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

Revision 1

18 September 2017

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

TABLE OF CONTENTS

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 new Regulation (hereinafter the Clinical Trials Regulation). The document provides recommendations on various ethical aspects of clinical trials performed with minors from birth up to the age of legal competence to provide informed consent. This will contribute to the protection of all minors who participate in clinical trials, whilst not denying them research benefits in terms of both participation in clinical trials and access to evidence-based medicinal products (recital 8). As the authorisation of clinical trials, including ethical approval, is the responsibility of Member States, common recommendations on ethical aspects of clinical trials in minors will facilitate a harmonised approach to the application of the Clinical Trials Regulation across the EU, thereby facilitating the conduct of clinical trials in whichever country the trial occurs.

There is a need to carry out trials with children, which cannot be performed with 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 possible, using age-appropriate information. In the ethical review, paediatric expertise is required to assess and balance the benefits, risks and burden of research with minors. The difference between minors and adults as research participants has implications on the design, conduct and analysis of trials. Trials should be performed by trained investigators with paediatric experience. Involvement of parents and children in the research development process is of importance, to be able to adequately address and incorporate their needs and preferences. Pain, fear, and discomfort should be prevented and minimised when unavoidable. The neonate represents a particularly vulnerable group of the paediatric age groups and requires even more careful trial review. Finally, various other aspects relating to the performance of trials with minors are discussed.

1. INTRODUCTION - RATIONALE FOR THE DEVELOPMENT OF RECOMMENDATIONS

Off-label use of medicinal products 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, especially when placed in the situation of a clinical trial, as they may be relatively incapable of protecting their own interests. Rather than being excluded from research, children deserve everyone's utmost effort to protect them from risks and burden, by minimising and mitigating those risks and burden. The Clinical Trials Regulation brings a balance between protecting children (i.e. minors in the meaning of the Regulation) and enabling research that provides evidence for good paediatric care so as to prevent the risks of off-label use of medicinal products. 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 dosage forms. Although the same ethical principles apply across age ranges, from children to elderly, additional protection is defined for research with minors.

The recommendations in this document aim to bring together ethical principles from various documents. The European Network of Paediatric Research (Enpr-EMA) established by the Paediatric Regulation has the objective to foster high-quality, ethical research on the quality, safety and efficacy of medicines for use in children and brings recognised expertise in performing clinical studies with children. Over time, with changing legislation or progressing experience and insights, in particular from Enpr-EMA, the need for further revision of this document may emerge.

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[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

2. SCOPE

This document is intended to provide recommendations on various ethical aspects related to the conduct of paediatric interventional clinical trials and studies falling under the provisions of the Clinical Trials Regulation on medicinal products for human use. These recommendations should serve as a starting point, and stimulate reflection on the best interests of the children involved in trials. Some situations may ask for deviation from these recommendations; deviations should be justified in the protocol to allow review by assessors and ethics committees. The recommendations in this document are also valid for other types of paediatric trials and studies.

This document is intended for all parties involved in trials with minors; these may include clinical trial sponsors, investigators and trial-related staff, participants, families, assessors in regulatory authorities, and staff in pharmaceutical companies, contract research organisations, or trial insurance companies.

This document is without prejudice to the Clinical Trials Regulation, other European or national legislation, and should be read in conjunction with the relevant laws and guidelines. Of note, legislation on clinical trial-related aspects mentioned in this document may differ across Member States (herein mentioned as 'national law').

There recommendations do not distinguish between non-commercial and commercial research. Compassionate use is not covered by this guideline, although some expanded access trials may fall under the framework of interventional clinical trials, nor are clinical trials with pregnant women, where exposure to medicinal products may occur before birth.

3. ETHICAL PRINCIPLES AND FUNDAMENTAL RIGHTS

The Clinical Trials Regulation and these recommendations should be applied in line with the Charter of Fundamental Rights of the European Union (2012), in particular its Article 24 on the rights of the child (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 health-related research involving humans of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (Geneva 2016), 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 (Oviedo, 1997) and its additional protocol concerning biomedical research (Strasbourg, 2005). 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 documents mentioned above might differ and emphasize specific ethical requirements, they share common grounds. 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.

The Clinical Trials Regulation underlines the importance of taking into account the wishes of minors with regard to their participation in clinical trials. The Regulation requires their full engagement with the aim to treat them as developing autonomous beings, whose maturity gradually evolves with age and experience, and whose will should be taken seriously. Although it is acknowledged that minors

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

form a vulnerable group, the focus should be on their developing 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.
- Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles and guidelines of good manufacturing practice for investigational medicinal products for human use and arrangements for inspections
- Commission Implementing Regulation (EU) 2017/556 of 24 March 2017 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014.
- 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)[4]
- 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(R2)), EMA/CHMP/ICH/135/1995
- 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 the role of pharmacokinetics in the development of medicinal products in the paediatric population (June 2006) EMA/CHMP/EWP/147013/2004 - Corrigendum
- 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), EMA[5]
- The rules governing medicinal products in the European Union. Volume 10 – Guidance documents applying to clinical trials authorised under the Regulation.

[4] Under revision

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

- 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).

5. DEFINITIONS/ GLOSSARY

5.1 Age groups and level of maturity

In these recommendations, when referring to a specific subset of the paediatric population, the age range is given for clarity. Age ranges are only meant to provide guidance regarding the proper involvement of minors in the informed consent process. Reference is made to ICH E11 for age groups, but some changes are made. The age group of children (2 to 11 years) and the age group of adolescents (12-18 years) are redefined into pre-schoolers (2-5 years), schoolers (6-9 years) and adolescents (10-18 years). The latter change is based on the WHO definition of adolescence starting at the age of 10 years. This definition was adopted to emphasise the need to take these children seriously.

Age only partly correlates with maturity, but is used as a practical instrument to delineate groups. Maturity rather than age should be the starting point for discussing a trial with minors, cf. Section 7.[6]

It is important to distinguish the age groups from 'physiological or metabolic' age groups, which can be used for other purposes, for example to define dose, inclusion criteria or outcome measures.

5.2 Assent and agreement

- The notion of **assent** is explicit 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 the minor's will to participate in a clinical trial with a legal value (necessary, together with the consent of a legal representative). It is a legal requirement in some Member States for minors of a certain age. Thus, assent is a statement of will with legal value according to national law.

- **Agreement** in this document is used by analogy to "assent" where it is not a legal requirement. Even though agreement is not legally required, this document recommends that the investigator systematically requests agreement from the minor, cf. Section 7.

The way in which the minor participates in the informed consent process, leading to a potential assent or agreement, depends on his or her maturity. The minor's assent or agreement is not sufficient to allow participation in research unless supplemented by informed consent of the parents/legally designated representative.

5.3 Child

The term "child(ren)" is used within these recommendations to mean minors in line with the Clinical Trials Regulation, in contrast to the ICH E11 guideline which refers to children as individuals aged from 2 to 11 years.

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[6] Nuffield Council on Bioethics (2015) Children and clinical research: ethical issues http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf

5.4 Dissent

Article 32(1.c) of the Clinical Trial Regulation states:

> "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"

Dissent means the expression of the minor's will to refuse participation in a trial. In case national law requires the assent of the minor, the lack of assent is equivalent to the minor's refusal to participate, i.e. dissent. A lack of agreement by the child may or may not be equivalent to dissent, depending on the maturity of the minor to express agreement.

The minor capable of forming an opinion may express dissent verbally, but also in other ways (cf. section 7). Dissent should be respected, in line with Article 32(1c) of the Clinical Trials Regulation.

5.5 Informed consent

Article 2(2.21) of the Clinical Trials Regulation and these recommendations define informed consent as:

> "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 specify the requirements for informed consent, and require that the child is involved in the process of informed consent.

5.6 Legally designated representative of the minor

Article 2(2.20) of the Clinical Trials Regulation and these recommendations define a legally designated representative as:

> "a natural or legal person, authority or body which, according to the law of the Member 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. Independent of applicable legal requirements, both parents should be encouraged to participate in the informed consent process. Orphans, or children whose parents no longer have parental authority, should not be excluded from clinical trials; informed consent will be requested from the legally designated representative. Parents/legally designated representative have the duty to protect their child, and consider the child's point of view, based on their knowledge of the child and the child's life.

5.7 Minor

Article 2(2.18) of the Clinical Trials Regulation and these recommendations define minor as:

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

The age of legal competence differs across national laws, for example adolescents from 16 years of age may not be regarded as minors in some Member States. This may have consequences for multinational trials, as the additional conditions applicable to clinical trials with minors will not be relevant for the clinical trials in the Member states where the children are not considered to be minors.

5.8 Paediatric population

According to the Paediatric Regulation, the term "paediatric population" refers to children aged between birth and less than 18 years. This term is used throughout these recommendations to cover all paediatric age groups.

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 on the child's behalf. Articles 29 and 32 of the Clinical Trials Regulation require that specific, written informed consent of parents/legally designated representative must be sought and obtained 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 tailored research information, competent in communicating and working with children and young people, and providing them and their legal representatives with the time and space to reach a decision without pressure.[7] When providing information, the investigator should take into consideration the fear and uncertainty of parents, especially when they are inexperienced with respect to the child's condition.

The information should be given to each parent, or legally designated representative, both in oral and written form. Article 29.2(a) and (b) describe the information that should be provided, keeping it "comprehensive, concise, clear, relevant, and understandable" in order to obtain credible informed consent. In particular, parents/legally designated representative should be explicitly informed of their right to refuse to the child's participation, and to withdraw the 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. There must not be financial inducement to enrol the child in the trial (Article 32(1d) of the Clinical Trials Regulation and Section 21).

In the complex relationship between parents and physician(s), especially in case of chronic or 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. This may not be identified by either party. Therefore, the investigator should not be the one making the decision on participation, but should focus on ensuring that relevant and adequate information is given and that this information has been understood.

Provision of information is a continual process during a trial.

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

Once an adolescent is no longer a minor, or when he or she is an "emancipated minor"[8], he or she should be asked to provide written informed consent as soon as practically reasonable, as for any adult capable of giving consent. Informed consent is no longer required from the parents/legally designated representative. The withdrawal of informed consent by the adolescent, in line with Article 28(2) of the Regulation, shall not affect the activities already carried out and the use of data obtained based on informed consent before its withdrawal.

Adolescents who are legally able to give informed consent should be given the same information as adults. However, such adolescents may still have some elements of vulnerability. In practice, these adolescents may decide to involve their parent(s) in the informed consent process.

