OVERVIEW OF COMMENTS RECEIVED ON DRAFT DOCUMENT "ETHICAL CONSIDERATIONS FOR CLINICAL TRIALS PERFORMED WITH CHILDREN"

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Association Internationale de la Mutualité (AIM)	Belgium
2	Association of the British Pharmaceutical Industry (ABPI)	United Kingdom
3	Beaufour Ipsen Pharma	France
4	Blood Products Working Party (BPWP)	EMEA
5	Bristol-Myers Squibb (BMS)	
6	Comissăao de Ética da Investigação Clínica (CEIC)	Portugal
7	Confederation of European Specialists in Paediatrics (CESP)	Belgium
8	European Federation of Allergy and Airways Diseases Patients' Organisation (EFA)	Belgium
9	European Federation of Pharmaceutical Industries and Associations (EFPIA)	Belgium
10	European Forum for Good Clinical Practice (EFGCP)	Belgium
11	European Network for Research on Alternating Hemiplegia (ENRAH)	Austria
12	Faculty of Pharmaceutical Medicine (FPM) of the Royal Colleges of Physicians of the United Kingdom	United Kingdom
13	German Association of Research-Based Pharmaceutical Companies (VFA)	Germany
14	GlaxoSmithKline Biologicals Rixensart	Belgium
15	Good Clinical Practice Alliance - Europe	Belgium
16	Hoffman La Roche	Switzerland
17	Institute of Clinical Research	United Kingdom
18	International Confederation of Childhood Cancer Parent Organisations (ICCCPO)	Netherlands
19	International Plasma Fractionation Association (IPFA)	Netherlands
20	International Society of Paediatric Oncology (SIOP)	Netherlands
21	La revue Prescrire	France
22	Medicines and Healthcare products Regulatory Agency	United Kingdom
23	Medicines Evaluation Board (MEB)	Netherlands
24	Medicines for Children Research Network (MCRN)	United Kingdom
25	Ministry of Social Affairs and Health-Sub-Committee on Medical Research Ethics Finland	Finland
26	Office of Pediatric Therapeutics (FDA)	USA
27	Only for Children Pharmaceuticals	France
28	Paediatric Network (PAED-Net)	Germany
29	Pharmaceutical Group of the EU (PGEU)	Brussels
30	Richard Ashcroft, University of London	United Kingdom
31	sanofi aventis	
32	Task-force in Europe for Drug Development for the Young (TEDDY)	

Table 2:Discussion of comments

GENERAL COMMENTS – OVERVIEW	
We do not see any advantage from this particular text because it seems reductionist. Belmont Report is one of the oldest texts about human rights in research. We favour the introduction of modern perspectives of autonomy (as Kant presented it) and responsibility. In fact, not only autonomy of the participants must be respected at all efforts, but also responsibility in a variety of perspectives (responsibility of all participants towards society, each other in the present and in the future) must be assumed.	No general change in depth of ethical discussion appears necessary. Belmont was cited to be explicit on some components of the ethical principles that are not to be found in other guidance
We believe that more effort in general should be put into communication about research and its terminology to parents and children so as to facilitate their comprehension and encourage appropriate decision-making. Therefore although this guidance is not specifically directed at the general public, we suggest that its existence, once approved, is vigorously promoted to the general public.	Agreed. No change requested
The establishment of training programmes for ethics committees reviewing paediatric clinical trial applications is strongly recommended.	Agreed. No change requested
Genetic research including pharmacogenetics and pharmaco-genomics with their possible long term implications (for example with regard to storage of data/samples) requires some guidance	No change requested
Change title to "Ethical Considerations for Clinical Trials on Medicinal Products in the Paediatric Population"	Included
Only use "legal representative" instead of referring to parents.	The document intends not to approach the ethical questions on a legal, but rather also on a social basis. In most cases the parents are the legal representatives.
Does the Executive Summary have to be repeated literally in following sections?	Will be amended once document is finalised.
Children are in the legal sense not able to consent, but they are able to consent from the age of 6-7 years. This is legally called assent.	Assent already defined. Sentence amended accordingly
The executive summary should balance the need to protect a vulnerable population with the right of children to participate at therapeutic progress.	Agreed, already reflected in the text
The final sentence "Finally, various other aspects relating to the performance of trials in children are discussed" could be removed without any loss to the content.	Section requires pointing to further topics covered.
The authors might consider to mention that although this document refers to drug research only it tries to catch the general spirit of modern times in child research and therefore welcomes representatives of other research areas to consider it as reference.	This aspect is covered in the "Scope" section.
The guideline is […] unnecessarily long […] looses focus on children	Although the focus is on children, it's important to include other ethical aspects which apply to clinical trials in children as well as adults.
Our specific comments below are intended to assist the Ad Hoc Group in moving from a predominately legal approach to a more child-centred and ethics approach in the phrasing and implementation of ethical considerations related to clinical trials preformed in children.	Agreed. No change requested

The draft guidance provided here will need to be further supported by specific operational guidance in informed consent and ethical review of clinical trials performed in children.	Agreed No change requested
It was felt that the document was very thorough and well written in general. There were some inconsistencies between sections and some sections could be contracted.	Comment acknowledged
The use of the term children generally is confusing for those who attribute that to certain age	Agreed. The use of terms has been clarified throughout the document
On the whole we find these 'ethical considerations' acceptable provided some recommendations are improved in order to meet public health demands and 'additional protection' of children involved in clinical trials.	Comment acknowledged
"Adolescents" missing	Added
This is useful guidance, which will assist trialists working across European borders in knowing the different ethical and regulatory expectations they will be working to in different jurisdictions, and also clarify for them what EMEA expectations are for licensing trials for medicines for children. This is consistent with ICH GCP guidelines in this area. The guidance here is rather more guidance than clear legal advice or prescriptive rules. We would welcome something more prescriptive, in the interests of researchers who want clear rules, and in the interests of the harmonisation of European regulation of medical research, however, it also recognises that the EMEA cannot run ahead of European legislation, and that there remains controversy over the ethics of trials in people unable competently to give consent on their own behalf in the European Convention on Human Rights and Biomedicine's research ethics protocol.	Comment acknowledged, no specific change requested
Throughout the recommendation there are various statements that are not specific to trials in children, but rather are general legal, regulatory, or GCP requirements for all trials in any patient group. While there may be reasons why the authors want to stress the importance of these general requirements for paediatric trials, this is also distracting and makes it difficult for the reader to focus on what is special for trials in children.	Comment acknowledged and amended, where possible, and kept, where thought to be of importance

Since it is a matter of fundamental rights, the respect of which constitutes, in value systems recognised in Europe, an indivisible obligation for the public authority to fulfil, the purpose is to ensure that the powers attributed to the Union by the Treaties are clearly limited by respect for the specified rights, and that each person legally implicated on Union territory may rely directly on these rights. The Union's field of competence is not affected: it is a question of ensuring that by its action the Union does not infringe on the enjoyment of fundamental rights, regardless of what they are, most of all because these international/European sources could have judicial effect, on the basis of the discretion of the courts (CJCE, CEDH and national ones) to 'refer' to its content. In this sense, it seems important to highlight that, annually since 2001, the European Parliament has drafted a detailed report on fundamental rights in the EU, assessing the respect for the rights laid down in the EU Charter, based on different international sources of information (United Nations, the Council of Europe, the EU institutions, ECHR and EC Court of Justice case law, Member States laws, relevant NGOs, etc) and to which citizens are allowed to have access. On the other hand, it is important to underline that the European Court of Human Rights (CEDH) may give, without direct reference to any specific proceedings pending in a court, advisory opinions on legal questions concerning the interpretation of the Convention on Human Rights and Biomedicine. Furthermore, the Universal Declaration on Bioethics and Human Rights (UNESCO), in the article 27, related to limitations on the application of the principles, specifies that: "If the application of the principles of this Declaration is to be limited, it should be by law, including laws in the interests of public safety, for the investigation, detection and prosecution of criminal offences, for the protection of public health or for the protection of the rights and freedoms of others. Any such law needs to be consistent with international human rights law".	Explanations and comment acknowledged, no specific change requested or deemed necessary
Moreover, it should be pointed out that the document should also focus on the racial and ethnic groups. They comprise important populations whose special needs and drug responses traditionally have been uncovered (for instance: significant differences in rates of drug metabolism, in clinical responses to drugs, and in drug side effects due to genetic variations). These patients, especially those from minority groups, need individualized care since the evidence shows that drug effectiveness and toxicity can vary among racial and ethnic groups. In particular an important reason to include minorities in paediatric drug studies seem to be to examine the effect of ethnicity on the disposition and effects of drug (VJ Burroughs et al). In addition we suggest the document should include more information about the follow-up during the development of the trial (visits, complementary invasive and non-invasive explorations).	Acknowledged and wording added to section 9
Consider a section on ethical considerations when enrolling children in a Compassionate Use Program or on a Named Patient Basis	Same ethical principles apply
Consider discussing when long-term safety studies should be performed in children	This suggestion has been taken up by adding remarks to several sections Covered in other documents (e.g., paediatric pharmacovigilance guideline)

General term “legal representative” should replace the term “parents” wherever possible. Wider category (LR) covers all possible cases. In the current version both terms are sometimes used interchangeably. Include in the guidance	The word “parents” is important to keep in fact, these are the legal representatives most of the times. See outcome above
Complex grammatical structures make the text of the guidance difficult to understand at times and therefore it is suggested that guidance be a subjected to a linguistic revision	
What happens if parents want to withdraw and child wants to stay?	See above consent and assent
The ‘annual safety report’ mentioned in the following sentence: “specific assessment of the adverse reactions associated with the administration of the investigational medicinal product in children should be performed in the annual safety report”, shall be made public in agreement with article 41.1 (second paragraph) of Regulation 1901/2006 on medicinal products for paediatric use.	Annual safety reports are not covered by Article 41 of Regulation 1901/2006 (explicit reference to studies as opposed to data). Public access to safety data covered in other documents.
Add a list of abbreviations	Abbreviations have been clarified
Table: Whilst we feel that the provision of a summary of the different positions across all EU states would be a helpful addition to the guidelines, the table in Appendix 1 is currently misleading as the questions are vague and may have been interpreted differently by different responders. It would be preferable to have more extensive responses rather than restricting to yes or no answers.	Comment acknowledged. The answers were compiled for overview.

