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Assent / Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe

Developed by Enpr-EMA's Working Group on Ethics

This document is intended to be used as an overview tool of the contents for assent/informed consent forms for all stakeholders (such as patients, sponsors and investigators) to support the conduct of high quality paediatric clinical trials in Europe across all paediatric age groups, from birth to less than 18 years of age.

Acronyms, abbreviations and definitions used in this document:

Age groups **(in this document)**	By the EU Ethics Guideline[i] definitions; 5.3 Child: The term "child(ren)" is used within these recommendations to mean minors in line with the Clinical Trials Regulation (CTR)[ii], in contrast to the ICH E11 guideline which refers to children as individuals aged from 2 to 11 years. 5.7 Minor: Article 2(2.18) of the CTR 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[iii], 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. **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), 7.1.2 Pre-schoolers (2-5 years of age), 7.1.3 Schoolers (6-9 years of age) and 7.1.4 Adolescents (10-18 years of age).
Assent and Agreement	In article 29(8) of the CTR[ii];"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. In addition, per EU Ethics Guideline[i]; 5.2 Assent and agreement: 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.
CTA	A Clinical Trial Application is a request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the EU. A CTA provides comprehensive information about the investigational medicinal product(s) and planned trial, enabling regulatory authorities to assess the acceptability of conducting the study.
CTIS	A Clinical Trials Information System will contain the centralised EU portal and database for electronic CTA submission and assessment process for clinical trials conducted in multiple Member States foreseen by the CTR. The European Medicines Agency (EMA) will set up and maintain CTIS, in collaboration with the Member States and the European Commission. It is expected to be in use starting from December 2021.

CTR	The Clinical Trials 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/e[iv]. The way clinical trials are conducted in the European Union (EU) will undergo a major change when the CTR comes into effect. The timing of its application depends on confirmation of full functionality of CTIS. The CTR harmonises the assessment and supervision processes for clinical trials throughout the EU[ii].
Dissent	Article 32(1.c) of the CTR[ii] states about: "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". As per EU Ethics Guideline[III]; 5.4: 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 CTR[ii].
Enpr-EMA	The European Network of Paediatric Research at the European Medicines Agency[v]
EU / EEA	European Union / European Economy Area
eYPAGnet	The European Young Persons Advisory Group Network[vi]
GDPR	The General Data Protection 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, repealing Directive 95/46/EC[vii]
Informed Consent	Article 2(2.21) of the CTR[ii]; "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."
Legal Representative	Article 2(2.20) of the CTR[ii]; "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." As per EU Ethics Guideline[i]; 5.6: A legally designated representative of the minor is defined as: 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.
MS	Member State (in EU /EEA)

Enpr-EMA Ethics Working Group (WG) between 2018-2020:

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Introduction

The screening and recruitment process related to clinical trials includes information that is usually new and unfamiliar to prospective trial participants/patients. Informed consent is a process by which a prospective participant/patient voluntarily confirms his or her willingness to participate in a particular trial, having been informed of all the main aspects of the trial, including any potential risks, inconveniences or costs. Informed consent is a legal and ethical requirement for clinical trial participation which must be documented by means of a written, signed and dated informed consent form (paper or electronic format). According to national laws, a child's / adolescent's own assent is usually not sufficient alone to allow his/her participation in a trial, unless supplemented by the informed consent of the child´s parent(s)/legal representative(s). The amount and type of information presented to the child / adolescent, in these discussions, depends on the child's / adolescent's age, mental and physical maturity, medical condition and other circumstances (e.g., an emergency situation). The information should be adapted to the language skills and understanding of the legal representative(s). Where appropriate, the sponsor / investigator should arrange for translation. During the discussion for consent / assent addressed to children, it must be verified that the legal representative(s) understood the information provided. Moreover, as the child's / adolescent's understanding evolves with age and experience, it is important to verify the child's / adolescent's opinions, according to their capacity to assess the information provided, and identify potential dissent or disagreement. It is important to remember that participation is a voluntary decision and no-one can be obligated to participate in research. The full patient information for the clinical trial must always be presented to the child's / adolescent's legal representative(s) / parent(s) both orally and in writing (this can be intergrated with other information electronically if deemed acceptable by national legislation and/or any other relevant guidelines).