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[7] RCPCH. Infants', Children's and Young People's Child Health Research Charter. 2016. http://www.rcpch.ac.uk/cyp-research-charter

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

As the legal age to give informed consent varies according to national laws, multi-state trials may enrol children of the same age who are minors in one, but able to provide informed consent in another Member State.

6.2 Informed consent of families with different cultural background

The information should be adapted to the language skills and understanding of the child and the parents/legal representative. Cultural differences may lead to misunderstandings. Where appropriate, the investigator should arrange for translations: a translator and/or a cultural mediator to be available in the planning of the study and during the process of informed consent and assent / agreement. This person should be familiar with medical terminology, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences. This person may need to be available throughout the clinical trial, e.g. to facilitate adverse events reporting.

6.3 Consent, assent and agreement at the beginning of a trial and continued consent process during trial

Consent, as well as assent and agreement, is a dynamic, continual process, and should not only be obtained prior to enrolling a minor in a trial, but also sustained during the trial. The child should be involved in this (cf. Section 7). This could be achieved, for example, by a brief discussion during trial visits, and documented. The discussion is part of the ongoing dialogue between minors, parents and investigators and should focus on new information that arises from the trial and may affect the willingness of the parents and minor to continue. Especially in long-term trials, the investigator should follow up on a regular basis and document the evolving maturity of the child, his or her ability to assent or agree, and act accordingly.

6.4 Withdrawal of the consent

In all cases, parents/legally designated representative should be made aware of the right to refuse participation in a clinical trial and entitlement to withdraw their informed consent, freely, at any time, without giving reasons. Parents/legally designated representative should be reassured that withdrawal from the trial will not prejudice the child, and will not affect the provision of normal clinical care[9].

Refusal to give consent or withdrawal of consent must not lead to liability or discrimination (e.g., with regard to insurance or employment) against the person concerned. Where applicable, the parents/legally designated representative need to be informed of risks that premature termination of the trial might present to the child's health. Similarly, if consent is withdrawn during for example anaesthesia, it may not be possible to stop the procedure immediately, as this might jeopardize the health of the child. Such a possibility should be described and explained during the consent process, to anticipate and manage expectations.

Where appropriate, a minor with sufficient maturity should also be informed of his or her right to withdraw from the trial at any time, with the same additional information as above for the parents/ legally designated representative.

Parents/legally designated representative who consent to a minor's participation, should have the opportunity to follow the research as it proceeds, unless clinically inappropriate (e.g., during an operation under general anaesthesia). This allows them to be able at any time to decide on whether or not to withdraw the minor from the trial. When the parents/legally designated representative wish to continue following the progress of a blinded trial, after participation withdrawal, they should be informed that a summary of the results, including one understandable by a layperson, will be available in the EU trial database.

[9] 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.

If a minor withdraws from a trial, the investigator is still responsible for reporting trial-related events of which he/she is informed. In addition, the investigator needs to assure appropriate care and follow-up.

6.5 Consent, assent and agreement in emergency situations

Research in rapidly evolving, life-threatening situations affecting children is necessary to advance outcomes and treatments in various conditions, such as initial manifestations of metabolic diseases, status epilepticus, acute trauma, including some conditions that are specific to children. In some emergency situations, treatment or intervention is required within minutes, and the patient's consciousness may be altered, the parents/legally designated representative may not be available to provide prior informed consent, and the children cannot be informed, nor express assent or agreement.

Article 35 of the Clinical Trials Regulation provides for derogation from the prior informed consent requirement in emergency situations - including for paediatric trials - under strict conditions. In particular, the trial should provide an expectation of direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or the diagnosis of its condition. In practice, if research decisions can reasonably be delayed until a parent is present to make a decision, the investigators should wait. If such delay is not possible, the trial may start without informed consent. In that case, informed consent should be sought as soon as possible after the inclusion of the minor in the trial (deferred consent). Under these circumstances deferred consent is considered acceptable. It should always be followed by a regular informed consent procedure. Once the parents/legally designated representative are present, the first step is to provide information about what has happened and, given the seriousness of the situation, ensure that they have a clear understanding of the trial. Subsequently, they should be invited to consent to continuing their child's participation in the trial, as appropriate. If the parents/legally designated representative do not give informed consent, they should be informed of the possibility to object to the use of the data that have already been gathered, conform Article 35(3). Children should be involved in the informed consent process, as much as possible given the circumstances, in a manner appropriate to the urgency of the situation; further information should be offered once they have recovered sufficiently, in order for the child to be able to provide assent/agreement. For such trials, there is no derogation from the requirement to respect the child's explicit wish to refuse to participate. The trial protocol should define the conditions under which deferred consent will be permissible, as well as the deferred consent process itself.

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 minor in the trial will be taken, information given to the parents/legally designated representative, their right to object to the use of the data, and the assent/agreement process.

Some Member States have developed, or legislated on approaches to mitigate the lack of prior informed consent. Some Member States recommend that, if available in such a timeframe, a third party is involved (e.g. a healthcare provider knowing the child) with the responsibility to protect the child's best interest. Conversely, other Member States prohibit asking third parties (e.g. teachers) to substitute for the legally designated representative. Where it is possible to identify participants before the emergency situation arises (for example risk of sepsis in immune-compromised children), parents can be informed, and prior informed consent and assent/agreement can be sought. Awareness of a trial recruiting within a community can be ensured through schools, medias, or outpatient clinics.[10] Researchers should ensure that possible avenues for prior informed consent are considered and where this is impossible, ensure they take into account children's and young people's perspectives and needs in these situations by involving them in the design of trials.

[10] 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/

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

Each minor should participate in the informed consent process together with the parents/legally designated representative, in a way that is appropriate to his or her age and maturity (Article 32(2) of the Clinical Trials Regulation). The aim is to recognise their evolving autonomy and maturity, and to treat minors as persons who have the potential from an early age to express altruism and play an active role on decisions for their own lives, within their familial and social environment. This involvement requires time and should be conducted at the same time as the informed consent process, so that the minor is optimally involved and has the opportunity to assent/agree or dissent (in line with Articles 32(1c) and 32(2) of the Regulation). 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. The central role of parents in the protection of their child should be recognised.

This document supports a systematic request for agreement (even if assent is not legally required), and recommends that the investigator obtains agreement from the minor even when not mandated by national law. The agreement and information process for the minor should be described in the clinical protocol.

Maturity is not a clear-cut criterion in contrast to age, and its evaluation can be difficult, but will help identify differences between children to support their involvement. The evaluation to what extent a minor is able to provide agreement should not be based solely on chronological age, but also on factors such as developmental stage, intellectual capacities (e.g. children with special needs and/or learning difficulties), and life/disease experience. The evaluation will rely on discussions between the investigator, the parents/legally designated representative and the minor, and needs to be documented. While seeking agreement is not possible in all children (dependent on age, condition and other factors), the information process and the minor's response should be documented. Where the minor's agreement is not sought, it is recommended that this be justified in the consent form signed by the parents/legally designated representative.

To provide age-appropriate information and assent/agreement forms, separate material should be used for children, using language and communication tools (visuals, cartoons, videos etc.) appropriate to the participants' age and maturity. Information on relevant aspects of the trial should be provided in terms that are honest, but not frightening (See Annex 2 for recommended contents). The information should be approved from the ethical perspective by the Member States concerned. It is strongly recommended to check the information material for sufficient understanding in the relevant population.

Assent/agreement, like consent, is a continual process, which should be checked during the trial, e.g. during trial visits.

The refusal of a minor, who is capable of forming an opinion, to participate in a trial, i.e. dissent, should be respected. "Forming an opinion" should not be understood as only applying to minors of a certain age or maturity, as young children are able to form and express their opinion in one way or another. Objections raised by a minor, including very young children, at any time during a trial should be analysed. If this analysis shows that the expressed objections are to be interpreted as refusal, the minor's will should be respected, and the minor does not have to provide reasons. This means that investigators should be able to recognize signs of resistance in children and evaluate whether these signs are part of the anticipated burden, or that for that individual child the experienced burden exceeds the anticipated burden (e.g. distress or fear). The investigator or trial personnel, with the possible help of other team members or a paediatric psychologist, should consult the parents/legally designated representative, respond appropriately to the minor's behaviour and try to reduce the burden. If the analysis concludes that the minor dissents, the minor should not be enrolled or should be withdrawn from the trial[11].

[11] In several countries the paediatric associations have identified signs of resistance of the child that should be taken into consideration.

7.1 Participation and agreement/assent according to age groups and level of maturity

7.1.1 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 discussed with the parents/legally designated representative to analyse whether the behaviour is merely an expression of the anticipated but acceptable burden, or is reason for concern on research continuation.

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

Within this age group, there is the emergent capacity to provide agreement. Age- and maturity-appropriate information is needed for all children who have some capacity of understanding, even if the evaluation concludes that agreement is not obtainable. Since textual information is not usable by most of these children, other types of visual information should be provided to ensure that the child is properly informed, e.g. videos, pictograms, cartoons or drawings, which can be taken home and discussed with the parents/legally designated representative.

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

7.1.3 Schoolers (6-9 years of age)

Within this age group there is a growing capacity to provide agreement. From the age of about 7, children may start to understand benefits and risks of research and conflicting or abstract information, but most children and parents would not be familiar with the complex concept of randomisation for example. Conversely, it has been shown that children with chronic illness may develop an increased capacity to make independent judgements based on previous life experience. This should be taken into consideration for the information and agreement material aimed at those children. Even though they are able to read and write, understanding can be enhanced by making use of visuals, such as videos, pictograms, cartoons and drawings. Children of this age group should be well informed, and agreement obtained preferably in writing. Their dissent should be respected, as they are capable of forming an opinion of their own.

7.1.4 Adolescents (10-18 years of age)

This group is treated differently across Member States. Some Member States consider that adolescents above a certain age are no longer minors, and have the legal competence to give informed consent on research participation. In other Member States, national law requires assent from all or part of this group. This section provides complementary guidance without prejudice to national law.

Adolescents belong to the paediatric age group, although they may have the capacity to make adult decisions or independent judgments in many other areas of life, as evidenced in publications. Seeking assent/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. This should be respected according to Article 32 of the Clinical Trials Regulation.

Information should be provided, and agreement from an adolescent who is still a minor should be sought and respected. This does not suppress the need for informed consent from the parents/legally designated representative (see Article 32(1.a)).

Protection of confidentiality, especially for research on socially sensitive issues such as illicit drugs, sexuality or violence, is an additional concern for trials with adolescents. 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 explicit in clinical trial protocols, and should be transparent to the adolescent concerned.