SPECIFIC COMMENTS ON TEXT	
Comment and rationale	**Outcome**
1. TITLE AND INTRODUCTION	
The title of the document refers to 'Children' whereas the Directive 2001/20/EC refers to 'Minors'. Alternatively, the term ‘paediatric population’ could be used, as in ICH E11 Suggested wording: Ethical Considerations for Clinical Trials performed in Minors.	Acknowledged, title changed. The recommendations will not be able to reconcile the differences in wording of the various texts.
Include guidance on the fact that, if a disease also occurs in adults, sufficient safety and efficacy data should first be collected in adults to support testing in the paediatric population.	Already stated in several places, e.g. section 1
Add "on medicinal products" to title, change "in children" to "with children" The document will be consulted by ethical committees, researchers, etc., in Europe and worldwide, from different areas, e.g. clinical nutritional trials, devices, etc. and are not used to EMEA bureaucratic language. They should understand the scope of the document by reading the title.	Comment accepted and included in title.
Ethical Considerations for Clinical Trials in Children Paediatric Populations	Acknowledged
Stress rationale, external sources and other guidances	Acknowledged, and amended
“This document is intended to provide guidance on the various aspects of ethics in relation to the performance in children (minors) of the age defined according to national regulations on the legal age of adulthood, (...)”	Acknowledged, amended accordingly
Suggested wording (or something similar): "Because of the special protection they deserve, children should not be the subject of clinical trials without careful consideration and special precautions."	Section has been amended with a slightly different wording

Add Reference to the ICH Guidelines 6 and 11. Clarify fact that ethical considerations should not only apply to European research, but also to participants recruited outside of the EU or EEA. Clarify fact that minors should be able to refuse assent	Acknowledged and changed by adding references to related sections
Need clarification or adding of minors, preterm, children and adolescents	Age-related terms clarified in several places
The point was made that we understand this document is not considered by the European Commission to be legally binding, rather a document for the consideration of ethical issues. There was considerable concern about this as the protection of paediatric trial participants from harm is essential to their well being.	Comment acknowledged Such recommendations cannot be legally binding.
Definition of "children"	Term "children" has been clarified
If clinical trials could be done with adults, and give enough data in children, then, there is no need for paediatric trials.	Agreed. This principle is expressed in several sections. Comment not included as such
Add the Guideline on Clinical Trials in Small Populations CHMP/EWP/83561/2005	Guideline is cited
In general, very young children are unable to consent but all children under the age of majority (minors) should give as fully informed assent as possible	Acknowledged, no change required
There must be a balance between protecting vulnerable children from unnecessary or inappropriate clinical trials and the requirement to ensure that medicines are adequately studied in all appropriate age groups. In the past extrapolation from studies in adults to treatment in children has been widespread and there are many examples of adverse effects. Methodologies such as population pharmacokinetics with sparse data analysis should be used where appropriate to allow smaller numbers of participants and fewer invasive procedures than in standard pharmacokinetic studies. Studies involving fewer children or more children but using less invasive procedures should be undertaken. The onus is on the investigator to demonstrate that the appropriate methodology has been employed and that evidence of this is provided.	These aspects are covered in several sections down the recommendations in more detail than in the introduction section. Proposals have been included as relevant in sections 9.1 and 10.
The statement "Growth and maturation processes, as well as specific diseases are not found in adults." does not appear to be correct in this generality. For instance, some kids may still grow beyond age 18, there may be tumour growth, psychological maturation may occur at all ages, and there definitely are specific diseases that occur only in adults.	The examples provided are acknowledged, however growth and maturation are essentially a characteristics of children. Wording slightly amended
2 SCOPE	
Experiences with the EU Directive on the implementation of GCP suggest that the "sponsor" should be clearly defined. We would therefore suggest it is stated that the principles of this guideline are meant to apply to both commercial and non-commercial sponsors.	"Sponsor" is defined in other documents. Not a paediatric issue. Scope amended to include references to non-commercial and commercial trial
"The recommendations in the document aim to contribute to the protection of the rights of ~~children (minors)~~ individuals within the paediatric population who are vulnerable, in particular for minors who are unable to give informed consent."	Agreed

Statement: "The recommendations in the document aim to contribute to the protection of the rights of children (minors) who are vulnerable and unable to give informed consent." What about children who can in fact give informed consent? As stated, this sentence implies that all children covered by the scope of this document (0 up to 18 years) would not be able to give informed consent, which is not necessarily true.	Accounted for in several places
"Scope" should include children and parents	This and further stakeholders included
Nothing mentioned about children with special needs	"Special needs" has now been mentioned. Principles and recommendations do not change for this sub-group of children.
Add reference to CESP guidelines	Already cited.
3 ETHICAL PRINCIPLES	
The Belmont report's principles should be quoted in correct order and should be put into context. It's scope is all biomedical and behavioural research performed on USA territory. It was published 1979. In the following decades, the meaning of the principles' wording has fundamentally changed.	The order was changed accordingly. See comment above
Delete the paragraph referring to the so-called 'Belmont principles'.	Not agreed
"Belmont Principles" should be described or listed	See comment above
The Recommendations is a really satisfactory document, which is comprehensive, detailed and written in clear and concise language. Nevertheless it seems useful to propose an integration of these recommendations at the light of some international/European legal/ethical sources. For instance: the Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (2005), the Charter of Fundamental Rights of the European Union (2000), the Universal Declaration on Bioethics and Human Rights (UNESCO, 2005).	Comment acknowledged, wording added to section 3 (and further references added to section 26 Annex 2)
4 Legal context	
Add: EuroSOCAP Guidance for Healthcare Professional on Confidentiality and Privacy in Healthcare (Brussels, 2006) and European Standards on Confidentiality and Privacy in Healthcare (Brussels, 2006) for specific ethical guidance for confidentiality and privacy in research performed on children	Now included
5 Definitions/Glossary	
In my opinion, the definition of "minor" in this guidance document needs to be further considered as it will affect both the consistency and interpretation of the guidance provided.	The definitions have been clarified and the use of the term "minor" has been revised for consistency

The opinion of patient representatives and parents, especially of parents of children with the given disease is crucial. If they are not represented as members, they should be heard as experts.	Members of Ethics Committee may be parents and as such are part of Ethics Committee. Paediatric expertise has another meaning (medical or healthcare). Parents and patients' representatives may be heard by Ethics Committee. Their role is in our view even more important at the stage of designing trials.
It should be clear that the consideration is with regard to the 'legal representative of the child (minor)'	Changed accordingly in several places
Children: a chapter to be inserted because this note for guidance addresses children more than minor. Legal texts take care of minor legal issues	Children defined in amended text.
In most clinical trials performed in children, the legal representative will be one or both parents, as commonly observed in practice.	Agreed, one or both parents will have to consent according to national law.
Revise section	Section was revised in several places
Definition of Minor?	Definition section amended in several aspects
Add "legal Representative" and reflection on "presumed will" and gifts to physicians	Added, and section expanded on presumed will
Discuss the notion of "presumed will" in young children? (CTD Art. 4 (a))	Proposal included
"Assent" is not "the child's will", but rather "the expression of the child's will"	Not agreed. Consent is the expression of the child's will.
"The capacity to make voluntary, informed decisions <u>for a child</u> (that is, to assent) evolves with age, maturity and previous life experience"	Agreed, amended in a different way
If one requires a written consent, it would be good to combine the child's wish or to resorting to a consensus decision between parents/ legal representative and the medical staff if the child is in age of understanding and especially if the wish of the child is negative.	The assent of the child should be documented and has been stated. The consent must come from the parents, but taking into consideration the child's wish. The medical staff is only there to inform but not to take part in decision making.
There is a lack of detail regarding the consent forms to be used in paediatric studies. There should be a need to clearly and unambiguously record the names and also to record sufficient details of the relationship of the person signing the consent form to the child. Whether they are a parent, aunt, uncle or guardian should be clearly recorded on the consent form. The fact that the person signing has the same surname as the child means nothing, especially where common names (e.g. Jones in Wales) are in use.	Acknowledged and added to section
Age groups not clear. Why not split the document according to patient's age: assent for child under 12, simplified or not consent for adolescent	The age groups have been clarified.
We agree that the ability of children to understand their participation in a clinical study will depend on their age and/or maturity, but the ICH guidelines referenced in this section does not address cognitive development and only addresses physiological development in relation to drug handling. A clear distinction needs to be made between physiological and cognitive maturation.	Section 5 has been restructured to emphasize on cognitive maturation

