23.8.2016

Submission of comments on **Ethical considerations for clinical trials on medicinal products conducted with minors** – Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

Comments from:

Name of organisation or individual
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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

General comment (if any)
The handling of children with cognitive disabilities older than 18 years is recommended to be included as the clinical standard of care is often for those children to remain within a paediatric practice beyond the age of 18 and this vulnerable population should still benefit from the considerations specified in the paper.
Proposal to use visual such drawings, cartoons, pictures for ICF process and agreement
For blood samples: micro volumes and micro-assay use should be considered whenever feasible.
This document goes way beyond ethical considerations and touches on many general study and good clinical practice topics. Examples include discussion of standard treatments used as comparators in Sn 8.3 – Opinion on the application dossier, Sn 9.1 – Design and analysis, Sn 9.2.2 – Superiority versus non-inferiority trials, Sn 12.2.1 – Standard treatments, Sn 13 –Assays in relation to age/bodyweight and blood sampling, Sn 17 – Paediatric forms and formulations to be used in pediatric trials, and Sn 20 – Adverse effects reporting. Other sections appear to be redundant to other guidance documents on topics of ethics in clinical research including Sn 18 – Individual Data protection, Sn 22 – Insurance issues, and Sn 24 – Ethical violations and non-compliance with GCP. In line with the title it would be appropriate to reference to existing guidances and focus this document on ethical considerations. One suggestion might be to split into two documents: 1. An implementation guideline and 2. Reflections from experts, which could be expanded to ethical guidance on those areas, which are succinct and require specific recommendations (e.g. trials with female teenagers of reproductive potential, research with neonates, and emergency research), or which have not been included, such as genomic research.
It is important to acknowledge, to respect and to promote the child's rights and growing autonomy in function of his/her age and increasing level of maturity. Additionally it is important to explain the research project in a manner that is adapted to the child's comprehension as well as to seek his/her perspective and to involve him/her in decision-making, as much as possible; this contributes also to facilitating the child's active participation in research. In a few sections of the document (examples include lines 362-364, 603, 635-698/Section 7.2), there seems to be an overemphasis on autonomy, possibly to the detriment of equally important ethical considerations and rights, raising the question: in which situations, does the opinion of the child become the only one that matters? Example in line 603:: The statement that "The child's will should be respected" assumes that autonomy is the only principle that should be considered when assessing the ethical principles surrounding participation (continued participation) of a minor in a trial. There is context to all scenarios, and a fitful pre-schooler who does not want to have a port placed when they require parenteral chemotherapy to treat newly diagnosed ALL, should not necessarily have their will respected. Objection of the adolescent and mature child should be respected. Deliberate refusal of the young child should be evaluated by the research team and

General comment (if any)
respected, provided that it does not jeopardize the child's welfare (e.g. instances where the child requires treatment that's available only in the context of research, there is reasonable expectation of therapeutic benefits and parents have given their permission). Age, cognitive abilities, maturity and personal experience with illness are factors, which contribute to some extent, to the capacity to give assent; that said, adolescents may not always be able to place a decision in a broader context and/or fully appreciate the long-term implications of their choice or decision. With this mind, it is useful to consider the context, to provide the child with all the attention, care and empathy he/she deserves, and to strike a balance between the protection of the child and his/her other rights.
The draft revised guideline introduces a number of requirements that could pose challenges to sponsors, with little or no benefit to the children participating in clinical trials. These include requirements relating to the preparation, content and format of informed consent information materials. If pragmatic and proportionate approaches are not taken with regard to these requirements, the guideline may have the unwanted adverse effect of discouraging appropriate clinical research involving minors.
Vaccine trials, and other preventive medicine trials, in healthy minors as well as the possibility of conducting low intervention clinical trials in the paediatric population, using products authorized only in an the adult population, but where the use of the investigational medicinal products is evidence-based and supported by published scientific evidence, are not adequately addressed in this document. It may be useful to provide some scenarios of where this may be appropriate or to confirm that it is not considered appropriate for trials involving minors. Although vaccine trials are mentioned once (line 1345), the document appears mainly intended to be applicable to drug trials in diseased minors. The majority of vaccine studies involving healthy minors should belong to the minimal risk/burden category of trials, as they only imply collection of blood samples, similar to what is currently done in the routine clinical pediatric setting for healthy children. The requirements outlined in this guidance might create some difficulty to conduct clinical research in this healthy population. We recommend that the guideline adopts an approach in which the requirements are more proportionate to the risk/burden posed by the research. Some proposals are included in the specific comments below.

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
168-214	Comment: The introduction appears to be directing the reader to believe that clinical trials are the best way to evaluate medicines in children with only a brief reference made to alternative ways of generating evidence. Although approaches like pharmacometrics are referred to later on in the document (section 9)- Suggestion would be that fair balance be given to these approaches from the outset. The key should be to establish the most appropriate way to determine benefit risk in children and this should utilise all available scientific resources.
168-214	The revised guideline introduces the term "agreement", and uses the term "assent" in a more restricted way than is the case in the current 2008 guideline. This important change is not, however, explained until section 5 (lines 329-380). It would be helpful to readers who may be more familiar with the current use of "assent" to include a brief explanation in the introduction. Proposed change: Add to section 1 "Introduction – Rationale for the development of recommendations" a brief explanation of the terms "agreement" and "assent" and the reason for the change in the use of the terminology.
186-187	The statement "Data on effectiveness and safety cannot reliably be derived from data in adults" is very broad, and appears at odds with the statement that the possibility of extrapolation should be considered (line 206) as well as the recently released EMA 'Reflection paper on extrapolation of efficacy and safety in paediatric medicine development' (EMA/199678/2016). Proposed change: The existing paragraph (Lines 186 – 194) should be re-considered in order to take the value of alternative statistical and methodological approaches (such as extrapolation) into consideration when designing research programs that intend to assess children. Original text: "safety cannot reliably be derived" Proposed revision: "safety may not automatically be derived"
188	Proposed revision: "pharmacodynamics **can** occur"
192-193	Comment:

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*
	This text is not adding value, propose removal. Proposed change (if any): ~~Unfortunately this has been demonstrated by previous calamities with the use of medicinal products.~~
193-194	The term “drug” is used. If the guideline is to cover vaccines, “medicinal product” should be used instead, or it should be made clear that the term “drug” refers to medicinal products throughout the text. Proposed change (if any): Replace “drug” with “medicinal product”. If “drug” is not replaced with “medicinal product”, the following change should be made: “Trials are therefore necessary in the paediatric population to develop a better knowledge of drugs’ (which should be understood to mean “medicinal products”) effects in children (safety and efficacy).”
195-207	Comment: Innovative study designs should be considered and utilized to obtain needed information in smaller paediatric populations minimizing the number of involved children, the length of time in trials and more efficient recruitment/completion of the trial making information available for use in the paediatric population more expediently.
195-201	Comment: We congratulate the authors on their noting that staggered approaches may not always be in the best interest of a child and should not arbitrarily be used in all cases. We propose to add published reference against staggered approach to help sponsors if receiving different advice. A “staggered approach” approach, however, may be appropriate in some cases: this should be determined based on an assessment of benefit/risk, in addition to the other factors mentioned on lines 205-207. We caution that this might not be aligned with CTR and PIP guidance as well as some treatment specific guidlines: the CTR specifies that the least vulnerable patients should be included, and the EU Commission guideline on paediatric plans 2014/C 338/01, mentions that "justification of the relevant age groups or subsets included in the study (and of staggered inclusion where applicable)" should be included in the plan. Further, trial feasibility must be an integral part of any policy considering the ethics of research in minors. Enrolling children in a trial

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	where there is a distinct likelihood that the trial will never complete jeopardizes the patient population. When vulnerable populations are involved in research, the appropriateness of involving them in the study that is proposed should itself be justified. When subjects are enrolled and are knowingly exposed to possible risks and inconvenience in a trial that won't be able to deliver its objectives, including generalizable results, we must challenge the ethics of such a trial. If the research question is meaningful and corresponds to an unmet medical need, but there are issues with e.g. the design, the procedures, the population, or the study conditions, this means that there are lost opportunities for the enrolled children (who could have been enrolled in another trial) and a waste of resources (which are often in short supply). Proposed change (if any): "However, a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but may lead~~s~~ to delays in data availability, and is therefore not recommended to be used in all cases. Such an approach ~~will~~ may ultimately result in prolonged off-label use for the younger age groups (especially neonates) and the impossibility of conducting any trial to provide age specific evidence for these groups. If there is a necessity to subject minors to a clinical trial, the choice of subsets of the paediatric population to be included should be made on the basis of the likely real-life target population for the medicine being tested, the possibility of extrapolation, ~~and~~ the scientific validity of such an approach and an assessment of the potential benefit/risk for trial subjects.
201-203	Comment: Many neonatal diseases do not have an adult counterpart (e.g., chronic lung disease, necrotizing enterocolitis, retinopathy of prematurity) therefore, the use of the neonatal population as the example in this statement does not make much sense. When a disease that occurs in adults is being studied, and the inclusion of a pediatric population can be considered, it is more likely that the population that should be considered is child or adolescent.
219-223	Comment: IRB/IEC should be included in the list of stakeholders that the document is intended as recommendations for
219-224	In this paragraph, the term "assessors" has replaced "ethics committees", and "patient representatives" are no longer mentioned, but the reason for these changes is unclear. Proposed changes (if any):

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	"The document is intended as recommendations for all persons involved in any stage of a clinical trial, including sponsors of clinical trials, ~~assessors~~, ethics committees, regulatory authorities, pharmaceutical companies, insurance companies (regarding trial subjects), investigators (including all trial-related staff) of clinical trials performed in children of all ages (minors, cf. section 5.8), families, ~~and~~ participants and patient representatives."
235-248, 282, Section 28 References (pp44-49)	All of the documents mentioned in the paragraph on lines 235-248 should be added to the list of references in section 28 (only the UNESCO 2005 document and ICH E11 currently appear in the references). In addition, we suggest to add the following important reference in the paragraph on lines 235-248 and in the list of relevant guidelines starting line 282: *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*
250-252	It would be helpful to provide a reference for the "four important ethical principles that should be adhered to when performing research with children". Proposed change (if any): Add reference, i.e. The Principles of Bioemedical Ethics, Tom L. Beauchamp and James F. Childress, Oxford University Press (2001)
310-317	Comment: It is stated that with the exception of 2-11 the definition of paediatric subgroups is in line with ICH E11 however in this paragraph adolescents are defined as from the age of 10 up to but not including 18 years of age – this is a lower age range than proposed by ICH E11 which defines adolescents as 12-16 or 12 to 18 years depending on region. It is proposed to align the definition of adolescents with ICH E11 and increase the top range of the definition of schoolers. While the sub-definition of the childrens age group into preschoolers and schoolers is certainly helpful regarding the way the consent process should be followed, it should be made more clear that this definition does not mean that these age categories should always be specified and used in clinical trials. Reference to the ethical, psychological or other relevant guidelines underlining the proposed age groups for the informed consent process would be useful. Proposed change (if any):

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	'…preschoolers (2-5 years), schoolers (6-**11** years) and adolescents (from the age of **12** up to ~~but not including 18 years).~~ 16-18 years (dependent on region'
313-315	Comment: The definition provided for the preterm newborn infant is inconsistent with the proposed definition that was provided in the pre-release draft of the ICH E-11 Addendum circulated in May 2016. In that draft, ICH defines the neonatal period for preterm newborn infants as " *… beginning at birth and ending at the expected date of delivery plus 27 days*." Proposed change (if any): Consideration of the ICH E-11 Addendum definition should be given in order to converge the global definition of preterm newborn infant.
323-325	"Although this may be difficult, as 'maturity' is not a clear-cut criterion in contrast to age, such an approach will foster more attention to differences between children and will support that they are properly involved in decisions that concern them." Unless there are defined legal terms of maturity, it will be very difficult to apply this recommendation in practice. Specific impacts is foreseen but not limited to requirements on Source data verification, impacts on submission of documents requiring HA/IEC approval.
329-380	Comment: There are two sections, 5.2 Assent and 5.3 Agreement. The difference between Assent and Agreement is not very clear, or it is not clearly stated when one should be used rather the other. Proposed change (if any): Clarify the difference and definition between the two.
341-343	Comment: Only patients who have appropriate decisional capacity and legal empowerment can give their informed consent to medical care. In all other situations, parents or other surrogates provide 'informed permission' for diagnosis and treatment of children with the assent of the child whenever appropriate. Proposed change: The authors should re-consider their use of the word 'consent' when discussing the legal process of allowing a parent/legal guardian the right to provide their permission for trial participation of the minor.