7.2 Difference of opinion between the minor and the parents/legally designated representative

Every effort should be made to understand and respect differences of opinion between the minor and his/her parents/legally designated representative. Objections from the minor should be respected. If a minor wishes to participate while the parents/legally designated representative oppose, the will and motives of the minor should be taken seriously. The investigator should aim to reconcile the differences of opinion in order to do justice to the (growing) capacity of the child to make adult-like decisions. If, after reasonable efforts to reach consensus, the minor and parents/legally designated representative are still in disagreement on participation, 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 trial 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 with children of any age (Article 10(1)).

The expert(s) may be permanent members of the assessment body (e.g. ethics committee), or experts advising on an *ad-hoc* basis. The ethical reviewers, including *ad-hoc* experts, should be independent of the sponsor, the investigator and the trial (Article 9 of the Clinical Trials Regulation). The experts' qualifications and experience should be documented and annexed to the ethics opinion.

Paediatric expertise goes beyond having professionally worked with children and could be defined as a combination of education, training and experience on various aspects of ethics, child development 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, and expertise in clinical pharmacology. If one individual cannot cover all aspects, more than one expert could contribute. In addition, expertise may be provided by nurses, health practitioners, and bio-statistical experts.

Paediatric experts should be available for the assessment of the trial application, as well as any substantial amendments. Ethics committees specialised in paediatrics could be considered where trials are complex, for serious paediatric diseases, or involving uncommon interventions (e.g. gene therapy). The Clinical Trials Regulation requires that at least one layperson participates in the assessment of trial authorisation (Article 9), some of whom may be parents.

8.2 Methodological expertise

It is essential in paediatric trials to minimise the level of risk and burden and the number of participants exposed to uncertainty. This may require smart trial designs, advanced statistical methods and specific assays (cf. Sections 9.1 and 13.1). Methodological expertise is required in the scientific and ethical review process to guarantee assays are of sufficient quality, designs contribute to valid and significant outcomes and meet all relevant scientific requirements (e.g. regarding the use of placebo).

8.3 Opinion on the trial application

All requirements on the trial application are specified in the Clinical Trials Regulation. The application should be carefully checked with respect to the need for additional protection of participating minors.

For paediatric trials in particular, in any case the following points should be checked:

– The trial does not replicate similar trial(s) based on an identical hypothesis;

- Protection and safety of children is ensured (including minimisation of risks and burden) and appropriate paediatric expertise available at all trial sites;
- There is a description of the way procedures are explained to the child during the trial, including a plan on how comfort is provided to the child in case of distress;
- In- and exclusion of children and choice of age groups to achieve the trial objectives are justified. In trials, the use of contraception and outcome of pregnancy test may be required. This should be part of the participant's information, including appropriate contraception advice.
- There should be equipoise ("genuine uncertainty within the expert medical community […] about the preferred treatment") at the beginning of a randomised trial, and no participant should receive care known to be inferior to standard of care.[12]
- The study protocol may indicate a range of patient's weights, e.g. greater than a minimum weight (e.g. in pharmacokinetic studies) as an inclusion criterion.
- Appropriate non-clinical data are available before the clinical trial with children. Such data (toxicology, which may include juvenile animal studies) or other predictive studies (e.g. modelling) are listed for example in the ICH E11 guideline.
- There is appropriate scientific evidence to support either the prospect of direct benefit for the participating minors, or a benefit for the population represented by the minors, according to Article 32(1g) of the Clinical Trials Regulation.
- There is a comprehensive review of available evidence (including experimental work and publications) on the investigational medicinal product to justify the trial hypothesis, the age range of children, and evaluation of expected benefit and safety.
- For trials with only expected benefit for the population, the "standard treatment(s)" should be documented.
- Validated treatment options, or the lack thereof, should be documented.
- There is evidence (or a justification of the contrary) that the protocol and information material have been designed with and reviewed by parents and patients (where possible), to minimise risks and burden and to take into account the wishes and needs of minors and their parents.
- The trial uses age-appropriate forms and formulations of the medicinal product(s).
- An independent Data and Safety Monitoring Board (DSMB) with paediatric trial expertise is identified in the protocol, if appropriate[13].
- The protocol should ensure that the sponsor regularly monitors and re-examines the balance of risk, burden and benefit of the research, so that the health and wellbeing of the participants are safeguarded.
- The protocol should justify the duration of follow-up of trial participants. Follow-up should include assessment of child development where appropriate.
- The protocol provides for independent publications of results, including of unfavourable results, and database publication within the timeframe required by both the Clinical Trials Regulation and the Paediatric Regulation.
- Where appropriate, the protocol addresses the provision of the medicinal product(s) to the participants beyond the end of the trial, unless the benefit to risk balance of the medicinal product tested is unfavourable.

[12] Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317: 141-145

[13] Refer to EMA Guideline on Data Monitoring Committees - EMEA/CHMP/EWP/5872/03 Corr

Annex 1 provides a non-exhaustive list of significant aspects for assessors reviewing a paediatric clinical trial.

9. Design of clinical trials conducted with the paediatric population

9.1 Prior considerations

To provide data on safety, efficacy, appropriate forms and formulations and evidence-based medicine use, clinical trials with children are necessary. Existing data in adults should inform paediatric trials. Extrapolation of clinical trial data from adults to children should be done scientifically and justified.[14] If no data from adults are available, for example in diseases that occur primarily in children, it is important to consider whether such data will be provided at all and whether waiting for them has added value.

Based on the experience gathered in the last ten years[15], a 'staggered' medicine development approach, starting by the older and going sequentially to the younger age groups, may lead to delays in data availability, and result in prolonged off-label use in younger age groups (especially neonates) and difficulties in conducting any trial in these groups once the medicine is on the market.

Scientific criteria for using extrapolation or requiring trial data in one or more paediatric subsets will be based on a combination of need for evidence in a defined subset of the paediatric population, availability of outcome measures in that subset, disease pathophysiology, and acceptable risk of uncertainty. The EMA guidelines on medicine development, methodology or therapeutic area should be consulted, and it is recommended to obtain scientific and regulatory advice especially when proposing to use unconventional design, endpoints, or analyses.

9.2 Design and analysis

The clinical trial design depends, among others, on the objective(s) of the trial and the scientific question(s) to be answered.

To ensure feasibility of paediatric trials, the investigator and/or protocol writer should ensure that children and families are involved in the design, analysis and conduct of the trial,[16] or justify exceptions to this recommendation.

It is imperative that the trial is designed to minimise risk and burden for participants and their families, e.g. by minimising number of blood tests or adapting scheduled trial visits.

The sample size should be as small as possible, but large enough to demonstrate efficacy with sufficient statistical power and provide a robust safety database. The risks and benefits of trials involving fewer children should be weighed against those of trials involving more children but using advanced data analyses or less invasive procedures.

'Smart' trial designs and advanced statistical methods are encouraged, including adaptive, or seamless designs. Pharmacometric techniques such as population pharmacokinetics, pharmacokinetic/ pharmacodynamic (PK/PD) modelling, and/or physiologically-based pharmacokinetics (PBPK) may be used to describe or predict the medicine's behaviour and select the doses in children. Investigators

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14 http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/04/WC500204187.pdf (not yet finalised)

15 https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

16 The Nuffield Council on Bioethics provided useful suggestions in their publication: Children and clinical research: ethical issues. 2015. http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf

The Royal College of Paediatrics and Child Health provides useful guidance http://www.rcpch.ac.uk/cyp-research-charter

should strive to improve trial designs and statistical methods to protect the minors while also ensuring scientific quality and validity. Alternative (less conventional) designs and/or analyses should be justified in the protocol. Different trial objectives may justify different designs including for example cross-over, non-randomised, uncontrolled, or observational studies.

The trial protocol should pay particular attention to the inclusion, possible detection, and harm prevention of certain genetic syndromes (e.g. G6PDH deficiency), or for ethnic subgroups. Like in adults, genetic variations may produce significant and informative differences in medicines metabolism, and adverse reactions. Minorities should, however, not be systematically excluded, as this would lead to lack of evidence for their treatment.

A scientific justification for the dose and regimen in the trial has to be provided in the protocol.

As is the case for adult trials, measures to avoid bias should be used in trials performed with minors. For example, unblinded and/or uncontrolled trials for the demonstration of medicine efficacy are subject to increased bias, and should be avoided whenever possible.

Adverse events will be reported in many cases by parents, or other carers. Whenever possible, the evaluation by the child should be obtained too. Patient-reported outcomes (PROs) and quality-of-life assessments for children are increasingly available and contribute to understanding their health status and the impact of intervention changes.

Trials with minors affected by rare diseases should aim to follow the same methodological standards as trials performed in more common diseases, although this will not always be feasible. These trials are often based on increased uncertainty due to less-known mechanisms of disease, lack of validated endpoints, or insufficient power. In addition, they have more complex logistical issues: fewer and more dispersed participants (a higher burden to children and their families), fewer reference centres, and often more trial sites.

9.3 Paediatric control groups

The use of control groups should be appropriate to the condition(s) under investigation and should be justified scientifically. The choice of active or placebo control for randomised paediatric trials requires a situation of equipoise.

9.3.1 Use of placebo

Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions, or vaccinations when there are already effective vaccines. However, the use of placebo may be warranted in children as in adults when evidence for an effective 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 and compliance by the trial participants and parents, 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 and in the placebo arm participants are protected against the (potential) harms of the test product.

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

[17] Reference is made in particular to the ICH E6 guideline.

9.3.2 Superiority versus non-inferiority trials

Equivalence and non-inferiority trials raise several issues in particular the choice of equivalence or non-inferiority margins, and the availability of adequate trial sample size, and their use instead of superiority trials should be justified. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non–inferiority trials. Equivalence and non-inferiority trials may however be informative. For example, comparing a medicine dosed once versus several times a day may offer an advantage, if tolerability is comparable.

9.3.3 Controlled trials using (reference) medicinal products without a marketing authorisation for children

As many medicines used in children have not been fully assessed and authorised, the choice of active control medicines should be discussed thoroughly. Medicinal products devoid of a marketing authorisation for children may be considered suitable controls if they represent evidence-based standard of care. Justification needs to be included in the protocol and requirements applying to investigational medicinal products should be followed. Definitions of standard of care may vary across sites or Member States; this should be integrated in the trial design and analysis.

9.3.4 Clinical trials using medicinal products containing radio-isotopes

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

10. The concept of benefit

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

Benefit can be defined as progress in treatment, diagnosis, or prevention for the children. It is a measurable clinical outcome that may be experienced by the child or the population. Benefit may be obtained through either increased efficacy or safety resulting in a better benefit-risk balance, or through the provision of alternative treatment with at least similar expected benefit-risk balance. Contribution to improved patient care is also a benefit, for example better route of administration, decreased dosing frequency, improved compliance, decreased risk of medication errors, reduced treatment duration, or availability of age-appropriate dosage form or formulation.