6. Informed consent	
Writing by parents on the informed consent form, e.g. "My child has understood the information … and gave oral assent."	It is preferred to have the child assent recorded directly (if possible). In infants/children who can't write, parents may write such a statement.
Change "revoked at any time (parents and legal representative need to be involved" to "revoked at any time parents or legal representative indicate so". Change "(b) the minor " to "(b) the minor and parents"	Not possible as this is a Clinical Trials Directive (CTD) recital
The order of consent and assent within this document and the general ethical framework the ordering gives rise to is questioned. The current ordering suggests an overriding legal concern that threatens the heart of the ethical concern: the articulation and expression of the will of the child.	The order of the sections does not imply a primacy Process clarified to emphasize the requirement for the consent to reflect the child's presumed will.
Change the order of Assent and Consent in the document, to reflect that the will of the child should come first.	Addressed above.
Company agrees that having both parents involved offers the best protection to the child, but seeks more guidance on how to handle situations where both parents are not readily available, e.g., in case of divorce. The guideline could be interpreted as meaning that involving one parent is acceptable, even when both are available. Define 'parent' as meaning 'both parents', if both are available. Provide more guidance for specific situations, where there are 2 parents but they may not both be readily available, e.g, divorce.	Brackets removed from "parent(s)/legal representatives" for consistency with CTD. Legal representation is defined in national law and differs in the various Member States. Added sentence on good practice to include both parents even when not required by national law
"Information should be given by an experienced Investigator …" It should be specified what kind of experience is referred to.	The evaluation of the 'experience' of the investigator is in the remit of the Ethics Committee. See also definition of expertise/experience in the text
The requirement that there must not be any financial inducement to enroll a child in a clinical trial other than compensation of expenses and time spent is more restrictive than the usual approach in the US	Confirmed. Requirement from the Clinical Trials Directive
Rewrite for clarity and additional phrase on possibility of discussion with parents of emancipated child	Not agreed. Adult patients (in this case emancipated adolescents) do not need parents' consent and may not agree to disclosure.
Parents/legal representatives need to consider more than simply 'benefits and risks'. Full operational guidance for informed consent/assent is needed.	Included, although phrased differently
There is no requirement in 2001/20/EC that the informed consent of the parents/legal representative needs to be obtained in advance of the assent of the child.	Acknowledged and process changed accordingly
Rewrite to: "The health interests and the will of the child should be carefully considered in the consent procedures by both the researcher (investigator) and the parents/legal representative. Where appropriate and to the extent possible, the assent of the child should be sought, in line with Article 4 (a), (b) and (c) of the Clinical Trials Directive."	Principle agreed, already mentioned in several other places
It was agreed that informed consent to legal representatives of children should perhaps be more extensive and detailed than it might be for adults consenting participation in clinical studies and more time should be given if possible for the legal representatives to consider the information.	Agreed Section has been expanded on especially in terms of the time needed to understand the information and the type of information given.

When the child can sign his/her own consent? "Gillick" principle	This case law related rather to medical treatment. Age of consent is defined in national laws
What will happen if parents can volunteer their children for non-therapeutic research?	Although the document addresses interventional trials, the scope acknowledges that the principles are the same.
Change before to after in the text: "Consent should be obtained from the parent/legal representative **after** assent is sought from the child".	This recommendation has been acknowledged and process changed to recommend that consent and assent should be obtained simultaneously. Other comments objected to investigators seeking assent of the child before informing the parents.
Adolescents participating in a trial and having genuine arguments against the parents knowing this, should have the possibility of not having consent of the parents. This should be mentioned more stringent in the text then the current wording.	Not included as this may go against the national legal requirements. In addition, the parents should know about the minor's participation in a trial of a medicinal product for safety reasons.
A definition of "emancipated" should be provided.	Acknowledged and definition provided
It should be made clear that declining to participate in a trial (in addition to withdrawing from a clinical trial) will not prejudice treatment.	Acknowledged and added accordingly
"no financial incentive should be offered (other than compensation of expenses and time spent)". The CT Directive does not specify that the compensation be for "expenses and time spent". Also, this requirement has been implemented differently in the national regulations of the Member States. For instance, the UK regulation specifies "No incentive or financial inducements … except compensation in the event of injury or loss." The Spanish regulation limits compensation to "extraordinary costs and loss of income through participation in the study." The German drug law only states "except adequate compensation", without further defining "adequate".	Comment acknowledged and sentence split to more literally cite the directive and to include the respective recommendations.
Why is it required here that the child's assent be only obtained after the consent of the parents? The CT Directive does not specify a temporal sequence in Article 4 a, b & c. (e.g. Article 4 f – h definitely need to precede a – c). Furthermore, asking for the child's assent only after the parents have already consented might be experienced as coercive by the child. Wouldn't it be preferable to inform both parents/legal representatives and the child first and then obtain consent and assent simultaneously after they had a change to discuss and agree on participation?	Comment acknowledged. Changes put in several places in order to clarify that in any case the child should not be addressed first in a discussion on the trial.
The written form of consent of parent(s)/legal representative is provided for by the Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (art. 15, sec. iv). For the expression "specific" see art. 16 of the Convention on Human Rights and Biomedicine and its Additional Protocol (art. 14)	Reference added
There is no mention of providing a fully translated informed consent to the parents of the child and to the child (if obtaining assent).	Acknowledged, however translations into multiple languages may not be realistic. Need for translator in this situation. Added to Annex 2
Suggest to replace "problems" with "considerations"	Acknowledged, changed to "differences"

Change “A cultural mediator” to “A cultural mediator familiar with medical terminology”. Change “Ethnic problems” to “Ethnic differences”	Included
Change the word “problems” in ethnic problems to “specificities”	Acknowledged and “problems” changed to “differences” in line with other comments
“a cultural mediator … should assist” - realisation?	Comment acknowledged. No change requested
Change title to “Informed consent (and assent for children) of immigrant families with different cultural background”	Acknowledged
Consent or assent is a dynamic, continuous process. It must be sought at the beginning and must be maintained during the trial. Company assumes this is referring to more than simply the fact that the subject (parents / child) is to be informed of any new information that becomes available but that there is truly a request to monitor whether the consent / assent is still applicable. During the trial, the investigator will continuously verify if the patient is still willing to continue in the study. Questions for further specification would be around frequency of rechecking the consent / assent, around how to document and around what to in case of a change in legal representative who withdraws consent. Provide more guidance on what is meant by ‘maintained during the trial’, e.g., frequency of re-consenting, how the ‘maintenance of consent’ is to be documented.	Acknowledged, section amended
It may be helpful to expand on these recommendations by addressing the issue of re-consenting when the child reaches the legal age of consent	Covered in section 7.1.3
Clarify monitoring of assent and consent	Acknowledged, wording in this section has been amended
This paragraph needs some clarification, especially the sentence “Consent or assent is a dynamic, continuous process”. How would this be ensured?	The paragraph has been amended
Why is a new consent required when there is a change of the legal representative? Shouldn’t it be sufficient to inform the new representative of the right to revoke the consent? A new consent might be required from the subject, though, if the child reaches the age of consent during participation in the study. Change to: “In the case of a change in legal representative during the trial, the new representative should be informed about the trial and the right to revoke the consent as soon as possible.”	In such a situation (e.g. following abuse) the new legal representative should be asked to consent. This is also considered good practice.
Investigators should devote sufficient time to provide information, and seek express and specific legal representative(s)’ consent as well as child’s assent, in accordance with national law.	Acknowledged

"A child should not incur any disadvantages in medical care if consent is withdrawn. The same level of care and information should be maintained during treatment or investigations." Read literally, this proposed statement may not reflect the reality that, in resource-limited settings, the quality of care may be better while participating in a clinical trial where the treatment regimen and environment are closely controlled and monitored. It is therefore important that the guidance be clear that either a refusal to participate, or a decision to withdraw, in a trial should not result in a penalty or loss of benefits to which the child would otherwise be entitled had the child not participated in the trial (or been offered the opportunity to participate). Should be reworded to ensure proper interpretation, in line with ICH GCP 4.8.10.(m): A paediatric subject should not incur any disadvantages in medical care if consent is withdrawn. Refusal to participate, or withdrawal from the trial, at any time, should not result in penalty or loss of benefits to which the subject is otherwise entitled.	Agreed. This is already expressed in the recommendations
It is not really advised how to handle cases when obtained child's assent is withdrawn by the child while parents/LR consent has not been withdrawn.	Covered
However, it should be checked that the withdrawal is not the results of the parents/legal representative's own convenience.	This comment was not included, as according to ICH GCP the parents do not need to give a reason for withdrawal.
It is acknowledged that legal representatives are allowed to follow research, however in case of blinded trials this might influence the blindness. Therefore the following sentence should be added: "In case of blinded trials or in case stopping rules are formulated it should be discussed how and when the legal representative could be informed without provision of the actual data."	The legal representative would have been informed of what a 'blinded trial' means. The comment has been used to emphasise the same point for after withdrawal.
"Withdrawal of the ~~informed~~ consent"	Acknowledged
Not incurring any disadvantage in medical care, if consent is withdrawn may not always be possible. For instance, in case that there is no alternative accepted treatment other than the investigational treatment that offers an at least equal chance of saving the subject's life or health, withdrawing the consent and consequently the experimental treatment will definitely be of disadvantage. Also, discontinuation of diagnostic procedures that were for the trial only and are not part of standard care can be of disadvantage. More general disadvantages could be that medications, treatments, or diagnostic procedures that were provided for free during the study may require payment or co-payment after consent is withdrawn. A child should not incur more disadvantages in medical care than is necessarily caused by the discontinuation of investigational treatment, if consent is withdrawn. The same level of care and information should be maintained during treatment or investigations, <u>except for procedures that were conducted for investigational purposes only</u>.	Agreed. Already mentioned in various sections. It should be noted that there should be genuine uncertainty (equipoise) at the beginning of an interventional trial; this differs from medical care.
For the expression "freely withdraw" please make reference to Convention on Human Rights and Biomedicine art. 16, and its Additional Protocol on Biomedical Research art. 14.	Acknowledged and added in several places

