Informed consent for paediatric clinical trials in Europe

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ABSTRACT

Objective Paediatric clinical trials are often conducted as multinational trials. Informed consent or assent is part of the ethics committee approval for clinical trials. The consent requirements vary between countries due to national laws and regulations, which are not harmonised in Europe. These discrepancies can present challenges for paediatric clinical trials. The aim of this study was to assemble these consent and assent requirements across the European Economic Area. The collated national requirements have not been publicly available before, despite a real need for this data.

Methods National consent and assent requirements for paediatric clinical trials were analysed and collated for 25 European Union Member States and 2 European Free Trade Association countries until the end of 2014. The data were retrieved from existing databases and through communication with the competent authorities and selected ethics committees. Results from a literature search for international or national guidelines, declarations and conventions and academic societies' publications served as comparison material.

Results Consent and assent requirements are heterogeneous across these countries. We compiled our findings in 'The Informed Consent and Assent Tool Kit', a table including 27 national consent and assent requirements listed by individual country.

Conclusions Wide variation in paediatric consents and assents presents challenges for multinational paediatric trials in Europe. The toolkit is available for all those involved in paediatric clinical trials and ethics committees, providing a new platform for proactive feedback on informed consent requirements, and may finally lead to a needed harmonisation process, including uniform standards accepted across Europe.

What is already known on this topic?

- There are noticeable differences between national consent and assent requirements for paediatric clinical trials in Europe due to national laws and regulations.
- The international and the ethics societies' guidelines are not based on uniform standards and rarely provide detailed consent or assent recommendations for children.
- A single source of comprehensive multinational data on informed consent and assent requirements of paediatric clinical trials across Europe is not publicly available.

What this study adds?

- The 'Informed Consent and Assent Tool Kit' is a publicly available resource for stakeholders involved in the running of paediatric clinical trials in Europe.
- These data provide a new platform for proactive feedback from stakeholders to maintain a common resource and approach to consent and assent requirements in Europe.
- These data hope to promote discussion for long-term decisions and practical changes leading to uniform ethics committee procedures across the European Economic Area.

INTRODUCTION

Clinical trials (CTs) in children are often conducted as multinational, multicentre trials, necessitated by small patient populations, rarity of disease and limited specialist facilities. As CTs need a separate competent authority (CA) and ethics committee (EC) approval in each participating country, the pharmaceutical industry and investigators spend much time and resources preparing documentation and correspondence to these submissions.

In January 2007, the European Union (EU) Paediatric Regulation ((European Commission) No 1901/2006)[1] came into force requiring the conduct of more paediatric CTs to facilitate the development and accessibility of medicinal products for children. A further EU CT Regulation will come into force after 28 May 2016,[2] but while this harmonises the clinical trial application (CTA) process, it does not address the diversity in review and conduct of EC approvals at each site.

The process of obtaining EC approval (with consent or assent requirements for children) is not harmonised in the EU. Despite internationally accepted ethical principles[3–11] and several EU-level guidelines,[12–16] this area presents a major challenge for paediatric CTs across the EU. Although the doctrine of consent is an ethical cornerstone of medical research conducted in humans, special provisions for children vary between and, in some cases, within countries due to differences in national laws and practices.

Within the European Economic Area (EEA), three regulatory frameworks govern the conduct of paediatric research: the Convention on Human Rights and Biomedicine (the Oviedo Convention);[12] Directive 2001/20/EC (European

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Commission Directive)[14] and the Paediatric Regulation ((European Commission) No 1901/2006).[1] Discrepancies exist between these three frameworks. For example, the veto power of a child to participate in research is not covered in the Paediatric Regulation, while the Oviedo Convention allows a more extensive decision-making capacity by the child than the European Commission Directive, which relies on investigator's consideration of the explicit wish of a child. The aim of this work is to describe the heterogeneity in consent and assent requirements for paediatric CTs and to provide a tabulated summary of these requirements by country as a tool for stakeholders preparing paediatric CT submissions in the EEA.

