in category 3 should never be approved when there is no prospect of direct benefit for the child involved, since the risks and burden of these procedures cannot be evaluated as minimal, regardless of the context of the child.

No or minimal risk and burden	Risks and burden that might be regarded minimal, dependent on the standard treatment	More than minimal risks and burden, regardless of the standard treatment
Category 1	**Category 2**	**Category 3**
– History taking – Clinical examination – Auxological measurements – Tanner staging – Behavioural testing – Psychological testing* – Quality of Life assessment – Venipuncture* – Heel prick* – Finger prick* – Subcutaneous injection – Urine collection with bag* – Breath condensate collection – Collection of saliva or sputum – Collection of hair sample – Collection of tissue removed from body as part of medical treatment* – Topical analgesia* – Stool tests – Bio-impedancemetry – Transcutaneous oxygen saturation monitoring (pulse oxymetry)* – Blood pressure monitoring – Electroencephalography – Electrocardiography – Vision or hearing testing – Ophthalmoscopy – Tympanometry – Lung function tests (peak flow, exhaled NO, spirometry) – Oral glucose tolerance test – Ultrasound scan – Digitally amplified chest or limb X-ray* – Stable isotope examination	– Urine collection via endo-luminal or suprapubic catheter – Arterial puncture – Umbilical catheter – pH metry – Nasogastric tube insertion and use – Transcutaneous oxygen or carbondioxide tension monitoring – Electrophysiological measurements (using stimulation) – Exercise testing (ergometry, spiroergometry) – Raised volume pulmonary function testing (infants) – Peripheral venous lines – Polysomnography – Fasting (≥ 1 meal) – Spinal CSF tap – Bone marrow aspiration – MRI scan – X-ray other than digitally amplified chest or limb X-ray – CT scan* – X-ray DEXA bone density measurement – Use of contrast media – Paracentesis – Skin punch biopsy – Airways or skin hyper-reactivity challenge test	– Heart catheterisation – Endoscopy – Biopsy – Surgery or modification of standard surgical procedure carried out as part of medical treatment – Sedation – Anaesthesia – Systemic analgesia – Hypoglycaemia test – Unstable isotope usage – PET scanning

***Feedback requested**:*

Q1. Is the proposed categorisation of these procedures still adequate?

Q2. Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

28. REFERENCES

Feedback requested:

If you are aware of any other relevant references you are invited to put them forward.

28.1 General guidance

- Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (Strasbourg 2005) http://conventions.coe.int/treaty/en/treaties/html/195.htm
- Charter of Fundamental Rights of the European Union (2012) http://www.europarl.europa.eu/charter/default_en.htm
- Clinical investigation of medicinal products in the paediatric population. ICH E11. CPMP/ICH/2711/99. http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/clinical-investigation-of-medicinal-products-in-the-pediatric-population.html
- 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. European Treaty Series – No 164. Oviedo, 4 IV 1997 http://www.coe.int/nl/web/conventions/full-list/-/conventions/treaty/164
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