For the necessity to make reference to the best interest of minors, please see the Convention on Human Rights and Biomedicine, art. 6, section 5, related to Protection of persons not able to consent.	Not included, as the notion of "best interest of minors" refers to medical treatment
Change to "Parent(s)/legal representatives should be reassured that the withdrawal from the trial will not cause disadvantage or prejudice to the child."	Acknowledged
Add "Refusal to give consent or withdrawal of consent to participation in research shall not lead to any liability and/or to any form of discrimination against the person concerned, in particular regarding the right to medical care."	Acknowledged
This could be a sticky point, we have provisions for administering drug to adults in ER situations?	This section refers to trials, not care. No change requested
Should there be some clarification on what constitutes emergency research, and how it should be reviewed and approved?	Acknowledged, clarification added
Clarify if emergency trial legislation applies to children	There is no European legislation concerning trials in emergency situations as the CT Directive requires prior informed consent. There is however an ethical need to perform research in emergency situations in children (as in adults) Covered by table in section 25 Annex 1
'Retrospective' consent is legally not possible in the UK	Acknowledged and amended
If a trial has been accepted by the MEC (Medical Ethical Committee) in case of emergency trials when it is not possible to obtain prior informed consent from the legal representative(s), the consent will be obtained by the approved protocol. This should be mentioned more stringent in this section. As a consequence, the sentence "Including a child into a trial without prior consent of the legal representative(s) would be a major concern" should be changed. The sentence "As for non-emergency… these situations" should be re-worded as this suggests that participating benefits the child, this is not ethically correct.	Comment not included, See above. The protocol cannot grant consent. The sentence has been clarified.
The guideline should encourage national authorities to stimulate a debate (to include patients and patient groups) in individual EU countries about informed consent in emergency situations.	Agreed. Not included as this proposal cannot be addressed by the recommendations
Areas of current controversy: Trials of emergency interventions. These are somewhat controversial in all cases, since even competent patients may not be fully competent to consent in situations which are time critical and they are under stress. The guidelines here are relatively clear and consistent with such consensus as exists. The guidelines should probably refer to "trials of emergency interventions", give examples, and set conditions on what is to count as an emergency, as per the US FDA and NIH Federal Regulations. It is not helpful to talk about "emergency trials", since this is ambiguous in meaning between "trials of emergency interventions" and "trials which are initiated and conducted as a matter of emergency" (possible example: may be small pox vaccination post a bio-terror attack).	Acknowledged improvement of heading. Emergency has been defined in section 6.6.

In emergency trials, in which a child might be included without parent/legal representative consent, obtaining the child's assent only after the parents'/legal representatives consent has finally been obtained could be detrimental for the child's health, if the child should not wish to participate in the trial. The resulting switch back from experimental to standard treatment or delay of the start of standard treatment that could have been avoided if the child would have been asked in the first place could be of serious disadvantage for the child's subsequent treatment. **Change** "Assent should be obtained once consent is granted." to: "In emergency situations, in which parent/legal representative consent cannot be obtained before the start of the investigational treatment, the child's assent may be obtained before consent is obtained, and should be obtained as early as possible in order to be able to respect the child's wish of not being included into the trial."	Assent from the child is required in the recommendations and if it can be obtained in these situations, it should be sought.
It seems, thus, necessary to modify following paragraphs in order to assure that, given the lack of specific provisions in the Directive 2001/20, emergency situations shall be effectively regulated in accordance with national laws, only where existing.	Acknowledged
7. Assent from Children	
From the appendix (table) one can see that there are very few countries that have legal provisions on this topic. So for all other countries, the only guidance provided is that these differences must be understood and respected. This leaves us still with no concrete guidance on this key area. This document gives no guidance around 'if the child says no and the parents say yes', except for the sentence at the end of section 7: "The child's will should be respected provided it is not considered detrimental to his health." It is not clear what is the recommended approach when the legal representative provides consent but the child specifically does not assent. Our interpretation of the guideline is that the trial should not proceed but a less ambiguous statement could be made.	A more explicit recommendation has been given for these situations.
Rewrite as this is true in a curative situation but not in a research protocol where rarely it will benefit the child: "The child's will should be respected ~~provided it is not considered detrimental to his/her health~~ especially if non-assent results"	The trial is required to bring about benefit iether to the individual or the group, and the existing wording ensures protection

This section is central to the ethical justification for involving children in clinical trials or any sort of medical experimentation. The section stresses far too highly the legal considerations, without clearly stating the primary ethical considerations. Suggest a full rewrite of this paragraph: "A child under consideration for participation in clinical trials as a research subject should be, according to given age and maturity considerations, fully informed of the research, what his or her involvement means, any discomforts or pain that might reasonably be expected, the risks and potential benefits, his or her alternatives to treatment outside the research proposed, and his or her right to withdrawal from the clinical trial at any point. The child should be carefully listened to and, as appropriate, his or her assent sought. Should the child's assent be withheld, this should be fully considered and respected, unless overriding interests in the health of the child are at stake. This process should be conducted in conjunction with the informed consent process undertaken with the parent(s)/legal representative. The central place of the child and his/her will should be fully recognised throughout the processes of assent and consent. The Clinical Trials Directive (see section 5.5 for relevant provisions from the Clinical Trials Directive) requires that the minor's will be 'considered'. While it is not a legal requirement that the child's will be determinant, it is recommended that the investigator obtain and document the child's assent (in age appropriate manners) in addition to the informed consent of the parent(s)/legal representative. If the child's assent is not provided and documented, this should be recorded in the consent form signed by the parent(s)/legal representative and investigator, with the reasons. The child's assent is not sufficient to allow participation in research unless supplemented by the informed consent of the parent(s)/legal representative. The process of informed assent should be designed in age appropriate manners that permit, to the extent possible, the child to understand and express his or her will with regard to the research. This process should included separate information sheets as well as assent and consent forms that are age appropriate. Informed assent forms should be age appropriate and should include full information as described above. The information provided to the child should be given in language and wording appropriate to age as well as to psychological and intellectual maturity. Assent, like consent, is a continuous process and should be sought during the trial as well. Objections raised by a child at any time during a trial should be considered and respected, unless they are seen to be detrimental to the health of the child. The child's objections should be recorded and, if not acted upon, the reasons for not following the will of the child should also be recorded. The child should not be required to provide reasons. The parent(s)/legal representative's consent should be checked. The child should be informed of the possibility to withdraw from the trial."	There should be no detriment whatsoever associated with not taking part in a trial. This principle is paramount for clinical trial ("equipoise"). We agree that in principle the child's assent must be obtained and respected.
Further guidance should be given on how best to judge the capacity of an individual child to be able to provide assent.	Acknowledged and commented on in section 7.
Consideration has to be given to the child's ability to withdraw assent and how this can be facilitated to enable the child to freely give and withdraw assent without penalty.	Acknowledged, wording in this section has been amended

It was felt that is a child who was able to give assent should be able to refuse assent and that this would be binding in the setting of a clinical study. (Amongst other comments)	Acknowledged
"If the child's assent is not collected, this should be recorded in the consent form signed by the parents/legal representative and investigator, with the reasons". This should not exist, otherwise we are in legal issues but still not dealing with ethics.	In infants for example assent will never be collected. Child here meant any age group.
There is insufficient emphasis on involvement of the child patient whenever possible. Whilst the central role of parents (or other legal representative) must be recognised so must the rights of the child to participate at all stages according to their level of understanding.	This has been emphasized in several places
Add section "Assent in non-interventional trial"	Recommendations are intended for interventional clinical trials (in line with the CT Directive).
The requirement of the 2nd sentence to start the assent process only after obtaining consent from the parents appears contradictory to the requirement of the first sentence to respect the child's emerging maturity in discussion and the decision-making process. Delete the first 2 sentences.	Acknowledged and changes in process, as noted above
We agree that a number of information sheets should be used in order to provide age appropriate information. However, this needs to be interpreted rationally and in the light of the experience of clinical researchers and the views of the patients and families themselves. It is easy for ethics committees to require a large number of different narrow age bands for information sheets, yet there is little evidence to recommend where these cut-offs should be. Indeed, we note with interest the comment in the penultimate paragraph, page 11 (7.1.2) that "Most children are unlikely to understand randomisation, as indeed are some parents". Ethics committees should avoid the creeping tendency to demand large numbers of age-specific information sheets. These should be developed in conjunction with researchers and parent/patient advocates, to ensure they are 'user-friendly' and do not cause unnecessary distress at a stressful time, e.g. at time of diagnosis of a life-threatening illness in the child. We would like to recommend that a limited number of standardised age band requirements for patient information sheets be used across Europe. This will facilitate collaborative multinational clinical trials that are essential for rare diseases in children.	Comment acknowledged, wording added to section 26 (Annex 2)
Change "The child's assent is not sufficient to allow participating in research unless supplemented by informed consent of the legal representative, only if in accordance with national laws providing for specific regulations."	Already covered elsewhere
In order to guarantee the transparency of clinical trial development as well as to be sure that children assent be "really informed", it seems important to better specifies conditions of information, …	Is now covered in section 26 Annex 2
Suggestion to use a questionnaire-like form for documenting adolescent assent	Noted
Children of age 3-4 and children until the age of approximately 14 may not be able to understand and to consent or assent. We know that there is no solution to that problem, but we should not give the impression that these theoretical notions are applicable in practice.	Disagreed. Understanding in our view is present before the age of 14. Seeking assent is strongly encouraged and actually required by the Declaration of Helsinki.