Importantly, the benefit should be clinically relevant, since it will be balanced with the risks and burden of the trial (Section 12). So-called social benefits, such as the sense of contributing to wider social good or the chance to learn something new, may be motivations for participants to enrol in a trial, but may not be regarded as benefits in the sense of article 32(1g) of the Regulation.

10.1 Prospect of direct benefit for the minor concerned

One may speak of prospect of a direct benefit for the minor concerned in cases where the clinical trial is expected to deliver clinically relevant outcomes in the treatment, diagnosis, or prevention of the condition of the trial participants. For example, the medicinal product provides a first treatment, a complement or an alternative treatment.

The estimation of whether there is ‘prospect of direct benefit’ for the participating minors is based on the scientific hypothesis made at the inception of the trial.

Therapeutic confirmatory trials generally belong to this category. Additionally, and depending on the design, early phase drug trials may offer the prospect of direct benefit.

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

Where a trial does not offer the prospect of direct benefit to the participating minor, there should be the prospect of some benefit for the population represented by the minor. Benefit for the population includes increased knowledge of the medicine and/or of the condition, better diagnostic tools, or better prevention. Examples of research generally falling in this category are observational studies and some PK studies.

Even though all research is expected to produce scientific value (increased knowledge), the Clinical Trials Regulation requires that paediatric clinical trials should be of relevance to the population represented by the minors concerned, and identified as such in the protocol. The expected benefit for the population is influenced by a variety of factors such as the severity or prevalence of the condition, pre-existing knowledge, the relevance and applicability of the results, and the likelihood that the trial will succeed in producing these results.

10.3 Classification of trials

Classification of trials according to the presence or absence of a prospect of direct benefit for the minor concerned may be a difficult task for both sponsors and assessors. Since the level of risks and burden that may be acceptable in a trial depends on this classification, it is also important that the classification is consistent within and between Member States.

Whether a clinical trial provides a prospect of direct benefit for the participating minors depends on the proposed interventions and additional procedures. 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 from the trial objective or design: clinical efficacy, or use of clinical efficacy or safety end-points (survival) and study duration;
- existing knowledge on the medicine activity from (pre)clinical studies with the medicinal product or comparable medicines;
- in case of existing knowledge on dose, in a dose-escalating study where activity can be anticipated with the lower dose.

In many cases, clinical trials may consist of a combination of the two categories above, with some procedures or interventions providing direct benefit, and others only a benefit for the population. For example, in an early phase trial in minors, there may be research with benefit for the population and PK sampling for therapeutic drug monitoring, which would provide direct benefit. Overall such trials would be considered as providing a prospect of 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 a trial. A paramount principle is that the child's interest should always prevail over that of science and society.

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

Burden is defined as the (mostly) 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. It is by definition mostly determined by the person bearing the burden. For minors, burden may include missing out on social activities, sports and even normal schooldays and for parents finding the time to fill out questionnaires, missing work days, driving their child to appointments, collecting samples, or recording diary entries. The trial burden is an important decision factor for children and parents on whether to enrol or withdraw, in particular for trials without a prospect of direct benefit for the child, and it also impacts their compliance.

Both risks and burden may be physical, psychological, or social, may be immediate or delayed, and may vary according to age, duration, previous experience, repetition or accumulation.

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 (risk and burden) as possible. Risks and burden should be prevented as much as possible and all procedures causing risk and/or burden should

be justified, including explanations on minimisation. Where possible within the limits of both the trial and the clinical setting, procedures should be combined, for example taking study blood samples at the same time as those required for usual clinical care.

11.1 Assessment of risk

Risks and burden are to be assessed in relation to the benefit (cf. Section 12). The recommendations on risk proportionate approaches in clinical trials is relevant for this exercise.[18]

To evaluate the total risk a trial carries for the minors involved, 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 that may not usually be of concern in adults, in particular adverse reactions not identified in adults and long-term development requiring longer-term follow-up.

Risk assessment is difficult in practice, as it may be difficult to pre-identify risks arising for example from novel treatment, if participants suffer from serious conditions, or if standard treatment is known to cause multiple adverse reactions. Therefore, elements that influence risks should be identified in the trial application. Additionally, identified risks should be associated to measures to prevent, minimise, monitor and manage them where unavoidable. Risk assessment also includes evaluation of invasiveness and intrusiveness of research procedures; the risks of the medicinal product tested and the control, including adverse reactions, reversibility of harm and preventability; and the risk of withholding active treatment in some cases.

The accumulation of research projects in the same population is another potential harm, in addition to raising methodological issues linked to potential PD or PK interactions, and confusion in attributing adverse reactions. For these reasons, concurrent trials of investigational medicinal products in the same minors should be discouraged. This does not exclude conducting a single clinical trial using two or more novel investigational medicinal products that have already been shown to be more effective or can only be used in combination, as may occur in some oncology or anti-viral trials.

The timing of paediatric studies in relation to the information obtained from preclinical data and in adults may also be considered a risk, either when studies are performed 'too early', or when the study of potentially effective medicinal products in children is delayed to obtain adult data that are not informing paediatric development.

The unavailability of age-appropriate paediatric forms and formulations in a trial may also incur a risk of unsafe use or inaccurate dosing (e.g. medication error).

Disclosure of a probability of a serious or an incurable disease based on a pre-symptomatic (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 trial sites with variable level of expertise and/or experience.

11.2 Assessment of 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, so efforts should be made to avoid or minimise this. Burden should be assessed in terms of magnitude, duration and repetition.

Since the magnitude of burden is (mostly) a subjective experience, assessment is difficult. Not only are there differences between age groups, but also between individuals due to the nature and severity of the condition, previous experiences of the disease or intervention, and other circumstantial factors.

[18] Risk proportionate approaches in clinical trials. 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. http://ec.europa.eu/health/files/clinicaltrials/2016_06_pc_guidelines/gl_4_consult.pdf [update once approved]

The variability of response to pain, discomfort and fear between children should be taken into consideration, in particular differences when children are affected by a chronic or acute disease. These experiences should be discussed with the children and their parents/legally designated representative. Coping mechanisms alter with age and maturation, and burden experiences change for example when medical procedures are not considered any more 'punitive'. As a consequence of its subjective nature, the magnitude of burden assessed through the ethical review may not match the burden experienced by children. Understanding the burden that children experience during certain procedures is important to evaluate paediatric trial applications. Conversely, having experienced certain procedures may have a positive impact on informed consent, because minors and parents understand what they agree to.

The burden experienced by parents and families (in particular siblings) is also relevant and factors such as logistics and missing out on social activities should be part of the assessment of burden. Both investigators and ethical reviewers should be aware that even though the assessment focuses only on the burden for the child, the burden may affect participation or compliance, impact the scientific soundness of the trial, and as such, deserves an independent assessment.

Physical and emotional pain should be prevented and minimised as much as possible, and effectively treated when unavoidable. Pain may be due to the disease or condition itself, and directly or indirectly related to the medical interventions. Examples of painful procedures include, but are not limited to, physical discomfort (exposure to cold, heat or light, noise), positioning or immobilisation, repeat examination of injured or traumatised limbs or part of the body, invasive procedures such as blood sampling (capillary, venous and especially arterial) and vascular access, oral or nasal tubing, endotracheal intubation and airways clearance, biopsies, lumbar puncture.

Physical pain and discomfort intensity must be assessed and regularly monitored, and treated according to guidelines, particularly in neonates and children who cannot express it verbally. Where sedation is needed, monitoring should be set up (cf. Section 11.3). Patient-controlled analgesia may be used where appropriate, i.e. in children of sufficient understanding. Using anaesthetic plasters or indwelling catheters can minimise pain.

Non-invasive procedures should be preferred, where possible. Population approaches and sparse sampling for pharmacokinetic data can reduce the number of blood samples from each child. Protocols should also specify the number of attempts to take a blood sample and failure escalation. In all situations, investigations/interventions should be performed using size-/age-appropriate assays, material and devices.

The parents/legally designated representative should be informed of whether a procedure is part of the usual care or the trial, and whether a direct benefit may be expected from them or not. Similarly, age-appropriate explanation in honest, but not frightening terms should be given to the minor prior to the investigation or procedure, e.g. explanations about possible pain and how that can be handled in order to decrease anxiety.

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. Minors in a trial should be hosted in a familiar environment - including appropriate furniture, toys, activities, and where appropriate, school attendance.

Fear should be prevented if possible, or if not, minimised; the need of the child for comfort and reassurance should be attended to, preferably by someone the child is already familiar with (including trial-related personnel). Separation of the child from parents or familiar persons should be avoided whenever possible. 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 and to allow further explanation. An assessment of the situation may be needed to reassure the child, or to decide to abandon the procedure, or 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. Risks and burden should be continuously monitored, as pre-specified in the protocol (Articles 28.1(a) and 28.1(e)). Burden

monitoring involves observing the child and proactively checking the child's perception, and providing ways for the child and parents to directly report to the investigator on the trial burden, for example using online tools.

Stopping rules should be included in the protocol, and this may be under the DSMB supervision. The use of a Data and Safety Monitoring Board (DSMB) with paediatric experts is recommended for trials where progress monitoring is feasible, and changes can be made to the trial conduct.

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 are based on probabilities and assumptions, the severity of the condition or disease studied and the benefit, risks, and burden of alternative treatments should be taken into consideration in the balancing exercise.

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)). Where there are scientific grounds to expect that trial participation will produce:
- a direct benefit for the minor concerned: then trial benefits should outweigh risks and burden;
- some benefit for the population represented by the minor concerned: then the clinical trial should pose only minimal risk to, and impose minimal burden on the minor concerned in comparison with the standard treatment of the minor's condition.

Emergency clinical trials are only allowed when there are scientific grounds to expect that the trial will have the potential to produce a direct clinically relevant benefit for the minor. Even then, the emergency clinical trial should pose a minimal risk and impose a minimal burden on the minor in comparison to the standard treatment of his or her condition (Article 35(1f) of the Regulation).

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

The crucial consideration for the ethical review is which level of benefit outweighs certain levels of risk and burden. It is important to keep in mind that direct benefit for the minor concerned may not materialise in the trial, as the investigational medicinal product may prove less effective than standard treatment, and/or may produce more adverse reactions. The prospect of direct benefit should never be used to induce participation or raise false hope for families.