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352	Comment: Use of the word “will” in this context is not generally used in this manner in everyday English language and may not fully convey to the reader the meaning of this statement. Proposed change: It means the expression of the minor’s willingness to participate in a clinical trial.
352-355	“This document supports a systematic request for agreement, and recommends that the investigator obtains agreement from the child in addition to informed consent of the parents/legally designated representative, even when this agreement is not mandatory by law.” A requirement without the support of law is difficult to reinforce, not because the sponsor company is not willing to obtain this guidance for IECs and trials sites will not able to provide clear guidance. Request that a clear reference points to supporting law sections for assent is defined and use the term agreement in line with those definitions.
356-380; 590-592	It is not clear who is accountable for determining whether or not the child is of sufficient maturity to give agreement, nor how this is to be documented. In addition it is unclear on what criteria the maturity assessment will be done - those criteria might vary from a cultural stand point. Some guidance may be helpful to ensure consistency of approach in multi-country studies Proposed change: If the determination of the child’s maturity to give agreement is to be included in the investigator’s report on the agreement procedure (see lines 625-627), this should be clearly stated. In addition some guidance on the criteria on which the maturity assessment will be based would be helpful.
362	Comment: Use of the word “will” in this context is not generally used in this manner in everyday English language and may not fully convey to the reader the meaning of this statement. Proposed change (if any): Dissent however, meaning the expression of the minor’s unwillingness to participate…
425	Propose to add depending on member state legislation (e.g. UK/ Ireland as of 16 years should sign "consent").
456-459	Cultural factors, e.g. based on socio-economic background or geography, may also influence the perception of obligations on the side of the parents.

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	Proposed change: “In the complex relationship between parents and physician(s), especially in case of chronic diseases and of rare diseases, but also in acute serious illnesses, or in the situation of less educated parents, there is a risk of perceived obligations and emotional subordination on the side of the parents. Cultural factors may also influence these perceptions.”
466-468	It is stated that as soon as the minor becomes legally competent, no trial-related procedure can be performed until a new consent is signed. This statement should be considered softened, as it should be possible to perform a phone visit, collect diary data at home etc. and then sign the 'adult' consent at the next clinic visit.
497-501	It seems as if the child has to re-consent at every visit; this is not feasible and may give the patient the wrong idea, if the investigator is asking this every time, the patient/parents may start questioning the treatment. Could be considered to link the re-consent to specific events, e.g., update of investigators brochure, rather than each visit. Documentation of consenting is required by GCP at a minimum. GCP also includes detailed description of the requirements. Request that reference to GCP and any applicable member state regulation is given in this section. Proposed change (if any): Clarify the expectation of discussions and consent, and the documentation recommendations at the beginning and throughout the trial and reference to GCP and any applicable member state regulation.
505-506	“In the rare event of a change in legally designated representative during the trial, informed consent should be sought again as soon as possible.” Request that reference to any existing member state requirements on the re-consenting time frame is included. "... As soon as possible unless governed otherwise by member state"
505-506	Propose to add "To avoid unnecessary, painful, and repeat study required lab tests and physical examinations, the consent should allow investigators to use data that was obtained as part of the standard of care of the patient before the consent was signed"
515-516	Comment:

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	Consideration should be given to adding a section on early termination or interruption of a trial for a potential safety concerns If a study is stopped for safety reasons – the subject having been exposed to the medication that lead to the safety concern. In other cases where a study may be stopped prematurely, the risks are similar to when a patient withdraws from the study. Proposed change (if any): 'The parents/legally designated representative need to be informed about the risks that premature termination of the trial would present to the subject's health, if applicable. Where if a study is terminated for reasons other than safety the risks are similar to when a patient withdraws from a study.'
518-521	Comment: First, clarification is required as to what is meant by "follow the research". Second, by limiting the example to use of 'general anaesthesia' the authors relay an image that other procedures conducted in a setting where there is no use of general anaesthesia are of lesser importance.
523-524	Comment: This passage could be interpreted to mean that results may be made available on the EU database during the trial. This should be clarified to state that the results would only be available when the study has fully enrolled all subjects, it has completed and reporting. Proposed change (if any): "…database, following completion and reporting of the trial."
530-532	We suggest specifying what is required for the reporting of adverse events after the withdrawal from the trial. For example that this concerns only ongoing adverse events at the time of withdrawal or new serious adverse events after the withdrawal. Otherwise, it is too unspecific as there is no time limit.
533 – 565 Section 6.6 Consent, assent and agreement in emergency situations	General Feedback: If there is a parent or legal guardian accompanying the unconscious child then obtaining IC should be possible (even if assent is not) although it will need to be done quickly under high pressure circumstances. But the document is silent on how the decision is made (and by whom) if a parent or legal guardian is not immediately available. It should stipulate that then the decision is made by the PI for the study (or his/her colleague also designated and qualified as a study doctor) according to satisfaction of well-defined inclusion/exclusion criteria in the protocol. In those cases, it would be legitimate to have a designated third party (social worker, ethicist, IRB member) be on-call to sign off on consent when requested by the PI if the parent/legal guardian is not