All communication between legal representatives, child / adolescent and trial personnel should be based on trust and equality between all parties, respect for the autonomy of the child / adolescent and transparency of the information given. The aim of transparency does not include patient information of a very sensitive nature for an adolescent. This information needs to be managed as confidential information by health care professionals according to national legislation (e.g. patients rights). According to the GDPR, children / adolescents and their legal representatives must be informed that the participant's personal data will be pseudoanonymised, where and how it will be stored and who will have access to it. It is good to note, that the purpose of a clinical trial is to gather reliable and robust data on an investigational medicinal product. This fundamental principle is confirmed by Article 3(b) of the CTR. The clinical trial protocol, authorised under the CTR, defines the purposes and conditions for which the data of clinical trial subjects will be processed. Subjects should be properly informed on the processing of his/her personal data. However, processing operations purely related to research activities must be distinguished from processing operations related to the purposes of protection of health, while setting standards of quality and safety for medicinal products by generating reliable and robust data (reliability and safety related purposes); these two main categories of processing activities fall under different legal bases. Therefore, **the requirement of informed consent by the CTR must not be confused with consent as a legal ground for processing personal data set out in Article 6(1) (a) of the GDPR**. Informed consent, in the context of CTR, is a safeguard not a legal basis for data processing, and it is important to distinguish between the requirement for consent for a subject to participate in a CT and the requirements for a lawful processing of personal data under the GDPR[viii].

The aim of this document is to create an informed consent and assent overview tool, publicly available for all stakeholders, in order to support the design and conduct of high-quality ethical paediatric CTs in Europe. This guidance document does not contain consent or assent templates, but merely general guidance about the contents in a form of listing various subject elements to be considered in every paediatric age group when designing consent / assent documentation. All such documents must be always designed case-by-case. This guidance was developed by the Ethics WG of the Enpr-EMA with the support of the European Young Persons Advisory Group Network, eYPAGnet. The document is based on the current and fortcoming (CTR) EU legal framework and ethical requirements, which can be adapted to various paediatric CTs on a case by case basis, and by following local requirements, when necessary. The guidance document can be used to prepare paediatric CT submissions in the EU, and to support and promote the inclusion of children in the consent/assent processes. This will also enhance raising awareness about children´s basic rights to be heard and to express their opinion about participating in a CT, according to their maturity.

Methods

The current EU legislative and regulatory legal texts specifically dealing with paediatrics (population from birth up to 18 years of age) including the EU Commission´s ethical recommendations for paediatric CTs was used as the primary data source for collection of informed consent, assent or agreement documents. Additional data sources with general comments were provided by the eYPAGnet on separate request. All related current European legal, regulatory and ethical guideline texts referring to the specific subject element in case were collected by WG members from across Europe. This data was then compiled and divided into the five basic subject elements (general to all trials) and 25 trial specific subject elements (varies between trial design) presented in two tables (1. and 2.). All items were considered for four paediatric age groups (0-2; 2-5; 6-9; 10-18) as defined in the EU Ethics Guideline[i] as well as their legal representative / parents.

After drafting the first document version, the eYPAGnet members (via its national YPAGs) were requested to identify any issues or missing practical details. They were asked to provide additional supportive "real-life" comments, methods and procedures to the implementation of each separate subject element in both tables suitable in practical discussion setting. These comments were incorporated into the guidance document as separate questions to be asked, or as example methods or texts to be used when designing informed consent or assent or agreement documents, or when recruiting paediatric patients or subjects to CTs.

Once all the data elements together with eYPAGnet "real-life" comments were collated together, the WG designed three level recommendations as "traffic light" symbols for all four age-groups, which could be used to separate the subject elements to be considered or not considered, or marking it as optional according to the age group per subject element. These were; A (a cross): Does not have to be included into the informed consent/assent/agreement process in this age group, B (a correct-mark): Should be included and discussed during the informed consent/assent/agreement process in this age group, and C (a circle): May be included / optional to include in the informed consent/assent/agreement process in this age group. This three-level recommendation was then reviewed against each subject element, across all age groups and all elements were sorted with the coloured symbols to separate these according to the suitability for each age group. This resulted in recommendations for all the considered age groups for each subject element.