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

In clinical trials with a prospect of benefit for the population, there is no benefit expected for the trial participants: individual benefit cannot outweigh risks and burden, since participants can only experience the risks and burden. The previous Directive (2001/20/EC[19]) did not indicate a threshold for acceptable risks and burden in these trials. The Clinical Trials Regulation has introduced a criterion as an extra protective measure for the assessment of risks and burden, which should be assessed with the participants' interest in mind. The risks and burden should be "minimal in comparison with the standard treatment of the minor's condition". The proposed definition of minimal risk is defined as the probability and magnitude of harm or discomfort similar to risks ordinarily encountered in a child's daily life, or during routine physical or psychological examinations.[20] Examples of investigations, tests or procedures are provided in Annex 3. This means that the levels of risks and burden for participants should be assessed relative to, and be reasonably

[19] 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.

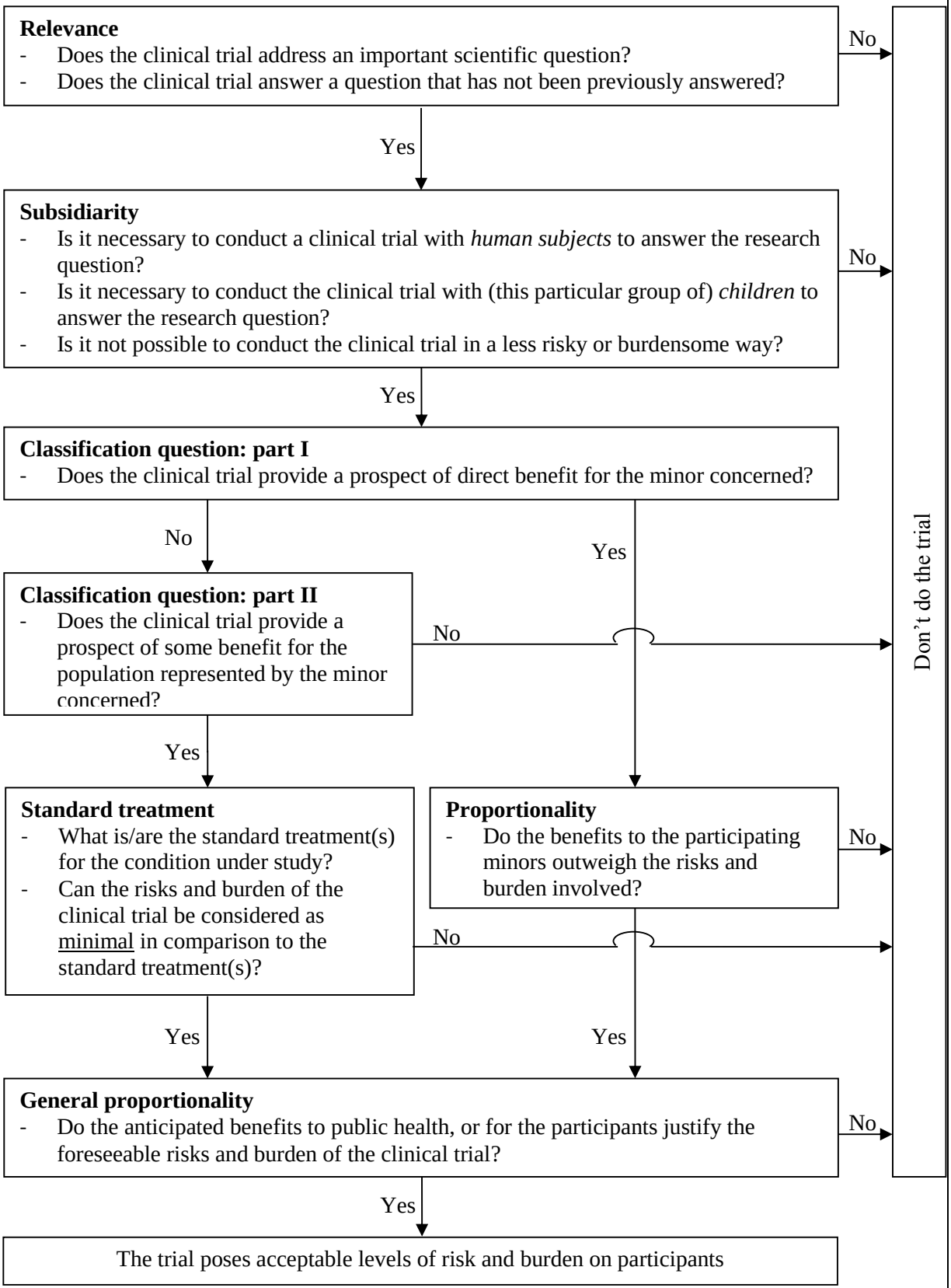
[20] Code of Federal Regulations: 45 CFR 46.101 http://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/#

commensurate with the standard treatment they receive (Article 3). There is no set definition that will apply to all clinical trials with minors; therefore, 'minimal risk and burden' will have to be viewed in the context of the disease, health status, prior experiences and standard treatment of the participants.

Even if the ethical review concludes that the level of risk and burden is minimal in comparison with the standard treatment, this does not necessarily mean that the trial is ethically acceptable. The foreseeable risks and burden should be justified and minimised (Articles 28(1a) and 28(1e) of the Clinical Trials Regulation respectively).

Overall, the elements regarding assessment of benefit, risks and burden for ethical review, schematically shown in box 1, should guarantee appropriate protection of the participating minors.

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. In paediatric medicine, the level of evidence may be poor, thus best practices or the usual healthcare provided to the minor would qualify as standard treatment in those cases. Standard treatment does not need to be curative and may include interventions to reduce pain, discomfort or fear.

Standard treatments may vary widely and where there are multiple standard treatments, each should be described in the protocol and respective risks and burden assessed.

Over time, depending on the condition of the minor or the phase of the disease, standard treatments can change. For instance, standard treatment may become palliative (end-of-life) care, and risks and burden may differ substantially from the risks and burden in the previous phases. This will require careful ethical review with the child's interest in mind.

12.2.2 Assessment of risks and burden for individuals

The ethical review can only assess the population under study, not the individual minors. Therefore, investigators are responsible for assessing whether the risks and burden of a trial are minimal for the 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 with the parents/legally designated representative, where possible the child, and the child's treating physician.

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

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

13.1 Type of assays and sample collection

The number of assays and investigations should be reduced as much as possible (using advanced techniques) and their type appropriate to the age and/or bodyweight (body surface area if appropriate) of the participants.

Where possible, alternatives to blood (e.g. urine or saliva) should be preferred for pharmacokinetic and pharmacodynamic studies, or developed where possible.

For blood and tissue assays, micro-volumes and micro-assays should be used, or developed when not available. Not using micro-assays should be justified in the protocol.

Procedures pain and burden should be minimised, in particular by pain prevention (e.g. local anaesthesia) and timing co-ordinated with daily activities as far as possible and defined in the protocol.

13.2 Volume of blood

Preterm and term neonates have very limited blood volume and, when sick, are often anaemic due to frequent routine sampling.

Micro-methods on dry spots and scavenged blood remnants should be used whenever possible, since they reduce trial-related blood loss. Opportunistic, population, or sparse sampling, or other innovative methods could also reduce the frequency and volume of blood sampling. Although not evidence-based, the following recommendations can be made: per individual, the research related blood loss (including any waste) as a general rule should not exceed 3% of the total blood volume over a period of four weeks, and should not exceed 1% at any single time. This recommendation leads to the allowable sample volumes, indicated in the table below.

Routine health care may require significant blood sampling (recorded in infants and neonates), and the indicated research related blood volumes may even be excessive, especially in (preterm newborn)

infants. This means that in individual cases, acceptable research related blood loss may be lower than indicated in the table below. Research related blood sampling and volumes should always be justified in the protocol and explained in the participant information material. Blood transfusions (or iron or erythropoietin supplementation) should not be used as a convenience to justify increased volume or frequency of blood sampling.

Body weight (kg)	**Circulating total blood volume (ml)**	**Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume**	**Maximum allowable sample volume at single time (ml) - 1% of total blood volume**
0.5 - 1.5	50 - 150	1.5 -4.5	0.5 – 1.5
2.5 - 5	250 - 500	7.5 – 15	2.5 – 5
5 - 12	480 - 960	14.4 – 28.8	4.8 - 9.6
12 - 20	960 - 1600	28.8 – 48	9.6 -16
20 - 30	1600 - 2400	48 – 72	16 – 24
30 - 70	2400 - 5600	48 – 168	24 – 56

Table: Maximum allowable research-related blood sample volumes. Total blood volume is approximately 80-90 ml/kg body weight, in neonates approximately 100 ml/kg body weight. Of note: when routine health care requires significant blood sampling, these maximums may even be excessive.

14. Genetic testing

Genetic testing may generate validated and clinically useful results, or conversely, results not associated with any known treatment or preventive measure; results may also be of unclear or unknown significance or be incidental findings linked to conditions unrelated to the original diagnostic. The information can reveal the patient's susceptibility to a disease, treatment response or carrier status. This information may relate to the patient's health or future reproductive choices, or to other family members. As a consequence, genetic testing disclosure may represent a benefit, or a risk or burden for participants.[21] Minors participating in a trial are entitled to access any information collected on their health, but disclosure of genetic findings in particular requires precautions, or expert counselling.

15. Trials with specific groups of minors

15.1 Trials with neonates (term and pre-term)

Neonates, especially preterms, represent the most vulnerable group of the paediatric population. Many treatments routinely used in neonatal care are still under-researched and off label. Therefore, trials with neonates are needed to produce evidence. When affected by serious diseases, neonates are multi-medicines users and affected by the risk of interactions. This paediatric age group suffers from diseases that are specific and differs pharmacologically from older children and adults. Neonates should be considered as a very heterogeneous group (for instance weight may vary between 0.5 and 5

[21] Sénécal K, Thys K, Vears DF, Van Assche K, Knoppers BM, Borry P. Legal approaches regarding health-care decisions involving minors: implications for next-generation sequencing. Eur J Hum Genet. 2016;24(11):1559-64. doi: 10.1038/ejhg.2016.61

kg). Trial sponsors should take into account the pharmacological complexity and potential for long-term effects, including developmental effects.[22]

15.2 Trials with healthy minors

In principle, healthy minors should not be enrolled in clinical trials as healthy volunteers, because they do not consent for themselves, and the trial will generally not provide direct benefit to them. Studies should not be performed with healthy minors when they can be performed with adults. Exceptions could be for example where healthy minors participate in palatability testing such as 'swill and spit tasting' for a new flavoured medicine.