METHODS

The working group (WG) of the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) collected specific legal requirements of consent and assent for children and adolescents from the national legislations of 25 EU member states and 2 European Free Trade Association (EFTA) countries (Norway and Iceland) during 2014. The primary data source was a repository of EC submissions from national authorities provided by the Contract Research Organization (CRO), PRA Health Sciences (PRAHS).[17] Secondary sources were publicly available data found on national websites of regulatory authorities, such as Medicines Agencies and National Ethics Committees. Additional data came through Regulinx,[18] a UK-based company specialised in consulting on regulatory affairs, and from the Finnish Investigators Network for Pediatric Medicines (FinPedMed).[19]

Table 1 provides a snapshot of the information collated in 2014. The data are arranged by country under three main headings. The first heading, 'Consent/Assent from child', includes data on the legal age of consent and mandatory or suggested age ranges defined for assent (or consent if assent is not used). The second heading, 'Consent from parent(s)/guardian(s)', includes legal requirements for the number of required signatories. The third heading, 'General informed consent information' includes official language requirements and consent template(s), guidelines or additional national information with existing web links.

In addition, the WG systematically searched online sources to identify subject-related articles, learned societies' recommendations and ethical guidelines, conventions and recommendations. The search was conducted in the PubMed (US National Library of Medicine, National Institutes of Health) database, EU Commission website, national competent authorities' websites and Google sources using the keywords: ethics, guideline, regulations, paediatric, minors, children, biomedical research, clinical trials, human rights and children's rights. The search resulted in 28 relevant documents related to medical research ethics on humans and, more specifically, on children. Ten had a worldwide scope, nine a continental or national scope, and nine were publications from academic societies.[2–14 20–34] These documents were compared with the current official and legal recommendations by verifying the consent-related and assent-related texts of these documents.

Finally, personal experiences of the WG members (ie, in the conducted multicentre trials and communication with ECs) were used for supplementary comparison. Once all the data sources for consent and assent requirements in the EEA had been collated, the WG compared and analysed the sources of discrepancy in practice across the jurisdictions. This revealed several discrepancies, which are addressed in the discussion section.

RESULTS

Assent and consent: differences in use and definitions

Both the term 'consent' and 'assent' are interpreted differently in legal texts between EEA countries. Generally, each country's national legislation includes legal age ranges and requirements for either consent or assent from a child, in addition to any legal (parental or guardian) signatures. The definition of these two terms rests on the need of these signatures: either given by the trial subject alone, or in conjunction with the parents/guardians. Usually, consent is defined according to the legal age limit of majority, which differs between countries. This is not the case in all countries, like the Netherlands where infant informed consent is needed, in addition to parental consent in children between 12 and 17 years of age. Assent is a non-legal agreement, and an additional parental/guardian signature (consent) is always required before the participation of the child in a trial is legally accepted.

Differences in consent and assent age limits and legal signatures

In most of the EEA countries, 18 years is the legal age for independent consent, but the following exceptions should be noted: 14 years in Austria, 15 years in Finland and Denmark and 16 years in the UK. These exceptions come with certain limitations and with the obligation to notify parents/legal guardians. However, across all the EEA countries, 32 different age groupings to the legal age exist for recommended additional assent or consent needed from the child participating in the CT. These groupings include, for example, 4–11 years, 12–14 years and 14–17 years. Only three countries (Croatia, Lithuania and Slovakia) have not specified age groups for assent or consent.

Differences are also seen in the requirement of signatures from parents or legal guardians. Seventeen countries (63%) require signatures of both parents in addition to the child's own assent or consent. Specific guidelines with consent form templates and additional aid material (eg, pictures) for children in paediatric CTs have been generally accepted by some EU member states (eg, Finland and UK).

DISCUSSION

The United Nations Convention on the Rights of the Child defines a child as everyone under 18, unless, 'under the law applicable to the child, majority is attained earlier'.[3] For children below that age, there are noticeable differences between national and organisational regulations on ethical consent in paediatric CTs. These concern specifically non-uniform age limits and age ranges, different definitions for legal consent and the requirement of parental or legal guardian signatures.