This chapter could be rearranged in order to be in coherence with paragraph 5.6, and it is welcome to add subsections, because a child of 4 is not like a neonate nor a 6 year old is like an 11 year old one. Indeed, a child before 6 is able to express its wish. And thereof should be taken into consideration.	The text in this section has been changed according to age ranges and takes the comments into account.
In the UK there is considerable regulation and case law on assent and consent to treatment. In some situations a child's consent or refusal may take precedence over that of their parent or legal representative. EU guidance should take such regulation and legal judgements into account and recognise that this may vary between Member States.	The recommendations only refer to assent and consent to clinical trials, not to medical care
Although neonates are particularly challenged to understand the conditions around them and cannot easily express their will, it is necessary that the will of the child, nonetheless, be addressed and listened to, to the extent possible. Rewrite as follows: "The child's capacity for understanding (neonates, pre-school children, included) should always be addressed with age-appropriate information and any expression by the child with regard to the proposed research should be fully considered and respected. The processes for informing the child and seeking its assent should be clearly defined in advance of the research and documented for each child invited into the research. While assent may not be possible in all age groups (e.g., neonates) or in all research conditions (e.g., emergency research), the information process provided to the child and the child's response should be recorded."	Agreed. Part on pre-specification and documentation of information processes included
There is no legal requirement to put consent in advance of assent, nor is this ethically or practically appropriate in most cases.	Acknowledged, process modified, see above
Move pre-school children section from 7.1.1 and put in 7.1.2	Acknowledged and changed with this intention
Change "It is recommended to obtain assent once consent has been obtained according to national law and as soon as possible" to "It is recommended to obtain assent as soon as possible even if parent/legal representative consent cannot be obtained before the start of the trial".	Agreed
… written consent of the child should be sought from 6 or 7 years. Note that ICH E6 does not mention ages (the last sentence of 7.1.2 could be ambiguous). Even if the child can write at 6, does the fact to sign a form have significance for him. At this age, we could provide him with a information leaflet which explains what will happen with very simple words. A position paper published by the LEEM (french organisation of the pharmaceutical industry) in 1993 recommended to request signature from 13. This paper made also a reference to spanish law which required child written consent from 12 years. Anyway, an advice from a legal person is useful to determine from which age it is relevant to request child signature.	We believe children can understand the meaning of signature before adolescence. It is not clear how a 'legal person' can determine the child's maturity. For legal requirements, this is expressed in national laws.
Difference of opinion between child and legal rep- the wording is not strong enough in saying national regulations should be followed where they exist- in Appendix 2 very few countries actually have regulations to cover this, so where does that leave a Sponsor if disagreements occur.	Paragraph has been amended
Absent a uniform interpretation of ICH E6, it may be difficult to create a brief guidance about what "respecting assent" means in the context of research.	Acknowledged, this section only addresses differences in opinion

The primacy of the child should be emphasised here along with the role of the investigator/paediatrician.	Investigators or paediatricians do not take part in the decision-making. They are informing the parents and the child.
For some clinical trials conducted in third (non EU) countries, considerations may need to be provided for cultures / countries where child assent is culture-dependent, i.e. all societies may not grant the same importance to the opinion of children, and this may therefore impact on the collaboration of legal representatives in clinical research. It is suggested to add: "Socio-cultural or ethnic conditions which may impact on the meaning of assent in given populations should be described in the protocol and presented to the ethics committee, which can take these factors into account to decide on the best approach to obtain assent."	Acknowledged. The same ethical principles however should apply to trials performed outside the EU. AAddressed in section 23 by requesting for example ethical opinion from a EU Member State (e.g. where the sponsor resides) for trials to be used for regulatory procedures.
Needs more clarity and guidance on what to do in such situation. It was strongly felt that if there is not unanimity of opinion, the trial should not go ahead	This is acknowledged and added to the recommendations.
This chapter has the virtue of giving the possibility to develop the various cases and to discuss the fact that the wish of the child should be very much taken into consideration in the parent/legal representative decision. Adolescents should be also discussed here. This paper should be careful to not be a legal paper, but as intended, an ethical one.	This comment has already been included.
Whenever parents do not understand randomization, we propose that children should not be enrolled	Whenever parents do not understand the information provided on the trial informed consent cannot be obtained . However, parents are not and cannot be expected to understand all technical aspects (such as randomisation or complex statistical analysis).
If the adolescent is emancipated in accordance with local law, there is no need for consent of parents or legal representative and the consent of the adolescent should suffice.	Acknowledged, clarified
"When an adolescent ceases to be a minor, informed consent should be sought." An adult must provide informed consent.	Clarified
"A legally emancipated child/adolescent is, in accordance with national law, able to provide informed consent. Seeking additional informed consent from parent(s) may be done only with the permission of the emancipated child/adolescent. In the case of a child who is also a parent, that child may only consent to research on his or her child in cases provided by national law (e.g. an emancipated child/adolescent). In all cases, nonetheless, the child-parent should be fully informed of the proposed research and his or her assent sought."	Partly included
Rewrite as follows: "When an adolescent enrolled in an ongoing clinical trial ceases to be a minor, informed consent should be sought from the research participant. The informed consent of the parent(s)/former legal representative is no longer required and may only be continued with the agreement of the minor who has become an adult."	Rewritten in another way
Consent in adolescents (still minor according to legal law) so remove the word "assent"	Assent is the correct word in most cases

This guideline should very strongly recommend that the consent from adolescents is sought, because adolescents are probably the most difficult age to deal with. Both the will of an adolescent should be taken into consideration since the maturation of the 'child' is almost fully acquired, and at the same time, an adolescent could show any off behaviour and refuse any kind of help. This should be discussed case by case, since only if a surviving chance might be lost, the parent's wish should prevail over the adolescent's wish.	Consent (legal meaning, see definition) may be obtained only where national laws allow. Discrepancy within Europe
Maybe both consents from the 'emancipated child' (very inappropriate word!) and from the parent/legal representative should be sought.	See above
"As soon as" an adolescent ceases to be a minor during course of his/her study participation, informed consent should be sought.	The words "as soon as" have been added to the text.
We propose that consent should be obligatory in adolescents.	see above
In this section the more stringent wordings "adolescents should be able to consent into a trial with confidentiality without informing the parents" should be used.	see above
According to German Law, an adolescent parent would have a legal representative to give consent to the trial. The adolescent could only give assent.	Reference to national law is included
The emphasis on preterm neonates in the parentheses is unclear. Precautions to ensure that information is sufficiently understood should be taken in all situations where consent is sought from an adolescent. Delete "(particularly preterm neonates)".	Pregnancy in adolescents may result in premature births.
8. ETHICS COMMITTEE'S COMPOSITION IN RESPECT OF PAEDIATRIC TRIALS	
We agree that ethics committees need paediatric expertise but its not necessary for that expertise to be in the form of a permanent member of the committee but on an ad hoc basis.	This is stated in section 8, no change requested
It may be useful to specify that the requirement for appropriate paediatric expertise only applies to the Ethics Committee providing the single opinion, as per Directive 2001/20/EC (Article 7), and not to any additional, local Ethics Committees.	No changes. Expertise is needed for any EC opinion.
To be in line with CT Directive 2001/20/EC, the term 'significant' should be replaced by 'substantial'.	Acknowledged, changed accordingly
The modalities for integrating paediatric expertise into ethical review practices should be worked out by paediatricians and experts in clinical trial ethics and ethical review. Additional operational guidance on the ethical review of paediatric research is required. The education of ethics committees in paediatric research is needed. This should not be carried out by the pharmaceutical industry, the CRO industry, or their forums.	Comment acknowledged. No change requested
Opinions of ethics committees on trial protocols, together with protocols themselves, shall be made public in agreement with Regulation 1049/2001 on public access to Commission documents.	Regulation 1049/2001 applies to the Commission and the Agency, not to Ethics Committtee
Change "significant" to "substantial"	Acknowledged and changed