In some situations, trials need to be performed with minors who are healthy at the time of enrolment. Prevention trials or paediatric vaccine trials (including immunogenicity studies) will fall into this category, but should only include the population likely to benefit. Trials in minors with intermittent diseases (e.g., flare-ups, seizures) are acceptable because children are affected, or at risk, even in the "healthy" phase. Proof of concept should be obtained in relevant animal models first and/or in adults whenever possible. Studies such as pharmacokinetic studies, which cannot be performed with adults, should be performed with the intended population as far as possible, i.e. the one affected by the disease.

15.3 Trials with adolescents

In trials with adolescents two aspects may deserve special attention: their growing fertility and their potential use of recreational drugs. There should be thorough explanation in the informed consent and assent/agreement process of the use of contraceptives and/or the use of recreational drugs.

15.3.1 (Future) fertility

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 as well, and their access to the benefits of research should not be delayed. Therefore, information and inclusion with the use of contraception should be made possible by the investigator for this group of participants. Similarly, in case of teratogenic risk through sperm, adolescent males should be informed and appropriate contraception should be ensured.

15.3.2 Potential interaction of the test drug with recreational drugs

Adolescents may be using recreational drugs and may not reveal this spontaneously. This possibility should be kept in mind in case of unexplained outlier data, or clinical / pharmacological interactions.

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

Dosage forms and formulations (composition) used in a trial should be described in the protocol.[23] Additionally, forms and formulations used in paediatric clinical trials should be reported in publications. The most appropriate paediatric form and formulation should be discussed with a pharmacist when writing the protocol, in particular the choice of excipients should match the age of children included in the trial (e.g., benzyl alcohol is contra-indicated in neonates).[24]

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[22] Guideline on the investigation of medicinal products in the term en preterm neonate, Doc. Ref. EMEA/536810/2008
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003750.pdf

[23] ICH E6, section 6.4.4

[24] 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)

Age-appropriate dosage forms should be used to avoid the risk of adverse effects, invasive administration procedures (for example, intramuscular injections, 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, the conditions for preparing them and the dose should follow Good Manufacturing Principles, as required by the Clinical Trials Regulation and Commission Delegated Regulation […[25], e.g. to avoid bacterial contamination, degradation of the medicinal product, and to protect from light. The conditions for use should be explained in the protocol and/or Investigational Medicinal Product Dossier as appropriate.

Bioequivalence to the marketed pharmaceutical form may need to be studied.

17. Personal data protection

In light of Article 93 of the Clinical Trials Regulation, processing of personal data in clinical trials, including paediatric trials, shall comply with the General Data Protection Regulation.[26]

The specificity of data protection with minors relates to future (unknown) use of data obtained with minors. The Clinical Trials Regulation recognizes that a sponsor may, at the moment of informed consent procedure for participation in a clinical trial, ask for consent for the future use of the data gathered outside the protocol, exclusively for scientific purposes. This consent for personal data processing should be assessed in light of the General Data Protection Regulation[27]. Biobank samples' retention and consent for further processing of personal data should be discussed in the protocol. It may be difficult to reach and obtain consent for data processing from trial participants after several years, including once participants are no longer minors. National laws may determine how to manage these situations, e.g. samples may have to be destroyed, or anonymous data may only be used. The parents/legally designated representative should be made aware that, in case of the future use of those samples, they – or their child if he or she is no longer a minor, may be approached to give specific consent.

Minors are less likely to challenge records about themselves, therefore there is an additional duty for sponsors to protect confidentiality of data (access, amendments and disclosure), for example educational performance records when studies are performed in schools, or when trials address issues of cultural sensitivity, sexuality, pregnancy, illicit/recreational drug use, or violence.

18. Unnecessary replication of trials

Although replication is an integral part of the scientific process and may be necessary for some paediatric results, it is considered unethical to replicate trials in minors unnecessarily. This can only be avoided by ensuring that the protocol takes into consideration existing literature and data, and that information gained in any trial is made rapidly available to sponsors and the public, as provided for in Article 41 of the Paediatric Regulation and Article 81 of the Clinical Trials Regulation.

19. Publication of paediatric trials and results

The Clinical Trials Regulation provides for systematic registration and public access to the data held in the EU trial database.[28] A summary of the results should be submitted within six months of the end of the trial, accompanied by a summary understandable by laypersons, both to be included into the database. In case of paediatric trials, efforts should be made to make the laypersons' summary

[25] Commission Delegated Regulation [… [update once repealed]

[26] Regulation (EU) 2016/679 on the protection of natural persons with regard to processing of personal data and free movement of such data, as of May 2018 repealing Directive 95/46/EC; OJ L 119/2016, p 1-88

[27] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC, OJ L 119, 4.5.2016, p. 1-88

[28] www.clinicaltrialsregister.eu

understandable by children who participated in the trial (those able to read, from 6 years on) using age-appropriate material, and preferably involving children and parents in the preparation.

20. Adverse effects reporting

In the Clinical Trials Regulation, adverse events and adverse reactions reporting requirements and timing are identical for paediatric and adult trials, in particular for suspected unexpected serious adverse reactions (articles 41-43 of the Clinical Trials Regulation).

Adverse reactions in children may differ in target organs, types, or severity from those known in adults.

Parents/legally designated representative, carers and older children should be instructed prospectively and strongly encouraged to report adverse events to the investigators in a timely manner. This is more difficult for younger children, who may not be able to identify adverse effects.

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 participants' safety for the children enrolled in the clinical trial.

21. Inducements versus compensation for minors

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 the minors. No financial contribution should be offered except compensation for the parents' expenses and loss of earnings directly related to the child's participation in the clinical trial. A small token of appreciation for participating minors may be acceptable, but needs to be explicitly allowed by ethical review.

22. Insurance issues

Damage compensation is mandatory in the Clinical Trials Regulation (Article 76(1)) and should be ensured by the Member State(s). Obtaining insurance for trials performed with minors, in particular neonates, may be difficult because of issues of long-term development. Insurance contracts should not waive liabilities regarding long-term effects or limit the liability period, and the ethical review in Member States should pay attention to this. Unrecognised congenital defects are generally excluded, but suspected unexpected serious adverse reactions related to these should be covered.

23. Trials with minors in non-EU countries

Sponsors of clinical trials performed in non-EU countries, of which the results are submitted in a marketing authorisation application or a clinical trial application in the EU, have an obligation to conduct clinical trials in accordance with the principles of Good Clinical Practice (GCP) and ethical requirements equivalent to the provisions of the Clinical Trials Regulation. The same should apply to paediatric trials where the medicinal product is not studied with a view to obtaining a marketing authorisation. Compliance with these requirements is assessed and supervised by Member States accordingly. Reports of GCP inspections carried out by Member States should be taken into account during the assessment of the authorisation of a clinical trial.

Where a clinical trial is to be conducted in countries that have limited frameworks for ethical review or regulatory oversight, the sponsor should consider submitting the study protocol for ethical and scientific review in a country with an established regulatory framework and ethical standards equivalent to those of the EU, in addition to submitting it in the country of the trial.

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, especially EU investigators and sponsors when submitting relevant applications in the EU and ethics committees during the assessment of such applications, to ensure that this is respected and that the paediatric specificities identified in this document, including assent/agreement, are taken into consideration for minors.

This is without prejudice to the laws and regulations of the countries in which the trials are carried out.

24. Ethical violations and non-compliance with GCP

Sponsors should notify, via the EU portal, the Member States concerned of serious breaches of the Regulation or of the protocol applicable at the time when the breach occurred (Article 52): this is particularly important as children are a vulnerable population.

Results of all studies, including those conducted unethically, will be made public in the EU trial database, and compliance (or not) with GCP should be made explicit in publications. Public information, with warnings on unethical aspects, contributes to education on how to conduct paediatric trials ethically and avoid repetition of similar errors.

25. ANNEX 1: List of issues for 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 with children, in the proposed age groups and with the proposed numbers of participants
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, where relevant)
18. The option of sperm and oocyte cryopreservation when the child’s fertility might 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. Risks and burden are minimized
26. The risks and burden have been weighed against the expected benefits for the children enrolled in the clinical trial with prospect of direct benefit for the minor concerned. The balance of expected benefit versus risks and burden should be positive for the clinical trial

27. The risks and burden are assessed in comparison with the standard treatment of the minor in the clinical trial with a prospect of some benefit for the population represented by the minor concerned. The risks and burden are regarded as minimal in relation to this standard treatment
28. Comprehensive, understandable Informed Consent and Information sheets for parents/legally designated representatives (as appropriate)
29. Consent, assent/agreement and information sheets: illustrated and understandable age-specific for children
30. Level of anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his/her family
31. The system for damage compensation in place in the relevant country
32. If available, opinions of other ethics committees for international multicentre studies
33. Publication of trial results and timelines, and informing participants and their families
34. Continuation of trial medication for participants, beyond the end of the trial, where appropriate

26. ANNEX 2: Information for informed consent and assent/agreement

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 maturity and age of participants (e.g., avoid abstract concepts, multiple options)[29]. 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.

It is important to note that younger children are more easily overloaded than older children or parents. Therefore, information sheets for children may be shorter and should be simpler than information sheets meant for parents/legally designated representative. However, 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 a clinical trial?
2. What is the purpose of the trial?
3. How long is the trial going to take?
4. Will I have the same doctor or investigator from start to finish?
5. Why have I been chosen?
6. Do I have to take part?
7. What will happen to me if I take part?
8. Why are pregnancy tests needed for girls taking part?
9. What expenses are compensated and how?
10. What will be asked of me and my parents, when we agree to take part?
11. What is the medicine that is being tested?
12. What are the alternatives for diagnosis or treatment?
13. What are the possible disadvantages and risks of taking part?
14. What are the side effects of any treatment received when taking part?
15. Is ionising radiation to be received, and which regulations are respected?
16. Is there possible harm to an unborn child?
17. What are the possible benefits of taking part?

[29] 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

18. What happens when the research study stops?
19. What if there is a problem?
20. Will my taking part in the trial be kept confidential?
21. Will my personal data be protected?
22. What will happen if I don't want to carry on with the trial?
23. What are the options if I stop taking part in the trial?
24. How is my General Practitioner/Family doctor involved?
25. What will happen to any samples taken from my body?
26. Will any genetic tests be done?
27. What will happen to the results of the research trial?
28. Who is organising and funding the research?
29. Who has reviewed the trial and what are the results?
30. Where can I find information about the results of the trial?
31. 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 of study procedures

The following list, ordered alphabetically, provides examples of procedures conducted for trial-related purposes. A procedure may be specifically initiated for the purpose of a trial, or, if initiated as part of the standard of care, it may be expanded (or modified) for the purpose of the trial. In the list, procedures are presented with descriptions of the techniques and of those risks and burdens that are related to initiating or modifying the procedure for the purpose of the trial. Where a procedure is conducted as part of standard of care, there is no trial-related risk or burden. The particulars of the procedure and the circumstances of the child influence the evaluation of the trial-related risks and burden and hence of its acceptability. In addition, the level of risks and burden increases with the increase in frequency of any procedure and with susceptibility to harm of involved/exposed organs.