It appears that these criteria, for unknown reasons, are not uniformly defined in European guidelines or recommendations. We also found that the international and the ethics societies' guidelines and recommendations rarely detail consent or assent procedures for children,[7 13 27–31] but often very generic instructions without specific definitions.[2–6 8–12 20–26 32–34] For the greater part, these criteria do not seem to be based on the developmental stage of the child and his/her competency level for informed consent or assent. Competency, in addition to health condition, is important for determining further actions if trial subjects reach the age of majority during the study and need to give their own (legal) consent to continue.[2]

The terms 'consent' and 'assent' are also not defined in general guidelines and are not harmonised across the EEA. Some European countries use the term consent for both minors

Table 1 The Informed Consent and Assent Tool Kit—informed consent requirements for paediatric clinical trials in Europe

	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
Country	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
Austria	Not specified Practice—14 years	8–13 years EC may require younger assents	Both parents	German	http://www.medunigraz.at/ethikkommission/Forum/index.htm http://www.ethikkommissionen.at/ http://www.uibk.ac.at/strafrecht/scheil/scheil-einfuehrung-in-die-arzneimittelpruefung-bei-kindern-und-jugendlichen---kks--kids-ip.pdf
Belgium	18 years	4–11 years (some sites do not use under 12 years) 12–14 years 14–17 years	One parent at recruitment, but both parents at some point for signatures	Dutch, French; German at site request	http://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/ethic_committee/templates_informed_consent/ Do not have paediatric templates
Bulgaria	18 years	6–11 years 12–14 years 14–17 years—use own consent+parental signature also required	Both parents	Bulgarian	No national EC websites available in English Bulgarian Drug Agency -> clinical trials http://en.bda.bg/index.php?option=com_content&view=category&layout=blog&id=14&Itemid=34
Croatia	Nothing specified	Nothing specified	Nothing specified	Croatian	Agency for Medicinal Products and Medical Devices of Croatia -> Central Ethics Committee -> http://www.almp.hr/?ln=en&w=o_SEPu Information on clinical trials not available in English.
Czech Republic	18 years	7–11 years 12 years—own consent 12–14 years 15–17 years	Both parents. Only by one parent if the other parent is not listed in the child's birth certificate, has died or is younger than 18 years.	Czech. Where the child's parents (or one of them) are foreign nationals, the information sheet shall be presented in bilingual format.	State Institute for Drug Control -> Details of clinical trials / Guidelines and Forms / KLH-22 V.1: http://www.sukl.eu/medicines/klh-22-version-1
Denmark	18 years	15–17 years—proxy consent	Both parents Exception—no parents if aged 15–17 and non-interventional no-risk study (EC dispensation required)	Danish	The National Committee on Health Research Ethics -> Guidelines about notification http://www.cvk.sum.dk/CVK/Home/English.aspx http://cvk.sum.dk/English/guidelinesaboutnotification.aspx -> 4.4. Medicinal product trials and clinical investigations of medicinal devices involving legally incompetent subjects; 4.4.1 Trials with children and young people under the age of 18 http://cvk.sum.dk/English/guidelinesaboutnotification.aspx#Afsnit%205.0 Act on Research Ethics Review of Health Research Projects
Estonia	18 years	0–7 years 7–17 years—mandatory	Both parents	Estonian	State Agency of Medicine -> Clinical trials -> Conditions and procedure for conducting clinical trials of medicinal products http://www.ravimiamet.ee/en/clinical-trials-medicinal-products-estonia
Finland	15 years	Written separate consent as soon as child is literate; under 15 years—own consent +parental consent; 15–17 years—own consent +parental notification if minor can understand the significance of research+direct health benefit is expected	Parent or legal guardian and the child, when they are literate, need to sign the consent. One parent by the law, but the other one can be informed (both can sign if they want).	Finnish, Swedish	Medicines Research Act 488/1999 Medical Research Decree 986/1999 Additional info: FinPedMed guidelines; legal and ethical regulation—templates for age groups 6–17 and parents Regulatory requirements for clinical trials in Finland Picture cards to support IC process