Legal framework and disclaimer

Each Member State (MS) of the European Union (EU) and European Economic Area (EEA) has national legislation and detailed requirements for informed consent and assent that are required for the conduct of paediatric clinical trials. Because these requirements vary amongst countries as discussed in more detail in the previous ToolKit table[ix] (Informed Consent and Assent Tool Kit for Paediatric Clinical Trials in Europe), which includes the national regulatory informed consent / assent requirements per country for 25 EU/EEA countries. Therefore, the information in this document should be used only as a guidance tool together with the local or national requirements, and researchers or sponsors must always check these national regulatory requirements when preparing consent / assent documents. As this document provides the overall "skeleton" of all elements linked to the current legislative framework, all future updates related to the legistation and regulatory documents will be updated by the Enpr-EMA secretariat upon the newest relevant available information.

When fully implemented, the EU CTR[ii] will harmonise the CTA process across the MSs once it becomes applicable (the timing of its application depends on the development of a fully functional CTIS). The legal framework of this document, which describes the content for patient information and informed consent and assent documents, is the current EU clinical trial legislation (Directive 2001/20/EC[i]) and EU Commission ethical guidance document[x], including many elements of the new CTR. After CTR implementation, the detailed definition of informed consent / assent requirements will still remain within the remit of each MS.

The additional practical examples were provided by the individual members of the Enpr-EMA Ethics Working Group[vi] and additionally, the individual members of the eYPAGnet[vii] providing important feedback on the critical questions which should be addressed and answered during the consent / assent process. All such opinions and views expressed in this document are those of the Ethics WG and eYPAGnet and should not be attributed directly to Enpr-EMA, EMA or other presented legal entities, companies or organizations.

Legend of symbols in this guidance document

This document includes two tables; Table 1: General information for informed consent and assent (agreements) and Table 2: Trial specific information for informed consent and assent (agreements). In both tables, in the second column is an asterix mark (*) in the title. This refers to the legal representative(s) / parent(s). Legal representative means a person empowered to act for another person, including a guardian or custodian, having legal custody of the child. In the context of clinical trials, this usually means a parent (or parents) of a person who is under eighteen years of age, a person's legal guardian, or any other person who is authorised by law to act for the child. However, in some European countries in Europe, the age limit for independent consent may be lower than 18 years of age[ii].

3-level recommendation symbols for all age groups:

 = Does not have to be included in the assent / agreement / informed consent process for this age group

 = Should be included and discussed during the assent / agreement / informed consent process for this age group

 = May be included / Optional to include in the assent / agreement / informed consent process for this age group

Contents of the guidance document pages:

Table 1. General information for informed consents and assents (agreements)

Age Group in years 0<2	2<6	6<10	10<18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
✗	✓	✓	✓	✓	**Language / translations / Methods used for providing information / Time used for information (paper or electronic)** Language must be concise, clear, relevant and understandable, adapted to the age and maturity of the recipient of the information. The assent / informed consent (agreement) **should be documented, and in case it is not possible to seek assent from the child the reasons for this should be explained.** The target is to obtain credible informed assent/consent with unbiased approval, understanding and willingness or refusal by both parties (child and legal rep.). The personnel providing the information should be competent in communicating and working with children and families, providing time and space for the discussion and decision. **Ensure that children are properly informed.**	• Do the legal representative(s) and the child / adolescent understand the information given? • Is there enough time to provide relevant information, for discussion and to answer questions? • Are the facilities suitable / safe for discussion? • Have the child / adolescent and legal representative(s) had time to read the information beforehand (e.g. at home) prior to the discussion? • Have you used correct grammar? Do you have the correct form of address (per age) for the addressee (child / adolescent) to avoid infantilisation?	Use visual and informative materials / sources (IT based or manual) to increase understanding (if appropriate) such as: • videos, DVDs • pictograms • pictures • drawings • cartoons • photographs • diagrams / charts / tables • social media contents, www-links • computer programs • physical instrument / tool / device • mimics of methodology • glossary / dictionary of terms eYPAGnet[6] notes: Max. 3 pages / 3 screen views (total) for the assent / consent document. Large enough font. Clear layout. No bullet-points. No pictures from "Clip Art". Different colours to highlight important info. Chart for visits is helpful. **Add list of additional resources if some of the information cannot fit on 3 pages. Support to create text to documents:** 1. **Readibility:** Flesch-Kincaid Readability Score testing tool. Available at: https://www.webfx.com/tools/read-able/flesch-kincaid.html 2. **Health Literacy:** Quick Guide to Health Literacy. Available at: https://health.gov/communication/literacy/quickguide/default.htm