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	available. In that case, there would also need to be a time frame by which actual informed consent from a parent or legal guardian must be obtained to continue the child in the trial. The inclusion of third parties in emergency situations would protect the child's best interest also in light of Member State variation.
542-543	Comment: Use of "derogation" not frequently used or understood in the written or spoken English language. Proposed change (if any): Rephrase to "Article 35 of the Regulation provides for the exemption from prior informed consent requirement, including for paediatric trials in emergency situations, with some restrictions."
546-547	Comment: Use of "derogation" not frequently used or understood in the written or spoken English language. Proposed change (if any): Rephrase to "Of note, there is no exemption for such clinical trials from the requirement to respect the child's explicit wish to refusal to participate."
548-552	Additional granularity regarding the ethical review of clinical trials in emergency situations should be provided. There should be a qualifier that trials in emergency situations should be carefully reviewed by ethics committees prior to approval and ethics committee should have previously approved that patients in an emergency situation are to be included without obtaining informed consent due to mitigating circumstances. There is a need to ensure that the benefit/risk balance warrants such an approach – e.g. the study concerns a clinical condition with high morbidity/mortality, there are no or limited alternative treatment options, robust efficacy has been seen in previous trials, etc. Propose to delete : "highlighting the right to object to the use of the data" as this might depend on member state legislation. Proposed change (if any): "Recruitment and inclusion procedures for such trials should be scrutinised from the ethical perspective prior to their approval and ethics committee should have previously approved the procedure. The following, in particular, should be carefully considered: whether the benefit/risk balance warrants such an approach (e.g. the study concerns a clinical condition with high morbidity/mortality, there are no or limited alternative treatment options, robust efficacy has been seen in previous trials, etc.), the time lag until consent is obtained, how and by whom the decision to include the child in the trial will be taken, information given to the legally designated representative, ~~highlighting the right to object to the use of the data obtained~~ in these circumstances, and the assent or agreement process."

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551-552	Propose to delete : "highlighting the right to object to the use of the data" as this might depend on member state legislation.
559-560	Sentence related to Article 35 of CT Regulation in Section 6.6 is unclear: "*Emergency situations described in this paragraph are not to be confused with those referred to under article 35 of the Clinical Trials Regulation*" - Indeed, Article 35, point 1.a says : "*due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial*", and to us, this is (at least partially) related to / in scope of section 6.6 (?) Link to CT reg: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf Proposed change: The difference in meaning should be given in this document to avoid misunderstanding and misinterpretation.
567	Section 7 includes references to assent, as well as agreement. We suggest the section title be amended to reflect this. Change (if any): Participation of minors in the informed consent process and assent/agreement
581-583	We recognise that a systematic approach to documenting the explicit wish of a minor from pre-schooler age who is capable of assessing the information and forming an opinion is an important step forward. The guideline should, however, allow for a more nuanced approach for the way that sponsors may operationalise this for studies with "no or minimal risk and burden" (Category 1 as per annex 3) versus studies involving Category 2 and 3 procedures. The procedures undertaken in Category 1 trials may in many cases be close to routine medical practice. In such cases, the provision of information and/or the use of specific agreement forms could in themselves present an additional burden (e.g. if there was a long and complex agreement process to undertake blood sampling that would be typical of normal medical practice). The agreement procedure and the materials used in that procedure should be proportionate to the level of burden and risk associated with the trial. Proposed change (if any): "This document supports a systematic request for agreement, and recommends that the investigator obtains agreement from the child in addition to informed consent of the parents/legally designated representative, even when this agreement is not mandatory by law. The

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	agreement procedure and the materials used in that procedure should be proportionate to the level of (perceived) burden and risk associated with the trial."
601-602	"Therefore, any objections raised by a child at any time during a trial should be analysed, including those of very young children." Objections should be also documented; requirement in documentation is to be included in the document.
601, 640-641	Propose to add for objections raised by the child: objections "clinically meaningful protest, related to the clinical trial which are different from the standard practice".
613, 617-618, 645-649,	The guidance appears to indicate a requirement to use visuals (e.g. drawings, cartoons) in the informed consent information materials for minors. Although visuals may be helpful in some cases, they should not be mandated, and the text should be qualified. Proposed change (if any): Line 613 – "…in visuals (where appropriate)…" Lines 617-618 – "…using visuals where appropriate, such as drawings, cartoons, etc." Lines 646-647 – "…other ways of providing visual information ~~should~~ could be ~~sought~~ considered…"
614-615	Comment: The current wording 'The information material should be ethically approved by the Member State concerned' may lead to confusion as this might appear to be inconsistent with Directive 2001/20/EC concerning the definition of the Ethics Committee, i.e. an independent body in a Member State…. Proposed change (if any): The information material should be ethically approved by the Ethics Committee appointed by the Member State concerned'.
615-616	A general requirement to formally test **all** information material which is planned to be given to a minor might not be realistically feasible in all circumstances: this could add a significant burden for sponsors, with little benefit to trial subjects. Testing of the information material could be considered, for example, if it includes description of a novel procedure.

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	Proposed change (if any): "The sponsor may consider testing the information material ~~should have been tested~~ in the relevant population where appropriate and feasible (e.g. material includes description of a novel procedure).~~, and~~ The information material should include provision of information…"
628-634	In some cases an assent is required. It is conceivable that the assent and agreement documentation could be the same. Proposed change: We suggest including a clear statement around this option in the text.
673	Comment: Adolescents (10-18 years of age) should be amended to be consistent with ICH E11. Proposed change (if any): 'Adolescents (12 ~~10~~-18 years of age)'
693-694	Comment: The language regarding "protection of confidentiality, especially for research on socially sensitive issues such as illicit drugs, sexuality, and violence" may also apply to some of the younger age categories. Proposed change (if any): 'An additional…violence. These issues should also be considered for younger children where relevant. In some…'.
696-698	Comment: Request clarification of text. Are the authors suggesting that an adolescent may never be considered to have the right to confidentiality of the information they share?
709	The wishes of the child should be considered in the case where he/she assents but the parents/legally designated representative does not agree (e.g. if for instance based on religious grounds). Consider if this should trigger an intervention by a third party (arbitrator, eg social worker, other pediatric care provider etc) to discuss.