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Table 1 Continued

Country	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
France	18 years	Based on EC—usually two or three age groups 4–6 years 7–12 years 13–17 years Picture ICFs for young children	Both parents	French	Comité de Protection des Personnes Sud-Méditerranée II : http://www.cpp-sudmed2.fr/Information-et-autorisation-des?lang=fr National Consultative Ethics Committee for Health and Life Sciences: http://www.ccne-ethique.fr/en
Germany	18 years	7–11 years 12–16 years 17 years—own consent +parental consent required	Both parents	German	German Ethics Council; http://www.ethikrat.org/—no information for clinical trials Landesärztekammer Brandenburg—information available ONLY in German. https://www.laekb.de/ ICF Guidance https://www.laekb.de/files/146A97FF999/AMG_Patienteninfo_Kinder_7bis11.pdf
Hungary	18 years	Under 6 years 6–10 years 11–14 years 15–17 years	One parent	Hungarian	National Institute of Pharmacy and Nutrition -> Laws and regulations (only available in Hungarian) -> Miniszteri rendeletek http://ogyei.gov.hu/search/index.php?searchPhrase=decree&from=10 http://www.ogyei.gov.hu/magyar_jogszabalyok/ -> Decree 35/2005 (VIII. 26.) of the Minister of Health on the clinical trial and application of correct clinical practices of investigational medicinal products intended for use in humans 7§ Clinical trials conducted on minors http://net.jogtar.hu/jr/gen/getdoc.cgi?docid=A0500035.eum
Iceland	18 years	Under 12 years	One parent—the EC can request both parents' signatures in some cases.	Icelandic or English. The study objective in Icelandic. Materials in Icelandic. (For studies involving groups of other ethnicity, an appropriate language is required.)	The National Bioethics Committee (http://www.vsn.is/en/node/189) The Parliament; http://www.althingi.is/english -> http://www.althingi.is/lagasafn/log-samthykkt-a-althingi/ ->The Act of Law, No. 44/2014, on scientific research within the health sector defines the conditions for biomedical research and the role of the bioethics committees http://www.althingi.is/lagas/nuna/2014044.html Several laws and regulations on data protection, medicines, biobanks and health information collections (2014), etc
Ireland	16 years (clinical trials) 18 years (all other research)	7 years, or according to capacity of child	One parent	English	List of Research Ethics Committees for clinical trials of IMP: http://health.gov.ie/european-communities-clinical-trials-on-medicinal-products-for-human-use-regulations-2004/ Research Ethics Committee Standard Application Form: http://www.molecularmedicineireland.ie/research_ethics National Consent Policy: http://www.hse.ie/eng/about/Who/qualityandpatientsafety/National_Consent_Policy/consenttrainerresource/trainerfiles/NationalConsentPolicyDOC.html Clinical Trial Regulation: S.I. No. 190/2004—European Communities (Clinical Trials on Medicinal Products For Human Use) Regulations, 2004 http://www.irishstatutebook.ie/2004/en/si/0190.html

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Table 1 Continued

Country	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
Italy	18 years	6–10 years 11–14 years 15–17 years—with own signature No official mandatory age(s) for assent. Different age-tailored assents are submitted voluntarily, and are evaluated by the ECs	Both parents	Italian	The Italian Medicines Agency http://www.agenziafarmaco.gov.it/en/content/clinical-trials the Italian regulation on CTs include the following: D.lgs 211/2003 http://www.agenziafarmaco.gov.it/sites/default/files/decreto_24062003_inglese.pdf DM 21/12/07 https://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Normativa/MD_21_December_2007_CTAform_English.pdf
Latvia	18 years	0–7 years 7–17 years	One parent or legal representative	Latvian	State Agency of Medicines of the Republic of Latvia -> Clinical trials and non-interventional trials -> legislation http://www.zva.gov.lv/?setlang=en -> http://www.zva.gov.lv/?id=396&sa=396&top=386 -> http://www.zva.gov.lv/index.php?id=381&sa=381&top=333&lang http://www.zva.gov.lv/doc_upl/MK_not_289_English_02062010.pdf
Lithuania	18 years	No set ages	Both parents	Lithuanian	The Lithuanian Bioethics Committee -> Biomedical Research -> favourable opinion on clinical drug trial http://bioetika.sam.lt/index.php?3202747546 Informed Consent http://bioetika.sam.lt/index.php?3221858831 -> http://bioetika.sam.lt/index.php?577320631—information available only in Lithuanian http://bioetika.sam.lt/index.php?3202747546
Malta	18 years	6–17 years	Parents or legal representative Practice—both parents	One of the official languages of Malta (eg, Maltese) or in a language understandable to the clinical trial subject and/or his legal representative.	Malta Health Ethics Committee https://health.gov.mt/en/appbodies/hec/Pages/Links.aspx Maltese Clinical Trials Regulations 2004 (LN490 of 2004) MEDICINES ACT, 2003 (ACT NO. III OF 2003); http://justiceservices.gov.mt/DownloadDocument.aspx?app=lp&itemid=16860&l=1
The Netherlands	18 years	12–17 years	Both parents. If parents are divorced and they both have parental rights, they both have to sign. For a single parent, without another partner with parental rights, one signature is enough.	Dutch	Central Committee on Research Involving Human Subjects (CCMO) -> Human Subject -> Informed Consent—information available only in Dutch. http://www.ccmo.nl/en/ -> http://www.ccmo.nl/en/minors