Table 1. (Cont.): General information for informed consents and assents (agreements)

Age Group in years 0<2	2<6	6<10	10<18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
✗	✗	◎	✓	✓	**Explanation of the concept of a clinical trial and the methodology used.**	• What is a clinical trial? • How does the clinical trial differ from normal routine care? • What is randomisation / double-blind / open label etc.?	NOTE: **Explain only the relevant methodology – a short version - used according to the current protocol. Avoid complex terms and flowcharts with too much detail.**
✗	✓	✓	✓	✓	**Dissent / Refusal / Disagreement / Respect for autonomy** **Voluntariness / Right to refuse / Right to dissent / Free decisions**	• What is the explicit wish of the child / adolescent (capable of forming an opinion and assessing the information)? • Has the child / adolescent understood that they may refuse participation or withdraw at any time during the trial? • Is the child / adolescent's free wish / decision respected (according to the age / maturity) by the investigator / trial personnel?	NOTE: The agreement of a child should be requested systematically, even if the assent is not legally required. **Children should be provided with age-appropriate information (with supplementary visual information where appropriate) and have the opportunity to form an opinion or decision.** Their refusal or dissent should be respected, objections should be analysed (reason), and possible help sought for anticipated burden (fear, distress etc.). **Resistance of very young children should be identified, and discussed with legal representatives.**

Table 1. (Cont.): General information for informed consents and assents (agreements)

Age Group in years 0<2	2<6	6<10	10<18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
✗	✗	✗	✓	✓	**Legal representative / Role / Sensitive issues of adolescents (not discussed with parents/ legal reps!)**	• Is there an opportunity for older adolescents to have a private conversation (without parents) with the trial personnel about confidential / sensitive issues?	NOTE: Legal reps. roles as empowered for decision making should be recognised, but there should be an additional option for the adolescent to express any concerns or worries so as to respect their autonomy (e.g. an independent person or mailbox or other method). - NOT the trial personnel, as this may create conflict.
✗	**If literate** ✓ **Other wise** ✗	✓	✓	✓	**Assent / Consent signature /certification / Re-consent** after legal age ([ii]Art.32); **In long-term studies**, check if there is a need to re-assent the child as the child matures. **Check, if assent (consent) is legally required for the child [i, ii].** **The child / adolescent must take part in the informed consent procedure** in a way adapted to their age and mental maturity. A child / adolescent capable of forming an opinion and assessing the information should also provide their assent to participate in the trial. The assent may additionally be in written form, and **must be according to national requirements.**	• Who can / must sign / write name on assent / consent forms?	For younger children, parents can explain by using "story telling" method.

Table 2. Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
1	✗	○	✓	✓	✓	**Title / Topic of the trial / Introduction / Purpose of the trial / Size of the trial (how many patients/participants, how many sites)**	• What is the purpose of this trial ? • Why is this trial needed? • Is there information about this trial available somewhere?	NOTE: EUCTR number and trial protocol code must be added. The trial must be registered in the official Trial Registry (EudraCT) before the start of the trial. Additionally, in other registries or websites according to national requirements.
2	✗	○	✓	✓	✓	**Introduction of the protocol (trial plan)**	• What data is needed & why? • What will be done?	NOTE: Use glossary of definitions or dictionary of terms if the protocol is very complex to explain.
3	✗	✓	✓	✓	✓	**Participation / recruitment / Child / adolescent selection**	• Why has the child / adolescent been invited to participate in this trial?	
4	✗	○	✓	✓	✓	**Information about the Institution / Organisation (e.g. hospital) & Doctor(s) / Investigator(s) / Nurse(s) / Trial personnel conducting the trial**	• Who are they ? (eg, family GP) • Do they have required professional expertise? • Will the doctor be the same throughout the trial?	NOTE: Include relevant information about all relevant partners and personnel involved in the conduct of the trial, including their expertise.
5	✗	○	✓	✓	✓	**Introduction of the investigational product(s)- / placebo / device used in the trial.**	• What medicine (s) / device is it? • What (pharmaceutical) form is it? • How does it work and are there side effects? What are the effects on contraception / use of alcohol / smoking? • How will it be administered / taken? • Has it been tested in children before? • What does placebo mean?	NOTE: The trial is intended to investigate treatments for a medical condition which occurs only in minors (children) or the trial is essential with respect to minors – same age group as the child / adolescent. **There must be scientific grounds; a direct health benefit for the child / adolescent or some benefit for the population the child / adolescent represents, and there should be only minimal risk and burden for child / adolescents when compared to standard care in that particular medical condition. Explain the scientific reason / rationale for using placebo – if used in the trial.**