We agree completely with the sentiment that "paediatric expertise goes beyond having dealt with children". We endorse the recommendation that the 'paediatric experts' on an ethics committee should "demonstrate at least some years of experience in paediatric care, and direct experience of clinical trials" (our emphasis). We have experience in submitting essentially the same clinical trial protocol through several national ethical approval processes. From this, it has become clear that the evaluation system works most smoothly and consistently in those countries where a single or limited number of ethics committees have develop expertise in assessing clinical trials in a particular childhood condition. It is very difficult for an ethics committee, even one with appropriate paediatric expertise as defined above, to be expert in assessing very complex trials such as are seen in childhood cancer. Countries should give consideration to the development of specialist or designated ethics committees for the evaluation of complex trial protocols for serious childhood diseases requiring complex treatments, such as childhood cancers.	Comment supported, wording added to section 8
ECs should comprise of patient representatives with paediatric experience	Lay persons present in EC could include patient organisations. EC can also hear patients representatives. This is different from what is meant by paediatric expertise (see above).
Change "Two or more experts" to "Two or more experts with experience in paediatric care"	Changed
The availability of paediatric expertise, documentation and recording of its use by the ethics committee is ultimately also a sponsor's responsibility (to verify) when conducting paediatric clinical trials. Suggest to modify the line as follows: "Expertise used should be documented and recorded by the Ethics Committee, and documented on the ethics committee composition, which is part of the essential documents for the conduct of a clinical trial to be included in the trial master file."	Acknowledged and section 8 modified
Penultimate bullet point: it was agreed there should be an exit strategy known to the participants before they give assent, but this is not always totally realistic.	"Exit strategy" added to section 26 Annex 2
We would add, whenever possible and if applicable, representatives of school or representatives of parents for out-patient child in age to go to school to evaluate medical and/or psychological impact.	Not agreed. The impact should be measured when drafting the protocol (see evaluation of risks and benefits). Parents' representatives are not considered as bringing the paediatric expertise required by the CT Directive for Ethics Committee. They bring another kind of expertise.
Expertise available to ethics committees should include neonatology.	Neonatology is included in paediatrics. Expertise relating to trials in the relevant age groups is mentioned.
"iv) patient or parents representatives"	See above.
Add "a paediatric pharmacist or external formulation expert, etc"	Ethics Committee may hear additional experts as needed (see also 'more than one expert'
This can be interpreted as if it is routinely requested to have a DSMB for paediatric trials.	Confirmed. This is the intention.

Some bullet points are specific for children, others are not. It is better to discuss them in two separate groups, the specific points and the non-specific points.	Bullet points follow order of trial steps
States that exhaustive review of evidence should be performed - this is unusual terminology.	Changed "comprehensive"
The protocol includes provision of the medicinal products to patients involved in trials after the completion of the trial - This may be problematic in certain countries.	Comment acknowledged
As written, it would appear that the default position is for there to be such a Board	Confirmed
The requirement for the provision of medicinal products to patients involved in trials after the completion of the trial has generated much controversy over the last decade.	Acknowledged
An Independent Data and Safety Monitoring Board is not always necessary, nor is it perhaps necessary to justify its absence in every case.	A DSMB is recommend in principle for paediatric trials
Clinical trials need to be monitored for more than simply 'the balance of risk and benefits'.	Acknowledged, paragraph amended
To add: "Replication of similar trials based on identical hypothesis should be avoided". This should be taken into consideration in the various specific Notes for guidance (NfG). There should be no systematic requirement of a paediatric trial for a same product class or same DCI products, once the data have been generated once. NfG requiring studies in children below 6 should only address relevant endpoints: for example, Coagulation Factors NfG: only inhibitor incidence, and for IVIg, no paediatric studies in the indications that have been for decades in children (PID; ITP in the child; Guillain-Barré Syndrome of the child…) should be required. This would be in contradiction with this paper recommendation.	Specific cases cannot be addressed in the document. The principle remains
"The Ethics Committee and the Competent Authorities should ensure that the sponsor permanently monitors the balance of risk and benefits of the research so that the health and well being of the children enrolled are safeguarded". Suggestion for sentence to appear in front of the guideline	Acknowledged
Clarity is required on what is meant by the term "national Competent Authorities". If this refers only to the regulatory authorities then the MCRN is concerned that while the regulatory authorities may focus on safety aspects, they may not make detailed assessment of the scientific merit or validity of the study. It is vital that Ethics Committees are assured of the scientific merit and validity of clinical trials.	Competent Authorities are authorities that are responsible for the authorization and supervision of medicinal products in EU member states. The role of Ethics Committee varies according to national law. If Ethics Committees do not asses the scientific merit themselves, they should obtain such an assessment. This is already stated 8.2 first paragraph: "If the Ethics Committee is not in charge of scientific review according to national law, it should however check that the competent scientific body has confirmed that the research is scientifically sound."
The following items should be added to the list of points presented under paragraph 1: "A justification for patient numbers", and "Trials should use medicines of demonstrated quality"	Acknowledged
"Negative results should be published or made available."	Agreed in 19.1 first sentence
Introduction to bullet list, add "safety"	Wording amended

Add "…, taking into account scientific developments or events arising in the course of research"	Mentioned in the sections on risk and benefit
Add "as well as confidentiality of personal information related to the child involved in the research and to his/her family, have been respected in accordance with national law and international law, in particular international human rights law."	In section 26 Annex 2)
Provision of the medicine after the trial is completed can not be guaranteed. However, the protocols or information sheets should make it clear what will happen at the end of the trial so that truly informed consent can be obtained. The protocol and/or the current form and/or patient information sheet should clearly state what will happen at the end of the trial with regard to provision of further medicinal product.	There should be provisions for post-trial drug access. Requirement for related details in information sheets included in Annex 2
For double-blind, controlled trials of products not approved for use in children, or for products with specific tolerability or safety concerns, a DSMB is recommended	See above
Add: No guidance is provided on the provision of study drug at the end of the trial. As most licences will be granted in adults first, it is important that this provision should be explicitly included in this guidance Include in the guidance	See above
9. PAEDIATRIC CLINICAL TRIAL DESIGNS	
The acceptance of innovative designs to minimize sample size is welcome, and this paragraph could be expanded. A section or paragraph regarding other novel strategies should be considered, i.e., PK assessments based on Simulation and Modelling approaches.	Addressed in other documents
Clarification is sought on what is meant by 'for follow up and cohorts' in this context.	Acknowledged
"For example, open and/or uncontrolled trials are subject to increased bias and should be avoided whenever possible" I disagree with this statement as written. I would agree with this for uncontrolled trials but not necessarily for open controlled trials. One could argue that blinded studies can also pose a risk for a child.	Not agreed
"Assessment in many cases will be based on the clinical evaluation of the parents…" Parents are not qualified to perform clinical evaluations.	Acknowledged and amended with explanation. Clinical means 'at bedside'
'Differences in product mode of administration' should not prevent the trial from being double blind. Indeed a double placebo should be used in these cases.	Agreed whenever possible
The wording in the third paragraph "for example, open and/or uncontrolled trials are subject to increased bias and should be avoided whenever possible" is addressing two issues. The word "open" should be deleted or clarified. A trial might be open as long as the endpoint can be measured unbiased. The important issue is the need for randomisation and therefore an adequate control group. The text should mention "randomized controlled trials should be performed". The current text is too vague. The text "The size of the trial conducted in children should be as small a possible…" is too reserved. This might endanger our goal to have trials large enough to provide meaningful data.	The word "open" has been clarified. The text to include randomized controlled trials has also been added and the sentence on 'size' of trials has been changed to emphasise that although kept to a minimum, the numbers need to be large enough to retain power and provide safety information.

The term “trial design CAN be set up following consultation …” may be interpreted by investigators as being an optional activity, when it is generally a beneficial process which should be undertaken where possible.	Acknowledged and changed accordingly
Use of placebo. This is an important paragraph but needs to be expanded to include, for example, an explanation on what could be the substitute for using a placebo. How will scientists decide on dosage in different age groups? Suggest paragraph on ways to approach this, for example, by using tissue/animal studies, or careful interpretation of pharmacodynamics in adults.	The use of placebo and other issues is addressed in other documents
The use of placebo and other control arms depends upon the scientific justification and the achievement of equipoise in scientific design. There are not specific differences between adult and paediatric trials here. The use of placebo (or not) does not present any specific consent issues in well designed clinical trials.	Agreed. However, many questions are raised by Ethics Committees when reviewing placebo controlled paediatric trials. Section 9.2 slightly rephrased
It should read “must not be used when it means withholding effective treatment…..”, rather than “should”.	Acknowledged
There seems to be ambivalence on the use of placebo in this guideline. This section is too reserved on the use of placebo controlled trials. Though, pragmatic trials in children may be useful to assess the effect of therapies in real life (where no placebo is used anyway), for licensing more stringent data are necessary. The crucial issue is the inclusion of a control group and randomisation (see also point 8). In line with ICH E10 and as also mentioned in the footnote to the declaration of Helsinki, placebo controlled trials or a placebo-arm in an active controlled trials are necessary, when without placebo a study cannot give an answer to the question. Therefore the document should be revised on this point and the need for placebo explained.	Comments accounted for, as also suggested by others.
Add “Placebo is permissible only …”	Acknowledged, amended in conjunction with other comments in a slightly different way
Non inferiority trials are simply designed to rule out the possibility that a new treatment is markedly less effective than a reference treatment. Such trial design cannot produce results that help healthcare professionals chose the best option among different intervention measures. Superiority trials should therefore be the rule in child research when efficacy of a new treatment is assessed against a reference treatment, which is in line with the Declaration of Helsinki: "The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures."	Not agreed. Non inferiority trials generally compare treatments on efficacy parameters. Safety may bring superiority.
By definition, any product "devoid of marketing authorisation", even if only in children, would have to be considered investigational in that population. In other words, how can it be said that "unauthorised products may be considered suitable as controls…"	This takes account of the current situation for children where treatments may have been studied correctly without having a marketing authorisation. Additional information added with regard to the definition of IMPs
Potentially differentiate according to type of trial	Not included in this section
It was felt that it would be useful to define unauthorised products – maybe to unlicensed or off label. It should be recognized that the publication of off label experience and the development of evidence based best practice may be limited.	Acknowledged
Studies comparing 2 irradiation regimens are possible in cancer developments.	No change requested