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Table 1 Continued

Country	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
Norway	18 years	16–17 years—with own signature 12–16 years—in special circumstances	Main rule: both parents sign the consent form if they have parental responsibility for the child. Required for all children under 12 years old.	Norwegian	The Norwegian National Research Ethics Committees -> Clinical Trials -> Regulations https://www.etikkom.no/en/ethical-guidelines-for-research/ http://www.legemiddelverket.no/English/Clinical_trials/Regulations/Documents/Norwegian%20regualtion%20for%20Clinical%20Trials.pdf National database for Laws and Acts -> Lov om medisinsk og helsefaglig forskning (helseforskningsloven)—information available only in Norwegian. https://lovdata.no/dokument/NL/lov/2008-06-20-44?q=helseforskning Act on medical and health research (Helseforsknings-loven) Guidance to Helseforsknings-loven (in Norwegian only) Additional info: Norwegian Medicines Agency: Website on clinical trials.
Poland	18 years	6–11 years 12–15 years 16–17 years	One parent Practice—both parents	Polish	http://www.eurecnet.org/information/poland.html No national EC websites available in English
Portugal	18 years	0–8 years 8–12 years 12–17 years	Both parents	Portuguese	http://www.eurecnet.org/information/portugal.html CEIC—National Ethics Committee for Clinical Research http://www.infarmed.pt/portal/page/portal/CEIC/English No national regulations/acts available in English
Romania	18 years	Under 6 years 6–10 years 11–14 years 15–18 years	Both parents	Romanian	National Ethics Committee of Romania http://www.adsm.ro/ro/comisia+nationala+de+bioetica+a+medicamentului+si+a+dispozitivelor+medicale# No information available in English
Scotland (UK)	16 years	0–5 years 6–10 years 11–15 years Consent with own signature under 16 years, if they are competent to do so	One parent	English	NRES Guidance http://www.hra-decisiontools.org.uk/consent/principles-children.html and http://www.ukctg.nihr.ac.uk/default.aspx
Slovakia	n.a.	n.a.	n.a.	Slovakian	The State Institute for Drug Control (SIDC) -> Clinical trials -> Instructions http://www.sukl.sk/en?page_id=256 ->> http://www.sukl.sk/en/clinical-trials/instructions?page_id=2821 No national regulations/acts available in English
Slovenia	18 years	9 years—assent 15 years—with own signature	One parent	Slovenian	Republic of Slovenia National Medical Ethics Committee ->> http://kme-nmec.si/—only front page No additional information available.
Spain	18 years	0–11 years 12–17 years—with own signature	One parent	Spanish	The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); A state agency within the Spanish Ministry of Health, Social Services and Equality -> Medicines for Human use—> Clinical research with medicines http://www.aemps.gob.es/en/investigacionClinica/medicamentos/home.htm The Ministry of Health, section about regulation of clinical trials: http://www.aemps.gob.es/en/legislacion/espana/investigacionClinica/ensayos.htm The Spanish Regulation about Clinical trials: the ROYAL DECREE 223/2004-section 7.3 (English version is available by request)

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Table 1 Continued

Country	Consent/assent from child*		Consent from parent(s)/guardian(s)	General informed consent information	
	Legal age of consent†	Mandatory/suggested age ranges defined for assent (or consent if assent not used)‡	Number of required signatories	Official language requirements	Consent template(s)/guidelines/information sources
Sweden	18 years	Written separate consent as soon as child is literate 6–10 years 11–14 years 15–17 years—with own signature	Both parents and the child, when literate, need to sign the consent	Swedish	The Central Ethical Review Board -> Documents -> Information for Research Participants http://www.epn.se/en/start/the-organisation/ -> http://www.epn.se/en/start/central-ethical-review-board-documents/ -Etikprövningslagen 2008. Regulatory requirement for clinical trials LVFS 2011:19 Läkemedelslagen—1992 Biobank law—2002 Personal Data Act 1998 National Medicines Agency -> Legislation -> Codes of Statutes -> 1996:17 Clinical trials of medicinal products https://lakemedelsverket.se/english/ -> https://lakemedelsverket.se/english/overview/Legislation/Codes-of-statutes/
UK	16 years	0–5 years 6–10 years 11–15 years	One parent	English	NRES Guidance; http://www.hra-decisiontools.org.uk/consent/principles-children.html and http://www.ukctg.nihr.ac.uk/default.aspx