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
6	✗	◎	✓	✓	✓	**Other treatments /Alternatives / options for clinical trials or diagnosis**	• What are the current / existing alternative methods / treatments if the child / adolescent does not want to take part in this trial?	NOTE: The risks of premature termination need to be explained to legal reps. (and children if they have capacity to understand). Reassurance should always be given that withdrawal will not affect normal treatment (alternative, standard) which should be available.
7	✗	◎	✓	✓	✓	**Possible benefits / expected benefits**	• Why might it be beneficial for the child / adolescent to be in this trial ?	NOTE: Explain the possible benefits (direct or some benefit for the population).
8	✗	✓	✓	✓	✓	**Procedures / tests / measurements according to the trial protocol** **Pain (physical and emotional) / discomfort / fear must be prevented and minimised.** Blood volumes and sample methods should follow guideline recommendations[3].	• What will happen? • What tests will be done and when? Why are these needed? • How do these affect normal daily life, food / drink / sports and hobbies? • How does it differ from current / standard care? • Does it mean taking any time off school?	NOTE: Non-invasive procedures should be preferred, where possible. Legal reps. and children should be informed whether the procedure is part of usual standard of care or if it is part of the trial (extra), and whether there is direct benefit or not. An explanation about the procedure in honest (not frightening) language must be offered to both the legal representative and the child prior to the procedure.
9	✗	◎	✓	✓	✓	**Time / timing / trial duration (whole trial, at specific site) Visits / trial schedule**	• How long will the trial take? • When are the trial visits? • How will it affect school / vacations / holidays / travel?	NOTE: Use flow-charts **The expected duration of participation must be stated.**

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
10	✗	○	✓	✓	✓	**Risks / disadvantages /side effects of the trial procedures / investigational medicinal product(s) / trial conduct / diagnosis**	• What might inconvenience the child / adolescent ? • Will there be extra pain / burden or side effects – related to either procedures / tests or to the trial medication?	NOTE: Risk / burden assessments must be done **prior to the trial** (via scientific / medical and ethical assessment conducted by competent authorities). Possible realistic / anticipated risks / burden during the trial must be described at a reasonable level during the assent / consent process.
11	✗	✗	○	✓	✓	**Genetic testing** Genetic testing may represent benefit, risk or burden. Follow the national requirements / legislation.	• What kind of test? Blood / saliva / other type? Why is it taken? • How will it be taken? • What information will be collected from the genetic test? • How will the information be used? • Who will be informed of the test results? • What is the duration of sample storage?	**A separate consent / assent may be required** for genetic tests. **Disclosure of genetic information to the child / adolescent requires precautions or expert counselling** (must be known what information is collected, how the information will be used, and how it is interpreted.) Explain the scientific reason / rationale and the procedure for giving the results in practice, if planned to do so in a trial. NOTE: Only if relevant (trial includes genetic testing).
12	✗	✗	○	✓	✓	**Use of ionising radiation** According to national regulations (e.g. legal acts for radiation).	• Is it used? How? • Are there any side effects?	NOTE: Only if relevant (trial includes ionising radiation)
13	✗	✗	○	✓	✓	**Biological samples / handling / storing / banking** Biobank samples, retention and consent for future processing of personal data should be discussed in the protocol. Follow the national requirements / legislation.	• What kind of samples? Tissue / blood / saliva / spinal fluid / other ? • Why are they taken? • How will they be taken? • Where are the samples stored and for how long? • Is it possible to cancel / withdraw consent for future use?	**A separate consent / assent may be required** for biological samples. Must comply with General Data Protection Regulation (679/2016) and national legislation. **The collection and use of samples must be described in consent/assent forms.** NOTE: Only if relevant (trial includes biological samples).