Several procedures, such as genetic or behavioural testing, carry a burden that is associated with the handling and potential impact of the results of the procedure. The results may have far-reaching impact on subjects and families, for example in terms of self-awareness, life choices and relationships. The handling of results should be described in the protocol, including the maintenance of confidentiality and the disclosure to participants and parents / legally designated representative, so that the levels of risks and burdens can be assessed.

The descriptions in the list apply to single or very infrequent use of the procedure. The examples presuppose that the procedures are carried out to the highest professional standards. New scientific insights into how children experience the procedure(s) may supersede the listed considerations.

The list should only be used as the starting point for the evaluation of risks and burden, and it should not be used dogmatically. Trial sponsors and researchers can use it in their efforts to minimize risk and burden related to trial participation. Critical and careful assessment in the ethical review is necessary for every trial. It is for the ethics committee to assess the levels of risks and burdens (e.g. minimal or more) and to conclude on the acceptability of the procedure(s) for the purpose of the trial, in knowledge of risks and burdens of any procedure(s) that are part of the standard of care of a trial participant.

Procedure	**Description of the elements of risk and burden to be evaluated**
Allergen challenge / hyper reactivity test	Skin tests involve, for a variable and individualised number of antigens, to scratch a subject's skin with a sharp instrument (prick test) or to inject a small amount of fluid into the skin (intradermal test), or to place a patch (epicutaneous or patch test) often in an inaccessible place (e.g. back). An airways hyper reactivity (bronchial provocation or bronchial challenge) test involves the controlled inhalation of agents that can temporarily induce wheezing and reduce lung maximum forced expiratory flow rates. Risks include erythema, swelling and itching that could persist for hours and respond little to treatment; the need for medication after bronchial provocation testing, as well as a rare anaphylactic shock. Burdens may include fear and discomfort experienced with the skin reactions, respiratory distress, the duration of the procedure and the need of staying in a health professional setting.
Anaesthesia (local, regional, general)	A range of agents and techniques are used for anaesthesia. Local, regional and general anaesthesia can be distinguished and generally represent an increasing level of risks and burdens. The level may also increase with deeper and longer anaesthesia. Risks include hypoxia, nausea and vomiting, cardiovascular, respiratory and neurological problems, and the need for specialist setting. Burdens include pain, fear, discomfort and need of staying in a health

	professional setting.
Arterial vessel access (one-off puncture, cannulation / catheterisation, umbilical catheter)	Techniques to access arterial blood vessels, to take samples or rarely to inject substances, involve immobilising an extremity/limb, puncturing the artery with a needle that is removed once the sample is taken, or using the needle as a guide to insert a catheter which will remain in place for some time (hours or days). Risks include acute pain, bleeding (haemorrhage) which can be serious for arterial access, vessel injury and, rarely, arterial vessel blockage, with a risk of necrosis. Using the same catheter for repeat sampling may reduce the pain and invasiveness, but may also increase the risks of excess blood loss and possible infection. Burden includes pain, as it can only be partly prevented, fear and discomfort (e.g. limitation of movement with catheters).
Behavioural and psychological testing, Quality of Life assessments	A number of instruments have been developed for behavioural testing in the target population. There seems no risk for harm in testing, and there is experience with instruments used for this purpose. Burdens may exist in the duration of the testing. For handling of results, please see introduction of this annex.
Biopsy (e.g. skin, bone marrow, bone, muscle, lung, liver, brain)	Biopsies may be taken from different sites of the body or organs, such as skin, bone marrow, muscle, lung, liver or brain, with generally increasing risks and burdens. Anaesthesia (addressed above) is additionally required for several types of biopsies. Biopsy procedures may be expanded for the purpose of a trial, for example by increasing the number of biopsied sites, increasing the amount of biopsy material collected, or choosing a different biopsy instrument. Biopsies of the skin are often done as punch biopsies. Risks include pain requiring pre-emptive local anaesthesia and possibly scarring. Sampling of the bone marrow may be done by aspiration and sampling of the bone may require a bone biopsy. Risks include pain requiring pre-emptive anaesthesia and bleeding. Biopsies of a muscle carry the risks to pain requiring anaesthesia, to leave a scar and to reduce muscle mass permanently, which can affect particularly patients with a muscle-wasting disease. Risks, but also diagnostic yield, seem to increase from using a closed-needle biopsy over using a small incision and conchotome to conducting an open biopsy. Biopsies of the lung differ in risks depending on the technique used (e.g. video-assisted thoracoscopy may have fewer risks than open lung biopsy). Risks may include the need for chest tube placement, need for specialist setting and for staying in a health professional setting. Biopsies of the liver carry the risks of hidden bleeding with cardiovascular impact and of the need for a specialist setting and for staying in a health professional setting. Risks associated with biopsies from other organs (e.g. brain) include pain, possibly structural and/or functional impairment and the need for specialist setting (e.g. paediatric neurosurgery with computer-assisted planning and

	execution). Techniques and experience with such biopsies are evolving fast.
Blood pressure measurement	One-off blood pressure measurements using inflatable cuffs does not incur risks or burden. For ambulatory blood pressure monitoring (ABPM), risks and burden include discomfort while carrying the device and possibly an impact on activities of daily life. For invasive blood pressure monitoring see arterial / venous vessel access elsewhere in the table.
Breath condensate collection	For breath condensate collection, neither risks nor burdens could be identified.
Bronchoscopy, bronchoalveolar lavage and lung biopsy	Bronchoscopy requires sedation (or anaesthesia; both addressed elsewhere) and often entails interventional elements such as obtaining fluid samples by bronchoalveolar lavage or tissue samples using a brush or biopsy forceps (transbronchial biopsy; other types of lung biopsies are covered in the section biopsy). Risks include respiratory complications (blocked airways, reduced oxygen), bleeding, air trapping (pneumothorax), need for chest tube and for specialist setting. Burdens may include distress and discomfort, need for being administered medication after the procedure, need for staying in health professional setting.
Clinical examination, auxological measurements including Tanner staging	The techniques used for manual and physical examinations are widely standardised, while the way of conducting the examinations may be adapted to the participant's situation. No risks are expected to be associated with impedance measurement for body composition, or with standard physical examination. Burden (embarrassment, discomfort, distress) is usually associated with examinations that are particularly comprehensive or intrusive such as those related to sexual development (e.g., Tanner staging).
Collection of hair sample	Hair samples are collected either close to the scalp (for drug level testing) or by extracting the hair follicle (for DNA analysis). The collection of hair samples does not incur risks. Removing hair follicles may be associated with some discomfort. For handling of results, please see introduction.
Collection of saliva or sputum	The collection of sputum may in some trials require inhaling salty steam to induce coughing. When using steam inhalation, risks include respiratory symptoms such as wheezing and coughing and burdens may include distress and discomfort. Otherwise, the collection of saliva or sputum without steam inhalation, does not incur risks or burden.
Computer tomography (CT) scan, Dual X-ray absorptiometry	CT scans are investigations using X-ray (electromagnetic radiation) that can be conducted with different machines and techniques, with and without intravenous administration of contrast agents. Radiation dose increases with the frequency of scans and may be reduced with high-resolution / thin-section methods and low-radiation scanning protocols. The procedure may also

(DEXA)	require venous access and sedation or anaesthesia (addressed elsewhere). D(E)XA scans are conducted with X-rays or photons, and radiation dose increases with the frequency of scans. Risks are related to the total amount of radiation dose from these procedures (possibly contributing to tissue damage, mutations and cancer) and to allergy / anaphylaxis with contrast agents. Burdens may include discomfort, fear, pain in case of contrast agent injection and need for specialist setting.
Digital radiography or digitally amplified X-ray (of chest or limb)	These radiographic procedures have been developed to minimise required radiation doses. This procedure does not incur risks, unless venous access, sedation and/or anaesthesia are used (addressed above). Burdens may include pain and discomfort if a restrainer is used in younger children.
Electrocardiography (ECG), electro-encephalography (EEG), polysomno-graphy	The procedures involve placing skin surface electrodes that are adhesive or fixated in a hat. EEG recordings are conducted over a short period of time (minutes) or may require recording over 24 hours, with video recording and in a specialist setting. Polysomnography involves recording overnight. These procedures do not incur risks. Burdens may include discomfort and fear, particularly in younger children, and need for staying in a specialist setting during the procedure. For ambulatory EEG monitoring, burdens include discomfort while carrying the device and possibly an impact on activities of daily life.
Electrophysiological measurements (including nerve conduction tests)	Electrophysiological measurement techniques differ significantly in using stimulation (which is painful in the case of nerve conduction tests) or not, in the required types of electrodes (needle insertion, which is painful, or surface), in the required cooperation and in the duration (minutes to an hour). Risks seem rare, but may include pain, paraesthesia or nerve damage, and infection. Burdens include pain and discomfort, for the time of the procedure.
Endoscopy of the intestinal tract (e.g. colonoscopy)	The procedure often requires venous access as well as sedation or general anaesthesia (addressed elsewhere) when conducted with a fiber-endoscopic instrument. In addition, colonoscopy involves a preparatory day with fasting and taking medicines and / or volumes of bowel-cleansing fluids. Colonoscopy may entail biopsy collection and interventional elements such as tissue removal. Video capsule endoscopy may be used for the upper intestinal tract, without special requirements. Risks include perforation, bleeding, bloating, nausea, pain. Burdens include need to drink abundant fluids and unpalatable solutions for bowel cleansing, fear and discomfort (frequent evacuation of loose and watery stools during preparation), including before and after the procedure, as well as need for staying in a specialist healthcare setting for at least several hours.
Exercise and functional testing (e.g., 6-minute walking test, bicycle	Exercise testing procedures are general measurements of cardiovascular and respiratory function under increasing levels of exercise. Different methods are used mainly depending on the age (e.g. bicycle vs. treadmill).