10. PAIN DISTRESS AND FEAR MINIMISATION	
The phrase "…should be limited to a minimum…" I disagree with this wording. Delete the phrase and change to read as follows: "In all situations, investigations should be performed using size/age appropriate material and devices."	Changed
"If sedation is needed, monitoring should be set up by a health care professional familiar with the procedure."	Proposal acknowledged, wording added to another sentence
"Children in a trial …" - Include reference to skilled health care practitioner or a social worker	Included accordingly
Add "It should be strongly discouraged to add distressing procedures to a trial over procedures normally performed in normal best practice".	This is already covered
To add "Awakening during the night; possibility or not to go out of one's room, be remote from one's parent or friends"…	Already covered in a more general way
For this purpose also, full information should be given to the child in order he be not surprised by unwanted gestures and be prepared to accept them.	Need for information already included
Reference should be made in this section to the ICH Guidelines on conducting clinical trials with children.	General reference is given to E11 already,
"Psychological pain" should be included	Acknowledged in a slightly different way
Finally the document should also focus more on pain and discomfort particularly in preterm and newborn, due the fact that the younger child cannot denounce it.	Acknowledged and wording added
11. ASSESSMENT OF THE LEVEL OF RISK AND ITS MONITORING	
We agree that it is important that the potential risk to each participant is considered both in designing and in assessing a protocol. However, it must be borne in mind that for children with life-threatening conditions such as cancer, exposure to an uncertain level of risk that permits evaluation of new drugs in the paediatric age group is essential for progress in treatment of these serious conditions. Retain a balanced view of the potential benefit of a new drug in the paediatric age group versus the risk of uncertain side effects, in children with life-threatening conditions such as cancer. If too much emphasis is placed on quantifying risk in difficult situations such as relapsed cancer, there is a danger that the very clinical trials that could benefit the patient become impossible to run due to difficulties in obtaining sponsorship and indemnity.	Acknowledged and wording added to 12
If no paediatric formulation is developed then what? Especially if we showed due diligence to develop a paediatric formulation. Do they need to give suggestions? The unavailability of age-appropriate paediatric formulations may also incur a level of risk. Need to add after level of risk (the compound should be evaluated for alternative dosing to reduce the risk i.e. crushed tablet in apple sauce).	Already addressed in a more general way
"The accumulation of research projects in the same population (over-studied population) is another aspect." I do not entirely agree with this statement. I would suggest that this be deleted.	Not agreed
Reference CIOMS Guideline 9	Already referenced in section 4.2
It was felt that this section was unclear, and that it could be truncated. The reference to country specific regulations as an example was felt not to be necessary.	Acknowledged, and changed

It is very important not to give emphasis to the community benefit in the prejudice of the individual benefit. The child's interest should always prevail over that of research (as is required under Article 4(i) of the Clinical Trials Directive. Direct benefit for the group, which is to be debated in depth)	This is already emphasized in the text
Add: "The input of patient organisations, parents and concerned children should be considered in the risk assessment."	Agreed. Already included when designing the trial
Area of controversy: risk assessment. Defining minimal risk is difficult and there is a large (mainly US) literature on that. The most useful source for a discussion of the issues is the recent Institute of Medicine report on the ethics of research with children. The EMEA guidelines are not all that helpful, because they quote three different sets of advice on risk assessment, which are not consistent with each other, and the reseacher will not find it easy to decide which one to apply (or indeed to choose some other).	Acknowledged, section 11.1 was amended to include this risk concept
Add "Research shall not involve risks and burdens to the child disproportionate to its potential benefits. …"	Acknowledged, covered by a different modification to this section
Restructure section on risk according to "prior to", "during" and "after" the trial	Section was revised to include another concept for risk explanation
Introduce a "Paediatric Independent Board for Ethical Monitoring" (PIBEM)	Not included as risk assessment is, amongst others, done by DSMB
Recommend setting up "long-term registries"	Discussed in Pharmacovigilance Guideline
Add "in the light of scientific developments or events arising d the course of the research. …"	Already covered
12. MEASURES OF BENEFIT	
It was felt that there is perhaps too much detail included here, and perhaps a couple of phrases to clarify the subject would be better. There seemed to be an omission of referral to research involving genetic material. It was agreed it would be useful to have a guideline on ethical issues of genetic research, or reference to an appropriate document.	Comment acknowledged, guidance needed but beyond scope of this document
This is a very dangerous topic, and is very much linked to the Anglo-Saxon type of ethics. Latin European ethics (from the Greek) emphasizes the care of individuals and alerts on the risk linked to the "community benefit". These arguments could be employed to convince patient associations to go one way or another for the good of the community, and not towards individual good or to protect ethical values.	Notion of group benefit is part of the Clinical Trials Directive.
Definition: "Benefit can be defined as progress in treatment, diagnosis, prevention (and improvement of symptoms or physiology)"	Definition of benefit maintained
Avoid misunderstandable terminology (esp. direct and indirect benefit)	Drawn from Clinical Trials Directive
The following sentence "This may be obtained through either increased efficacy or safety resulting in better risk-benefit balance, or through the provision of an alternative to existing treatment with at least similar expected benefit to risk" is too lax and would not provide for trials helping healthcare professionals to choose the best option. We propose the underlined sentence be removed.	Providing alternatives may be a benefit as such.

Add the following text: "Selection on basis of ethnic groups is only permitted in case scientific data are available on adverse reactions, differences in pharmacokinetics and pharmacogenomics related to ethnicity are documented."	Comment added
Add "Any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden."	Risk to benefit balance is covered
13. ASSAYS IN RELATION TO AGE/BODY WEIGHT – BLOOD SAMPLING	
First sentence is not complete: "Assays, investigations and blood sampling volumes should be described and justified in the protocol"	Added
It was felt that local anaesthesia should be offered in any situation that may cause the child distress. It is rare for a general anaesthetic to be given for trial purposes only, as most ethics committees would not agree to this due to the associated risks.	Agreed. Comment acknowledged and changes done in this section
It should be noted that topical anaesthesia is not currently authorised for use in all age groups, especially preterm neonates.	Comment acknowledged.
"Alternative sampling (e.g. urine or salvia sampling) for pharmacokinetic studies should be preferred."	Acknowledged and included
Stopping rules in every protocol: no more than x attempts to withdraw blood should be made, blood sampling only by experienced nurses and MDs	Acknowledged and included
In the draft it is stated, that "specific facilities" should be used. The current formulation of the text is too strict. No sponsor of a clinical trial can establish specific laboratories and other facilities for the conduct of clinical trials in children. This would result in an over-burden for the European pharmaceutical industry. The second part regarding materials is acceptable. Delete the requirement of specific facilities or replace "specific" by "appropriate"	Agreed
Regarding acceptable blood sample volume, the document is on the lower side of what is accepted by ethics committees in other regions. E.g. the University of Pittsburgh (USA) IRB accepts 2.5% of total blood volume per blood draw and 5% in a 30-day period. If the trial goes for considerable time, several blood draws might be necessary and justifiable, and this document's recommendation would be too tight. Better characterize the proposed volumes as recommendation where deviations should be justified.	Several sets of recommendations exist, none are evidence based. As stated, figures given are recommendations. See also following comments
Re-word to "… should not exceed 1% at any single time – care should be taken to avoid unnecessary repeated sampling and enough time to elapse between sampling for blood volume to recover"	Acknowledged and covered by various changes
80 ml/kg for a new born of 3 kg is 240 ml. This is the same volume as a blood donation (made by an adult)! This seems far too much. 1% at which frequency	80 ml/kg refers the total blood volume; clarified
A guidance regarding time span is not given. It is proposed to add "per child 3% of total blood volume per 2 weeks". In addition, the amount corresponding with 3% of 80 ml/kg body weight should be mentioned which is 2.4 ml/kg. Furthermore, it should be mentioned that in case of simultaneous trials the 3% per 2 weeks remains the maximum. This is not explicitly mentioned.	Guidance for time span for total blood sampling and for blood sampling in simultaneous trials has been included.