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729-732	The need for appropriate vaccines expertise, where appropriate for the clinical trial in question, should be acknowledged. Change (if any): "Paediatric expertise is preferably provided by a paediatrician with at least some years of experience in paediatric care, some years of direct experience of clinical trials with children in similar age groups, expertise in clinical pharmacology <u>(or vaccinology as appropriate)</u> and expertise in ethics."
739-742	It is not clear why the use of placebo should be mentioned in the context of scientific requirements for which the involvement of methodological expertise is required in the review processes. Placebo is not used in all paediatric trials (e.g. vaccine trials in healthy minors), so it would be more appropriate to make reference to "control group". Change (if any): "To guarantee that these designs and assays are of sufficient quality, contribute to valid and significant outcomes, and meet all relevant scientific requirements (e.g. regarding the use of ~~placebo~~ <u>control group</u>), methodological expertise is required in the scientific and ethical review processes."
749 and 1423	The guidance states that similar trials based on an identical hypothesis should be avoided. We believe that this statement requires further clarification, since trials conducted by different sponsors and for different medicines within a particular therapy area (for example, antibacterials) are likely to be similar and have identical hypotheses – this conformity is dictated by both regulatory guidance and by PDCO in PIPs. Please change the statement to clarify that this is referring to similar trials <u>for the same medicinal product</u>.
749-750	Comment: In drug development sponsors are often asked to conduct replicate studies to ensure that the conclusions around benefit risk are robust. The example would be in adult phase 3 trials where sponsors are expected to run confirmatory studies. In paediatrics, there may be instances where there may be value in having 2 different sponsors with different IMP's run comparable studies. That way the sponsor can confirm that the answers are reproducible and be confident in the conclusions drawn. Secondly, in the case of PIP's, if the guidance states that replicate studies should be avoided, does this mean that a sponsor, with for

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	example a second in class IMP, could argue for a waiver if a study has already been conducted? This could have implications regarding how companies approach paediatric development and how the EMA may need to be encouraging collaborative development between sponsors.
770-771	Comment: Although the concept of involving parents and patients in the design of protocols is understood and in general welcome, the feasibility of this concept is very questionable. It is not clear how experienced parents or patients willing to contribute could be easily identified especially in the case of the study of acute conditions. In line with text in line 800-803, this text should be modified. Proposed change (if any): The protocol has been designed with and reviewed by experts such as paediatric specialists familiar with the care of the relevant patients, parents if feasible or patients (if feasible or applicable based on age and level of understanding) or by an appropriate patient organisation.
781-783	The guideline makes reference to the possibility of providing medicinal products to patients after completion of the trial where appropriate, "unless the benefit to risk balance of the medicinal product proves negative". The sponsor may make their own assessment on safety and efficacy, however, the final decision on benefit/risk lies with regulatory authorities. It would be more appropriate for the guideline to use language consistent with the Clinical Trial Regulation (see Regulation 536/2014, Annex I, D.17(ae)). Proposed change (if any): "The protocol may include a provision for the medicinal products to be given to patients involved in the ~~clinical~~ trial~~s~~ after the completion of the trial until marketing authorisation where such additional care is necessary because of the subjects' participation in the clinical trial and where it differs from that normally used for the medical condition in question ~~unless the benefit to risk balance of the medicinal product testes proves negative~~"
800-803	The draft revised guideline has introduced a requirement that "investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition) and of families in the development of information material, and where feasible also in the design, analysis and conduct of the trial. Exceptions to this recommendation should be justified." The current guideline **recommends** consultation with patients from relevant age groups or patient representatives: this advice is more appropriate, as such consultation may not be required for all studies. For example, a sponsor may re-use or adapt information material and/or study designs from a previous study for which children or their families were consulted: conducting a further consultation would add a burden on the sponsor with little

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	or no value. In addition, a proportionate approach to the need for consultation should apply, in which the risk/burden associated with the trial is taken into account. See also comment above on lines 770-771. Proposed change (if any): "To ensure feasibility of trials to be performed, the trial should be designed with the involvement of appropriate expertise, such as paediatric specialists familiar with care of the relevant patients. It is recommended that the trial design be set up following consultation of the patients from age groups to be involved in the trial (in older children or adolescents) or from patient representatives, taking into account a proportionate approach based on the risk/burden associated with the trial and the sponsor's prior experience with similar trials. ~~the investigator and protocol writer should ensure that there is involvement of children (suffering from the relevant condition) and of families in the development of information material, and where feasible also in the design, analysis and conduct of the trial. Exceptions to this recommendation should be justified.~~"
804-806	Comment: Chapter 9.1 is intended to describe general design features of paediatric clinical trials. However, the sentence 'The size of the trial conducted in children should be as small as possible but large enough to demonstrate the appropriate efficacy with sufficient statistical power and to provide a robust safety database' may suggest that in minors only confirmatory efficacy trials are possible/allowed. Given that a high proportion of trials in the paediatric population is dedicated to PK assessments and exposure evaluation where efficacy can only be a secondary endpoint, the requirement of sufficient statistical power for efficacy assessment appears to be unjustified. Proposed change (if any): The size of the trial conducted in children should be as small as possible but large enough to **ensure that the trial objective can reliably be reached** ~~sufficient statistical power,~~ **as applicable~~, and to provide a robust safety database~~.**
819-821	Original text: Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they are agreed with competent authorities when used with a view to provide data for regulatory purposes. Proposed changes: The recommendation is to agree on alternative designs with competent authorities, which is interpreted as either EMA or national agencies. However, paediatric plans are agreed with the PDCO. There should be no need for companies to first have to agree