**Consent/assent from child*: this information has been mainly collected via the normal daily work and notes of the CRO Company, PRA Health Sciences (UK), when preparing EC submissions for national authorities. Some of this information is not available in English, nor publicly available in regulatory authority's web pages. In addition, some English-translated text versions may include inaccurate terms or explanations, which could give rise to different interpretations. Therefore, the authors cannot guarantee 100% accuracy for all national requirements. In addition, this table is a snapshot of the data gathered in 2014, which might have subsequently changed.

†*Legal age of consent:* legal age of consent means the age from which a child is able to give and sign their own independent legally valid consent according to the national law/act/regulation. Children below this age limit are incapable of giving legal informed consent and need parental/legally authorised guardian's informed consent with a signature to participate in a clinical study. Parental/legally authorised guardian's informed consent may be obtained/sought in addition to the child's own consent/assent, or when the child above the age limit is incapable to sign consent due to a difficult physical condition.

‡*Mandatory/suggested age ranges defined for assent (or consent if assent not used):* these mandatory or suggested age ranges are defined in national regulation/law/act, for a child below the legal age of consent and for own informed consent or assent (depending on the terminology used in legal texts). This consent or assent is obtained in addition to the legally valid parental/legally authorised guardian's signed informed consent. This type of child's own assent/consent supports the child's integrity and rights, creates the opportunity to hear their own opinion, supposed will and possible dissent, thus respecting the child's autonomy in the informed consent process.

(older children below legal adult age) and parents (legal guardians). Usually, the term assent refers to a child's or minor's agreement to the trial (not legally valid on its own), while consent is documented through legal signature(s) by the parents (guardians) or the child, when the child is above the legal age.

There are more than 1000 ECs in Europe,[35] which result in substantial variability of EC compositions and practices,[36–38] with consequently a certain degree of inconsistency in the required consent and assent documentation for multinational and multicentre trials. Moreover, much time and resources may be needed to obtain approvals. To manage these inconsistencies and to reduce the duplicative workload, sponsors are recommended to perform an iterative or sequential review at each participating institution or country.

The European Medicines Agency (EMA) has evaluated the impact of the Paediatric Regulation after its first 5 years of being in force.[39] So far, the regulation has not yet led to more paediatric CTs in Europe, although there are plans to conduct CTs with enrolment of more children.[39] Still, the initiation of new CTs may be hampered by the practical obstacles of complex EC processes.

Currently, it is not possible to seek European-wide legislative changes for EC practice harmonisation, as the practice for one EC will not necessarily work for another without concerted effort to achieve harmony. However, an expert group has designed model consent and assent forms for different paediatric age groups,[40] which could be applied across Europe. Furthermore, better definitions of the concepts of 'understanding', 'capability', 'capacity for autonomous decisions' and 'moral understanding of altruism' could greatly support a harmonisation process.

To solve these problems, we suggest the following measures:

- Uniform, commonly accepted standards and guidance across Europe/EEA
- Definition of the lowest age limit to consent and assent requiring own signatures in addition to parental (legal) consent until the legal age of majority permits independent consent
- Fundamental discussion to create more detailed definitions of assent and consent and to decide whether these terms could be harmonised and used with similar principles for paediatric population
- Standardised structure and reading level requirements of consent and assent documents, including recommendations for legal guardian's (parental) signatures
- A master consent/assent template in all national languages being publicly and readily available.

'The Informed Consent and Assent Tool Kit' was updated mainly until the end of 2014. As national-level regulations and laws may change over different intervals, the accuracy of the data and linked documents are dependent upon regular review. The Enpr-EMA's central aim is to enhance and promote the conduct of paediatric CTs in Europe. This toolkit being publicly available free of cost on the Enpr-EMA website meets this aim. Please go to: http://www.ema.europa.eu/Partners&Networks/Networks/Enpr-EMA/Enpr-EMA activities, or directly at: http://tinyurl.com/h2xrlvr. With this toolkit, we hope that all stakeholders will proactively provide feedback via the Enpr-EMA, to keep this toolkit up to date and fostering discussion on harmonisation of EC procedures needed for paediatric trials across Europe.

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