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
14	✗	✗	✗	✓	✓	**Possible future effects (Infertility, birth defects, miscarriage)**	• Can the trial medication or treatments have some effect on the foetus via mother or father, in case of the child / adolescent´s pregnancy / child / adolescent´s girlfriend´s pregnancy? • What happens if this situation occurs? • Who will be told about this?	NOTE: Information about the potential teratogenic risks during pregnancy / fertility (both females and males) should be discussed, and also the possibility to use contraception, and what type of contraception should be used if it is required. Explain what should happen if pregnancy arises during the trial.
15	✗	✗	✗	✓	✓	**Special situations: emergency / emancipated minor / pregnancy / breastfeeding / unexpected problems** If during the trial the child reaches the age of legal competence for giving consent (as defined in national laws) consent must be obtained at that point before the child / adolescent can continue	• How will these types of situations be handled if they occur? • Who will be contacted? • Is there a need for prior consent?[2]	NOTE: The protocol should define emergency situations and conditions (e.g. time lag until consent is signed) for deferred consent (can be delayed and sought as soon as possible after inclusion). Consent may be deferred in certain emergency situations. **Emergency: Shortened time for decision - full explanation should follow later.**
16	✗	◎	✓	✓	✓	**Confidentiality / Personal Data Protection** Must comply with EU General Data Protection Regulation (679/2016) for data protection[i]	• What data from patient files and what additional information is needed & why? • How will the data be used? • Who has access to this data? Must be clearly stated (using names, if required) who has access to data, how it is used and how the anonymisation is done.	NOTE: Regulatory Authorities have legal permission to have access to research documents and data during inspections and audits. The data will be stored anonymously and the researcher will have access to it. Explain what anonymisation means.

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
17	✗	○	✓	✓	✓	**Discontinuation by child / adolescent / Right to withdraw / Discontinuation for medical reasons (safety) by the sponsor.** The procedures in place in the event of adverse reactions, including the documentation and time sensitive reporting throughout the duration of the trial must be explained during the consent/assent process.	• How it may happen / when / for what reasons? • What happens ater? • What are the options for further care/ medication?	NOTE: Identification of possible risks, minimising and monitoring the risks - **assent / consent should include an explanation about the probability and magnitude of harm anticipated in the trial and how this will be minimised, followed and handled. Stopping rules must be included in the protocol**. NOTE: Check with the relevant national authorities regarding the right (or not) to have information already collected deleted and samples already collected destroyed.
18	✗	✗	○	✓	✓	**Compensation/Expenses/NO incentives/inducements used** **Child / adolescents should not have to pay for IMPs / auxiliary products used for administration and procedures by the protocol** - unless the national law provides otherwise. All compensation should be according to national requirements.	• What expenses are expected during this trial? (exact level) • What costs will be covered by the trial / sponsor / hospital? • How will expenses be compensated?	NOTE: **No financial contribution / inducements should be offered**, except **compensation for the parents/ legal reps.expenses and loss of earnings directly related to the child´s participation**. A small token of appreciation may be acceptable - but needs to be approved by the Ethics Committee (EC) through review / assessment. Children do not need detailed reimbursement information if not directly related to personal compensations (e.g. travels, meals etc.). Legal reps. need all information of the compensations and reimbursements.