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	with the PDCO on the paediatric studies and thereafter still have to go for scientific advice to get this also agreed with EMA/national agencies. The PDCO represents all member states and agreement with the PDCO should suffice. Proposed change (if any): Alternative (less conventional) designs and/or analyses should be justified and it is recommended that they are agreed with competent authorities or PDCO when used with a view to provide data for regulatory purposes.
840-841	The guidance recommends "Whenever possible, the evaluation by the child should additionally be obtained". It appears that this is with regard to the reporting of adverse events based on the assessment of parents or other carers. It is not clear what the sponsor is supposed to do with such evaluation from the child. Proposed change: Delete : ~~Whenever possible, the evaluation by the child should additionally be obtained~~
844-850	Comment: Recommend that trials in rare diseases for minors aim to follow the methodologies for rare diseases in adults, rather than the methodologies for more common diseases. Proposed change (if any):Trials performed in children affected by rare diseases should aim to follow the same methodological standards as those performed in ~~more common diseases~~ adults with rare diseases…
911	Comment: There may be potential for the minor to experience a personal health benefit. Proposed change (if any): Rephrase to "the participating minors cannot necessarily expect a personal health benefit".
1002-1034	On section 11.1, concerning "Assessment of Risk", we would suggest to consider the inclusion of wording on patient reported outcomes (PROs). Proposed change (if any): text could be added as follows: *"When self-reporting measures such as patient reported outcomes (PROs) are used the following should be considered in order to minimize patient burden* • *Limit the number of PRO's also considering the number of items in each questionnaire.* • *Use questionnaires validated for the appropriate age group when possible.* • *Administer scales in the local language.* • *Staff should assist and support the children if needed without responding to the questions."*

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1035-1115	The new section on "Burden" does not mention that even non-painful procedures (e.g. ECGs, vital signs, ocular assessments) can cause anxiety and be considered a burden to the child and parent. Each additional assessment may cause the parent to think that the new drug must carry a lot of risk if it requires so many assessments. Proposed change (if any): "… Coping mechanisms alter with age and maturation, changing the burden experiences, for example when medical procedures are not considered any more as 'punitive'. Some non-painful procedures (e.g. ECGs, vital signs, ocular assessments) can cause anxiety and be considered a burden to the child and parent."
1097	Comment: Cited "repeat examination of injured or traumatised limbs or part of the body…" Proposed change (if any): suggested edit to "…or part(s) of the body…"
1118-1119	"Risks and burden should be continuously monitored and monitoring should be pre-specified in the protocol." Continuous monitoring implies mostly implies using electronic equipment (eg ECG monitoring). This is not what is intended here, therefore continuous should be removed. Additionally clinical assessment such as the one described in the next sentence are usually not described in detail in the protocol. Therefore we propose to delete the latter part of the sentence. Proposed change (if any): Risks and burden should be ~~continuously~~ monitored ~~and monitoring should be pre-specified in the protocol~~."
1159-1195, 1233-1236	In section 12.2, it is not clear whether placebo-controlled clinical trials fall into the "prospect of some benefit for the population represented by the minor" category. As, in each such trial, ""minimal risk and burden" will have to be viewed in the context of the disease, health status, prior experiences and related standard treatment", we assume that placebo-control may be acceptable in some cases.

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	Proposed change (if any): Add text to clarify that placebo-controlled clinical trials may fall into the "prospect of some benefit for the population represented by the minor" category.
1200-1202	Proposed change if any: - Is the trial pertinent to the paediatric population?
1229-1236	The evaluation of the risk and burden based on standard treatment is not relevant in the context of studies of vaccines and other medicinal products with healthy volunteers in cases where there is no standard of care (e.g. as no vaccine is available). Proposed change: The box headed "Standard treatment" should be preceded by the question "Is there a standard treatment?" If yes, the assessment should progress to the "Standard treatment" step in Box 1. If no, the assessment should progress directly to the "General proportionality" step.
1290-1291	The use of advanced statistical techniques may not be possible in all cases. For example, in vaccine trials the immune response always needs to be measured individually. Proposed change (if any): "When applicable, advanced statistical techniques such as population approaches and optimal design techniques should be applied to reduce the number of samples required."
1292-1293	Micro assays are not always optimal especially in the older age groups other assays might be preferred. Propose to delete that not using micro-assays should be justified in the protocol Proposed change (if any): ~~Not using micro-assays should be justified in the protocol~~
1292-1294	Comment: Conscious sedation is less invasive than general anaesthesia and may be more appropriate than use of large amounts of local anaesthetic. Its use should be referenced.

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1298-1299	Comment: While presented as an example, it is unreasonable to assume that even the most technically savvy clinicians can complete procedures on the first attempt in all scenarios. Micro-preemies can frequently require 2 attempts at intubation or line placement, in emergent scenarios (code) patients have collapsed cardiovascular systems and may require a 2nd attempt or multiple sites for attempt at access. Therefore, this guidance would be better suited to describe that protocols should set a pre-specified limit on numbers of attempts. If the most adept clinician for a procedure hasfailed on the first attempt at a very difficult procedure, is it equitable to then relegate the task to someone on staff who is less likely to succeed only because the 1st attempt failed? Proposed change (if any): ~~For example, it is recommended that after one unsuccessful attempt, another experienced person take over the procedure.~~
1301	Propose to add that sponsor should seek out PK/PD/ Biomarker assays that limit the amount of blood that is needed.
1333-1334	In vaccine trials and other clinical trials in disease prevention, healthy minors are the target population which therefore needs to be enrolled. The postulate on lines 1333-1334 (“*In principle, healthy minors should not be enrolled in clinical trials as healthy volunteers, because usually a trial does not benefit them or the population of healthy minors.”)* is therefore inappropriate as currently written. Proposed change (if any): “In principle, <u>with the exception of clinical trials on vaccines or prevention trials,</u> healthy minors should not be enrolled in clinical trials as healthy volunteers, because usually a trial does not benefit them or the population of healthy minors.”
1337-1338	Comment: The ‘swill and spit taste testing’ should have a focus on acceptability and not just taste, and the aim to minimise additives in paediatric medicines. Proposed change (if any): Suggest broadening this text to “Exceptions could be where healthy children participate in palatability <u>dosage form</u> acceptability testing such as swill and spit taste testing for products in development of a new flavoured medicine”