ergometer / treadmill apparatus)	Risks include inducing cardiovascular or respiratory symptoms, wheezing, shortness of breath, vertigo. Burdens may include discomfort, exhaustion, pain, need for prolonged recovery.
Fasting (1 meal or more)	Fasting may be required for hours or overnight, for one or more meals, mostly to facilitate conducting other procedures such as blood sampling or endoscopy. Risks may include modest to moderate hypoglycaemia (usually subclinical), and are related to longer fasting, younger age and pre-existing conditions. Burdens may include hunger and distress, increasing with duration of fasting and generally with younger age. The test requires a specialist setting, often as an inpatient or day-hospital.
Heart catheterisation	Heart catheterisation procedures may be done for imaging purposes (e.g. of anatomical situations and functional changes), functional assessments (e.g. pressure in specific parts of the heart and vessels, oxygen content in samples) and interventional purposes (e.g. placing of stents, opening or occluding atria). Venous access and, often, sedation or anaesthesia (addressed elsewhere) are required. For the purpose of a trial, a procedure required as part of standard of care may be expanded such as in depth of anaesthesia or duration. Risks include blood loss and bleeding, cardiovascular function depression (depending also on the anaesthetic agent), hypoglycaemia and acidosis, deterioration of heart or lung function, need for specialist setting. Burdens may include pain, discomfort, distress and need for staying in a health professional setting.
Heel prick	Heel pricks are conducted to collect small volumes of blood, and in some trials this procedure is conducted frequently. Risks increase with frequency and include pain and infection (local / skin or exceptionally involving the calcaneus). Burdens include distress and discomfort, from the prick and also from restraining that is often necessary.
History taking	For history taking, neither risks nor burdens could be identified.
Hypoglycaemia test	The procedure is for measuring hormonal stress responses to hypoglycaemia. Hypoglycaemia is induced by insulin and is monitored during the procedures. It requires one or more venous accesses, for sampling and possibly for correcting hypoglycaemia. Risks include consequences of hypoglycaemia, which may include seizures in patients with a history of seizures or with a cardiovascular or cerebrovascular disease. Burdens include the discomfort and distress with the hormonal responses.
Intramuscular (IM) injections	The IM route is used in particular for vaccines. Although IM injections may represent a quick, apparently easy and reliable injection route, IM injections are not considered an appropriate route for young children with limited muscle mass. Combined anaesthetic injection can be responsible for allergic reactions and chemical interactions. The risks include the possibility to induce toxic muscle necrosis with some

	substances, and the injection can produce nerve damage or bone infection if the injection technique is not optimal. The burden is linked to the pain, and fear of needle.
Intrathecal (subarachnoidal) sampling or injections	Sampling is extremely uncommon. The injections are therapeutic in nature. They require sedation, experienced operators and specialised environment. They may need imaging to guide the operator. The injection can be into the spinal canal, or the subarachnoidal space. The risks are haemorrhage, infection, hypoventilation, urinary retention toxic or traumatic spinal lesion, and death. The burden includes pain, distress, fear, and immobilisation.
Isotope usage	Isotopes, radioactive or stable, are part of a number of procedures for imaging or quantifying metabolic processes and organ function capacity. Risks of radioactive isotopes are related to the amount of radiation dose, and they increase with the frequency of the procedure; for these isotopes, venous access and sedation or anaesthesia (addressed above) may also be required. Stable isotopes do not incur risks. Burdens may include discomfort, fear, pain and need for specialist setting.
Lung function tests (peak expiratory flow, exhaled NO, spirometry, passive expiration tests)	Lung function testing (spirometry etc.) primarily requires cooperation (for airway hyper reactivity test, see above) and different equipment may be needed in different age groups. Such procedures are usually repeated when conducted as part of a trial. Infants and young children often require sedation, and techniques may involve briefly interrupting airflow or compressing the chest and abdomen. For these lung function tests, no risks could be identified. Burdens may include discomfort, fear in young patients; the testing may be tiring and burdensome for patients with serious respiratory disease.
Magnetic resonance imaging (MRI) scan	MRI scans are conducted using protocols that differ in duration of image acquisition, with and without intravenous administration of contrast agents. The procedure may require venous access and usually requires sedation or general anaesthesia in younger children (addressed elsewhere). Risks include those related to contrast agents, such as nausea, hypersensitivity reactions and accumulation and functional impact of contrast agents in several organs. Burdens may include discomfort, claustrophobia, fear, pain from venipuncture and heat sensation in case of contrast agent injection and need for specialist setting.
Nasogastric tube insertion and use, pH metry	Such tubes are used for different purposes, such as gastric decompression, avoiding aspiration, providing enteral nutrition and measuring the acidity of gastroenteral fluid. Risks include changes in bowel function, misplacement dislocation, reflux, bleeding, infection and ulceration. Burdens may include gagging, discomfort during most of the time of the tube presence.

Ophthalmoscopy	Ophthalmoscopy may include slit-lamp investigation with and without the application of a medicine, e.g. to contrast the cornea surface and / or to dilate the pupils. Risks could not be identified, but when a medicine is used to dilate the pupils, risks include increased intraocular pressure, disturbance of vision, dry mouth, neurological symptoms, nausea. Burdens may include fear, discomfort and, when a medicine is used, distress with its repeated application and hour-long vision changes.
Oral glucose tolerance test	The test involves overnight fasting (see above) and requires a venous access (line) or multiple venipunctures (see below). In addition to the risks and burdens of fasting and of venous access, nausea and vomiting can occur rarely. A specialist healthcare setting is usually required.
Peripheral venipuncture, peripheral venous access	Peripheral venous access is widely used for taking samples or administering agents. For venipuncture pain can generally be reduced with local anaesthetic agents and varying the site of access. Risks include vasovagal reactions, minor bleeding and vessel damage. Burdens include moderate pain and possibly significant fear and distress.
Positron emission tomography (PET), single-photon emission computed tomography (SPECT), other nuclear medicine scanning procedures	These procedures are imaging investigations involving the administration of a radioactive substance and measuring its radiation coming from within the body. Radiation dose increases with the frequency of scans. Venous access is required (see below). Risks are related primarily to the total amount of radiation dose used for the procedures (possibly contributing to tissue damage, mutations and cancer). Burdens may include fear, pain and need for specialist setting.
Pinprick glucose test	This procedure does not incur risks and burden related to the test, in addition to those of fasting (when required) and of venous access (both addressed elsewhere).
Sedation	Sedation involves the reduction of the level of consciousness, irritability and arousal by administering a medicine(s) from a range of different types of sedative agents. Sedation may be used for conducting (facilitating) any of a number of procedures, in particular in younger children. The level / depth of sedation that is intended or achieved varies largely, from minimal conscious sedation to general anaesthesia when used at or beyond the level of deep sedation. Venous access is often required. In addition to sedation, analgesia is used for some painful procedures. Risks include hypoxia, aspiration, nausea and vomiting, cardiovascular problems, and this is generally related to the level / depth of the sedation, and the need for specialist setting. Burdens include pain, fear, discomfort and need of staying in a health professional setting.
Spinal tap (lumbar puncture)	This procedure involves a needle puncture in the (lower) back between two vertebrae to access the cerebrospinal fluid (CSF) space, close to the spinal cord (medullar part of the central nervous system). It requires cooperation, local

	analgesia and in some circumstances fasting, venous access, and possibly sedation. A spinal tap that is conducted as part of standard of care may, for trial-related purposes, be extended in duration to collect further samples. Risks include headache, vomiting, local fluid accumulation, infection, CNS herniation (in certain patients). Burdens may include pain, fear, discomfort including related to positioning and restraining, need for staying and monitoring in health professional setting.
Stool tests	This procedure does not incur risks and burden.
Subcutaneous injections	Subcutaneous injection is painful, especially when the volume injected is large. Pain can be somewhat reduced with local anaesthetic agents and varying the site of access. Subcutaneous injections may require long injection times (large volume) and therefore immobilisation or restriction in activities due to the need for carrying the injection pump. Risks include vasovagal reactions, allergic reactions, infections and bleeding. Burdens include pain and restrictions of activities.
Tympanocentesis (myringotomy, paracentesis), pneumatic otoscopy	These procedures are used to assess and to treat conditions affecting the middle ear. The tympanic membrane is opened by a small surgical incision (centesis), usually with a limited level of pain after the procedure. Pneumatic otoscopy involves shifting the tympanic membrane, which may be painful in acute disease states. Risks include infection and vertigo / dizziness, and need for specialist setting. Burdens may include discomfort.
Ultrasound scan	No risks could be identified, beyond those of venous cannulation (if required, for example for administration of IV contrast agents). Burdens may include discomfort related to positioning and pressure, or of bowel cleansing if required.
Urine collection	Urine samples can be collected with different methods, as follows. The procedure, in particular when catheters are used, involves skin cleaning, positioning, fixation, and manipulation. Risks of using a transurethral catheter include pain and urinary tract infection / sepsis, increasing with the time that a catheter stays in place; and temporary incontinence and painful voiding. Risks of using a suprapubic catheter include pain and rarely sepsis, increasing with the time that a catheter stays in place. Using a collection bag or similar external devices (e.g. urosheath) does not incur risks, but bacterial results can be unreliable due to skin contamination. Burdens are discomfort (catheter linked to a urine bag), embarrassment and distress with the preparation and conduct of the procedure.
Use of contrast media	Contrast media are used for angiography (catheter or in conjunction with CT or MRI, also addressed above) and ultrasound including echocardiography. Vascular access is required, and catheter angiography may require sedation or anaesthesia (addressed above).

	Risks include hypersensitivity and anaphylactic reactions (agents for angiography) and vascular events (agents for ultrasound). Burdens include discomfort at administration of the agent, need for stay in a health professional setting.
Venous vessel access (cannulation / catheterisation, umbilical catheter)	Accessing large venous blood vessels to take samples or to inject voluminous, or concentrated substances, or substances with low or high pH, involve immobilising an extremity/limb, puncturing the vessel with a needle that is either removed after sampling or injection, or replaced by a catheter to remain in place for hours or days. Use of an existing venous access (line) may decrease the need for repeat venipuncture and hence its associated risks and burdens. Risks include bleeding (haemorrhage) of variable extent, vessel or other organ injury and, rarely, venous thrombosis. Using any existing catheter may reduce the invasiveness of vessel access, but may also increase the risks of diffusion outside of the vessel, toxic necrosis and infection, locally or disseminated (including septicaemia and endocarditis). Burden includes pain that can be prevented, fear and discomfort (e.g. limitation of movement with permanent catheters).
Vision or hearing testing	The procedures can be conducted in different ways and with different techniques, requiring or not collaboration of participants. These tests do not incur risks. Burdens may include the time required to conduct the procedures in a reliable fashion.
Water deprivation test	Water deprivation may need to last up to 7-8 hours. There is a small risk of significant dehydration and hypovolemia. Burden is significant as thirst is poorly tolerated by many children. Also, the test requires a specialist setting, often as an inpatient or day-hospital.

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