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
19	✗	✗	◎	✓	✓	**Insurance** **Information about applicable damage compensation must be included.** Compensation should be asssured for damages. Member States should ensure that a system for compensation for damages is in place and appropriate – also Sponsor´s responsibility.	• What possible damages could be expected during the trial (i.e. what may go wrong) and how are these covered by insurance? (Exactly)	NOTE: **Damage compensation is mandatory as per CTR and should be ensured by Member States.** Insurance should not waive liabilities regarding long-term effects (delayed effects are typical in children when they grow up).
20	✗	◎	✓	✓	✓	**After Trial / Follow-up measurements**	• Will the trial medication be available after the trial? • What happens after the trial?	
21	✗	✗	✓	✓	✓	**Results of the trial**	• When is it expected to have trial results? • Will child / adolescent / legal reps. be informed of the results?	NOTE: Information about availability of trial results must be stated. The information should include a summary of results presented in terms understandable to a layperson, and must be available through EU database (portal).
22	✗	✗	◎	✓	✓	**Information about the Competent Authority (CA) authorisations and Ethics Committee (EC) review / approvals** including the appropriate expertise used in the assessment. The reviewers should be independent of the sponsor, the investigator and the trial.	• Who has reviewed / approved the trial? • Has the review been undertaken by people who have official authority, and expertise for the assessment? (Is this legal and safe?)	NOTE: Should be explained who has reviewed / approved the protocol, **but they have not decided on behalf of potential child / adolescents!** NO need to include information about EC approval in the young child´s assent, as they do not understand the concept of "ethics".

Table 2. (Cont.): Trial specific information for informed consents and assents (agreements)

Element Nr	Age Group in years 0-2	2-5	6-9	10-18	Legal representative(s)	Elements to consider / Information which must be included into the assent/consent document	Questions to be addressed	NOTES and example methods / texts to be used
23	✗	✗	◎	✓	✓	**Information about the Sponsor / funding of the trial**	• Who will fund this trial? • Do they pay the trial personnel directly?	- NOTE: Should be stated that the hospital receives money; not the investigator directly. **Need to be clear interest differentiation between the investigator and sponsor.**
24	✗	✗	✓	✓	✓	**Contact information**	• Who can be contacted at any time / for any reason during the trial? • How should they be contacted?	**NOTE: Always give contact information to all participants.** NO need to have contact information in assent /consent for very young children.
25	✗	◎	✓	✓	✓	**Confirmation of understanding** In the consent / assent discussion it must be verified that everyone (legal reps./ child) have understood the information.	• Were answers provided to all of the questions asked by the child / adolescent and/or legal reps.? • Are there still issues that are unclear and need to be resolved?	NOTE: You may use an additional summary leaflet, but it depends on the complexity of the trial.

References:

[i] European Union Commission ad hoc Expert group. **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. Eudralex 10, Chapter V-Additional Information. Available under the documents relevant to clinical trials authorised under Regulation (EU) No 536/2014, these documents will be listed in two separate pages on the Eudralex Volume 10 website at: https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1

[ii] European Union. **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. 16 June 2014 (will become applicable no earlier than 28 May 2016). http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm (accessed 16 Dec 2014). Available on Chapter VI-Legislation at: https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1

[iii] **The Paediatric Regulation** is comprised of: **Regulation (EC) No 1901/2006** of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use; and **Regulation (EC) No 1902/2006,** an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/paediatric-medicines/paediatric-regulation

[iv] EU Commission. **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 Status relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities 2011. L 121/34–44. http://ec.europa.eu/health/human-use/clinical-trials/directive/index_en.htm (accessed 16 Dec 2014).

[v] European Network of Paediatric Research at the European Medicines Agency (**Enpr-EMA**). Available at: https://www.ema.europa.eu/en/partners-networks/networks/european-network-paediatric-research-european-medicines-agency-enpr-ema

[vi] **European YPAG Network** - **eYPAGnet** - Young Persons Advisory Groups. Available at: https://eypagnet.eu/

[vii] 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 (**General Data Protection Regulation, GDPR**)

[viii] EUROPEAN COMMISSION DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY, Health systems and products, Medical products – quality, safety and innovation. **Question and Answers on the interplay between the Clinical Trials Regulation and the General Data Protection Regulation.** Available at: https://ec.europa.eu/health/human-use/clinical-trials_en Highlights section.

[ix] **Informed consent requirements for paediatric clinical trials in Europe** in 2015 (Updated in 2019) -ToolKit table. Available at: https://www.ema.europa.eu/en/partners-networks/networks/enpr-ema/enpr-ema-priority-activities and related article; Informed Consent for Paediatric Clinical Trials in Europe"; Authors: Pirkko Lepola, Allison Needham, Jo Mendum, Peter Sallabank, David Neubauer, Saskia de Wildt. Arch Dis Child 2016; 101:1017-1025. Available at: https://www.ema.europa.eu/en/partners-networks/networks/enpr-ema/enpr-ema-priority-activities