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1342	Comment: There is a contradiction between this statement and the example of a taste test above. Healthy children could take part in such a study, and the population of healthy children may expect some benefit and future populations of children with a disease might benefit. This passage should be clarified to ensure the consistency of guidance of conducting trials with healthy minors.
1346-1348	Comment: Diseases which includes flares, relapses, acute manifestations are not absent when the patient is not in a phase of flare etc. The disease is there, as an underlying condition. A patient with lupus or epilepsy for example, has the disease and should not be considered a "healthy patient" (in the sense of a patient with no disease) in between flares or acute manifestation of the disease. Studies in these chronic diseases should be accepted. Proposed change (if any): 'Trials in children with ~~intermittent~~ diseases with intermittent manifestations (e.g., flare-ups or seizures) are ~~may be~~ acceptable because even in the "healthy" phase the children are affected.'
1353 - 1359	Comment: Abstinence is the most effective form of birth control and as such should be referenced as a preferred method in this section, in particular as it can be assumed that a percentage of the minor female population who has had menses have not and will not have sexual intercourse during the trial. Careful counselling on the ramifications of intercourse while participating in a trial with therapies that are known teratogens should be undertaken. Further, guidance and specific recommendations would be useful for those adolescents who will have sexual intercourse (in spite of the recommendations). Guidance could include e.g. best practices about adequate birth control with their risks/ limitations; right to privacy and (limits of) confidentiality; religious and cultural considerations.
1354	Comment: It would be helpful if a definition could be provided for child-bearing potential in this age group e.g. a range from a certain age or commencement of menarche.
1357-1358	Comment: Consideration should be given to adding a section on use of contraception is adolescent males.

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	Proposed change (if any): 'Trials with adolescent males Inclusion with the use of contraception should be made possible by the investigator for this group of participants. There should be thorough explanation of this as part of the informed consent process'
Before line 1360	Sections 14, 15 and 16 describe points to consider in trials with 3 specific paediatric populations (neonates, healthy minors and adolescent females). A further situation to consider in this guideline is "Trials with children of parents who are minors". The enrolment in clinical trials of minors whose parents are also minors presents additional challenges which sponsors are already encountering. Some guidance on how to manage such cases would be helpful. Change (if any): Add a section providing guidance on "Trials with children of parents who are minors"
1360-1373	Comment: Throughout this section clarity on terminology should be included when reference is made to 'form'. Proposed change (if any):"Dosage form".
1360-1373	Comment: The detail within this section is more extensive than would be expected for a document covering ethical considerations. The EMA have a comprehensive guidance document on formulation development for paediatrics (EMA/CHMP/QWP/805880/2012 Rev. 2) and should be referenced as needed. Recommend significantly reducing the amount of detail in the section as proposed. Proposed change (if any): With a focus on the suitability and safety of the dosage form for paediatric use; where available age appropriate dosage forms should be used although there may be a need to use an enabling dosage form in early clinical studies. The dosage form to be used should be described in the clinical protocol. Considerations for dosage form development are contained within the EMA guideline EMA/CHMP/QWP/805880/2012 Rev. 2.
Line 1383-1393	The request seems reasonable, however, in practice it will be close to impossible to comply. It would mean that the date by when a minor becomes adult, must be actively followed-up, and the minor (then adult) must be actively sought in public through the investigator. Aside

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	from issues around confidentiality, the risk of non-compliance of such a complex, long-term requirement will practically result in prohibition of future use of data obtained in children.
1386-1393	The guideline recommends that "yearly check-ups regarding the contact data of the patient and his/her parents are advisable" with regard to the need for consenting to use of biobank samples. This recommendation provided is not feasible for example in vaccines trials in healthy volunteers where thousands of persons are enrolled. In addition this recommendation would require active follow up of when the minor becomes an adult. Aside from issues around confidentiality, the risk of non-compliance of such a complex, long-term requirement will practically result in prohibition of future use of data obtained in children. Proposed change (if any): "In such cases, ~~yearly check-ups regarding the contact data of the patient and his/her parents are advisable~~ the preferred option is to seek re-consent. If this is not possible, the sponsor should seek a waiver from consent from the relevant ethics committee(s)."
1391	Comment: "*The trial documents should be archived for a duration of 25 years after the end of the trial and medical files of the subjects shall be archived in accordance with national law (Article 58).*" Proposed change (if any): For Advanced Therapy trials traceability records must be retained for a minimum of 30 years.
1414-1418	Summary of the results of the trial should be understandable by a layperson (as in the new EU regulation), but moreover understandable by the children having participated in the trial. This very difficult to achieve especially in the case of inclusion of very young children in the clinical trials. It is therefore recommended to drop this requirement. Proposed change (if any): ~~In case of pediatric trials the summary should be understandable by the children that have participated in the trial.~~
1417-1418	It is unrealistic to require that the laypersons' summary for paediatric clinical trials is understandable to children that have participated in the trial, particularly when the trial involves younger age groups. The laypersons' summary is to be made available to the general public via the EU CT Database and should, therefore, be written for one primary audience, i.e. the general public. Alternative means of communicating the results to paediatric trial participants should be considered, where appropriate.