Sometimes data is used from routine blood sampling. To restrict this to 3% of blood volume for neonates would be constricting. Perhaps it should read" blood taken in excess of samples that would be taken for routine monitoring should be restricted to 3% of total blood volume". Even this could be difficult for small premature babies. These babies often have multiple transfusions in part due to blood sampling which is necessary for their care. If samples were being taken over a long period they might need more than this (i.e. 2.5mls in total from a 1 kg baby).	Acknowledged. Transfusions cannot be a justification to draw large quantities of blood
Some paediatric experts have expressed their concern about the blood volume mentioned on the text. For some specific purposes and cases the volume might not be enough. Therefore we kindly ask you to reassess the limits of the blood volume of preterm and term neonates.	See above
14. STUDIES IN NEONATES	
The guideline should recognise the complexity of most studies involving children, and recommendations for pharmacovigilance studies should refer to the recent EU guideline on pharmacovigilance in children.	Reference was included
15. HEALTHY CHILDREN/VOLUNTEERS STUDIES	
Add following sentence “Healthy children should not be enrolled as healthy volunteers in painful and interventional procedures.”	See assessment of risks
The title should not read ‘volunteers”’, since children enrolled in a clinical trial have a very different status than adult volunteers who enrol in phase I mainly for money purpose and without any individual benefit. Here, the children population should be the population intended to be treated, as written just below!	Acknowledged and clarified
Another example of a situation where studies can sometimes be performed in healthy children is where taste and acceptability testing of medicines is required. It would be helpful if guidance was given on the ethics of taste and acceptability testing in child volunteers and child patients.	Comment acknowledged and section 15 has been expanded
Prevention trials in children with intermittent diseases are acceptable because even in the “healthy” phase the children are sick.	Acknowledged and included
16. VACCINES	
Add “[…] Prior to its use in children, a new adjuvant should have demonstrated its safety in appropriate pre-clinical studies and in adult studies.”	Not included as addressed in other documents eg EMEA/CHMP/VEG/134716/2004
17. PAEDIATRIC FORMULATIONS TO BE USED IN PAEDIATRIC TRIALS	
We recommend that a specialist in GMP is involved in ensuring that clear and accurate information is provided, taking this concept paper (EMEA H/8227/02 of April 4, 2002) into account.	Comment acknowledged
What about the lack of a formula for children, then what happens, for instance with a drug like […]? Can they address circumstances when a drug is not available in a paediatric formulation, but perhaps a different dose regimen?	No change required

18. INDIVIDUAL DATA PROTECTION	
Would you provide examples?	Regarding this section, no further examples
The meaning of "Protocols should specify the level of protection of educational records when studies are performed in schools (access, amendments and disclosure), and the information given to parents or legal representative." is unclear. There should not be a need to access educational records for the purpose of a trial. Explain in more detail or delete.	Comment acknowledged and term clarified
Add "Any information of a personal nature collected during biomedical research shall be considered as confidential …"	Added
19. UNNECESSARY PUBLICATION OF TRIALS	
Member States and EMEA are requested to supervise if all useful and up-dated information figure in the international database. In case of detected negligence these authorities should take the necessary steps as to have these obligations respected. A non respect of the publication rule leads to the refusal or withdrawal of the marketing authorisation.	GCP issues addressed in other documents
It was felt that the mechanism for sharing FDA information has not been very well defined although under the new Regulation regular meetings (by teleconference) will occur with the FDA. Most journals require you to register your randomised control study before starting, and the international agreement through the IFPMA is that all Phase 2b trials onwards should be registered at inception. The new Paediatric Regulation requires registration of all paediatric studies in the EudraCT database and similarly the clinical trials database for US trials.	Transparency will be increased by the Paediatric Regulation
It should be added in this section that pharmaceutical properties of formulations used in clinical trials should be described in the protocol and subsequent publications.	Wording in section 17 amended
Is the investigator more prone to objectivity than the sponsor? The protocol should maybe foresee that publication should be made together by both the investigator and the sponsor!	Paragraph amended
And 24: The 2 sections are contradicting each other. Section 19.1 requires that all paediatric trials are published, whereas section 24 states that trials that were conducted unethically should not be published. Either delete the 1st sentence of the 2nd paragraph in section 24, or add a statement to section 19.1 that pediatric trials that were conducted unethically are exempted from the publication requirement.	Comment acknowledged and section clarified in conjunction with other comments
I do not understand the semantics of the phrase "is susceptible to modify the initial hypothesis for the trial". This needs rewording and clarification.	Section has been reworded with this intention

20. ADVERSE REACTIONS AND REPORTING	
As the paediatric population participating in clinical trials is rather small, sound post-marketing studies are compulsory for all new authorised paediatric medicines. Post-marketing studies must be notified for approval to the competent public authorities. Furthermore, these studies must be notified for advice to the reimbursement authorities which should have the opportunity to comment the usefulness of the study and make a recommendation to the approval or non-approval of the study	Measures to ensure post-marketing risk management and studies (conditional approval, approval with special obligations, commitments) are part of the Paediatric Regulation provisions, inlcuding risk management plans requirements
It was suggested that there should be a cross reference to risk management for paediatric products and this section should be expanded. The spontaneous reporting of adverse events should be encouraged and the legal representatives of the child and the child should be carefully instructed regarding their responsibilities on this throughout a trial It should be mentioned that long-term reporting of adverse events will be required under pharmacovigilance guidance and further clarification is needed as to how this will work in practice.	Comments acknowledged and changes made, where applicable
Limiting reporting to serious adverse reactions seems particularly inappropriate in children and when 'additional protection is needed': "Rules and obligations are identical to those of adult trials, in particular the notification of serious adverse reactions observed in clinical trials is applicable to paediatric clinical trials (article 17 of Clinical Trials Directive). We propose that non serious adverse reactions should also be looked for and reported.	Reporting rules are not limited to serious adverse reactions.
adverse events might be necessary to be monitored for decades in appropriate settings	Comment added.
It is important that investigators document ADRs properly.	Agreed
21. INDUCEMENTS VERSUS COMPENSATION FOR CHILDREN	
In addition, the CT Directive does not say that only the parents/legal representatives can be compensated and not the child. Change "Parents/legal representative can only be compensated for their time and expenses." to "Only compensation as specified in national regulation is permitted."	Recommendations refer to the situation when parents/legal representatives receive compensation
22. INSURANCE ISSUES	
Patient insurance schemes in Denmark, Sweden and Finland compensate for injury in connection with medical treatment. Comment: In some Member States it is impossible to get insurance for clinical trials in children using plasma-derived medicinal products.	Medical care is a different framework, insurance issues to be addressed in a different forum
Add: The medical records which can or would pose a risk of labelling the child by insurance company as pre-existing conditions should be protected by the privacy requirements of local laws.	Already covered by a reference to privacy of personal data
It was accepted that this is a difficult issue with liability being moved out to 5 or 10 years in some countries even for adult studies.	Comment acknowledged

However, unrecognised congenital defects are generally excluded" should be changed into "Unrecognized congenital defects are usually excluded. However, SUSAR's that can be related to these unrecognized congenital defects should be covered in insurance contracts."	The comment on SUSARSs has been added.
23. TRIALS IN CHILDREN IN NON-EU COUNTRIES	
The medical records, which can or would pose a risk of labelling individuals within the paediatric population by insurance company as pre-existing conditions, should be protected by the privacy requirements of the applicable national laws.	See above
This guidance should be relevant for European Union researchers and sponsors carrying out research in Third Countries, as well as for ethics committees and Member State Competent Authorities reviewing such research or the data/results of such research.	Acknowledged
It was felt that this section should also refer to ICH 11 as well as ICH 6. It was agreed that this needs to be a general premise and incorporated nearer the top of the document. It was suggested there should be a section on the need for due diligence in training investigators in GCP if they have no experience. Refer to ICH 11 as well as 6	Comment acknowledged, references included
To include also studies with a product with or submitting a MA in the EU, performed in third countries … Indeed, it should not be possible that these rules not apply if the study is not submitted in the product MA file.	Comment included in text.
There should be no differences in the general conditions between EU countries and non-EU countries. According to […], clinical trials […] must be conducted in accordance with the principles of GCP and the ethical requirements.	Comment acknowledged, second paragraph has been strengthened in this respect
24. ETHICAL VIOLATIONS AND NON-COMPLIANCE WITH GCP	
Where unethical behaviour has occurred, the authorities should consider referral of the sponsor or the investigator to the appropriate body for further investigation e.g. the National Panel for Research Integrity or its equivalent.	Beyond the scope of document
The sentence "sensitivity analysis with and without non-GCP data should be performed" should be replace by "Sensitivity analysis should only be performed on GCP-data; non GCP-data should be excluded."	Not agreed
"… results of studies conducted unethically should be refused from publication": in contradiction to 19.1, publication of all results	Acknowledged and clarified
25. ANNEX 1 (RESPONSES TO QUESTIONNAIRE)	
There are several notes on a few answers contributed within the comments to Annex 1 in Portuguese language.	Answers included in the table
The table in general is considered useful, but it seems that some information is not clear, and other seems to be incorrect (e.g. the consent in Germany needs to be given from both parents as it was presented officially by the representative of the German Ethics Committee group at a Meeting on the Paediatric Regulation).	Table has been updated, information on Germany corrected

Table of obligations: Regarding Germany, the entries in row 5 (“One Parent consent”) and 6 (“2 Parent consent”) are misleading. In Germany, consent by both parents is a basic requirement, even if the parents are divorced or else. Even in cases of emergency both parent have to consent. The only exception is given if in a divorce one parent has been given the sole right of custody, but this situation is a clear exception in Germany and should not be regarded as standard.	See above
26. Annex 2	
Several additions to Annex 2	Acknowledged