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	Proposed change (if any): "In case of paediatric trials, the summary results should be communicated to ~~should be understandable by~~ the children that have participated in the trial if appropriate, and based on their level of understanding."
1431-1434	The sentence regarding inclusion of information on paediatric studies, PIPs, waivers and deferrals is confusing. No such requirement exists in the Clinical Trials Regulation, and the Paediatric Regulation does not require inclusion of information on the status of PIPs. Proposed change (if any): "This is supported by the general provisions on transparency in the Clinical Trials Regulation ~~and by.~~ It is also supported by the Paediatric Regulation, which demands that information on the results of studies in the paediatric population, as well as on the status of the paediatric ~~investigation plans,~~ waivers and deferrals, should be included in the ~~product information~~ summary of product characteristics and, if appropriate, the package leaflet."
1440	It is incorrect to suggest that adult data are always poorly predictive of safety in children. Proposed change (if any): "Adult data ~~are poorly~~ may not always be predictive of safety in children"
1440	Comment: The use of the word "are" in this sentence is too strong. Proposed change (if any): Change to "As adult data ~~are~~ **may be** poorly predictive …".
Lines 1444-1447	Please consider to also include the option of a systematic assessment of adverse events (AEs) like the The Pediatric Adverse Event Rating Scale (PAERS).[i] The PAERS is a clinician-rated scale designed and validated to assess adverse events occurring in paediatric patients who are treated with psychotropic medication in clinical studies. Reference: [i]March J, Karayal O, Chrisman A. CAPTN: The Pediatric Adverse Event Rating Scale. Paper presented at: Scientific Proceedings of the 2007 Annual Meeting of the American Academy of Child and Adolescent Psychiatry; October 23 to 28, 2007; Edited by Novins DK, DeYoung. Boston, MA; 2007; 241.
1477-1480	The guideline states that, in the context of clinical trials submitted in a marketing authorisation application in the EU, "the trial protocol

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	should be submitted for ethical and scientific review in the EU Member State in which the sponsor or its legally designated representative resides". It is not clear what the legal basis for this statement is or how this is to be done, particularly in the context of the Clinical Trial Regulation, the scope of which is limited to clinical trials conducted in the European Union. This statement should either be removed or revised to make clear that it is a recommendation (not a requirement). Proposed change (if any): "Similarly, ethical standards should be no less exacting than they would be for research carried out in EU countries ~~and that, in addition, the trial protocol should be submitted for ethical and scientific review in the EU Member State in which the sponsor or its legally designated representative resides~~."
1477-1484	These two paragraphs are not completely aligned. Trials may respond to local public health needs/priorities while NOT adhering strictly to "the ethical standards" used in EU countries. For example, the standard of care in wealthy and resource limited settings is (almost by definition) different than that in resource limited countries. Requiring a common SOC in order to be "ethical," will result in studies not being conducted that are in fact responsive to local public health needs. This is not a major issue for multisite international research for development of products for global use. It is an issue for products being developed for use in resource limited settings only, e.g. for certain tropical diseases. As it stands, the paragraphs are not sensitive to the special needs of programs seeking review through the Article 58 procedure. The most useful documents informing this issue are CIOMS guidances (1992, 2000), and NOT the Declaration of Helsinki (which fails to address it).
Annex 1	If annex 1 is kept, add agreed upon PIP
Page 38; Annex 1	Point 3 in the list of issues to be considered in a clinical trial involving minors is not applicable to vaccines. Proposed change: "3. Evidence of direct benefit for the child, or benefit for the population <u>(not applicable to vaccines)"</u>
Annex 1	11 add "validated Quality of Life" forms.
Section 25 – ANNEX 1: List of issues to be considered in a	Comment: It is not clear what value this Annex adds to the Ethical considerations document. The list includes the host of considerations that one should consider for a bench to bedside pediatric development program, many of which are based on good clinical practice and should be addressed in the requisite guidance document on the individual trial-related topic, and have little to do with consideration of

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clinical trial involving minors	ethical principles. This annex would be more valuable if it served to focus on the ethical considerations one should take into mind for a clinical trial involving a minor.
ANNEX 2	List of items: Proposed change (if any): consider adding: • "can I stay on the new medicine if approved, and what kind of treatment will I get from now on?" • “can I stop the study drug and stay in the trial?”
ANNEX 2: Line 7	Comment: Use of the wording: “increases attractiveness“, could be misinterpreted as trying to influence the reader of the (clinical trial) information sheet. Proposed change (if any): Rephrase to “…~~increases attractiveness~~ improves readability…”.
Annex 3:	General comment: the risk and burden on the minors can depend on their age. For example an oral glucose tolerance test might be more burdensome in younger children compared to adolescents. It would be appropriate to reflect this perhaps as a footnote to the table Proposed change (if any): Add footnote perhaps as follows: consideration should be given to the age of the paediatric patient when examinations are categorized (eg a category 1 examination might become a category 2 examination in younger subjects).
Page 43/49 - Annex 3 categories	Several of the proposed categories seem to be inappropriate, based on the associated levels of risk or burden. We propose the following changes to the categories listed in Annex 3: Currently listed in Category 1 • “Tanner staging” – Move to Category 2: This assessment is very much disliked by paediatric subjects • “Ophthalmoscopy” – Move to Category 2: This can be unpleasant for patients • “Lung function tests (spirometry)” – Move to Category 2: These tests are hard work and not part of usual standard of care in asthma in children • Digitally amplified chest or limb X ray- Move to Category 2 as both procedures imply irradiation of the child

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	<u>Currently listed in Category 2:</u> • ”Airways or skin hyper-reactivity challenge test” – Move to Category 3: bronchospasm is a possible outcome • “Umbilical catheter” – Move to Category 3, unless catheter is already in place or clinically indicated.– • “MRI scan” and ”Polysomnography” – Move to Category 1: it is not clear how these in and of themselves are risky, as they are non-invasive. If sedation is required for MRI, this would in any case fall under Category 3. • “CT scan” – Move to Category 3: we understand that CT scanning involves more radiation than PET scanning • “Transcutaneous oxygen or carbondioxide tension monitoring” – Move to Category 1 • X-ray DEXA bone density measurement – Move to category 3 as some countries (eg Germany) limit these tests due to the level of radiation • Add “insertion of arterial lines“ - This procedure might be required for multiple blood draws or arterial monitoring of blood gases, acid base balance etc..; <u>Currently listed in Category 3</u> • “PET scanning” – Move to Category 2: we understand that PET scanning involves less radiation than CT scanning. • “sedation” – Move to Category 2 • “hypoglycaemia test” – Move to Category 2 • Add: “central venous catheters” –especially when inserted close to the hart
page 44	References: add EMA document "Informed Consent for Paediatric Clinical Trials in Europe 2015 - update 15 May 2016 from EnprEMA (European Network of Paediatric Research at the European Medicines Agency).

Please add more rows if needed.