Comments of the [redacted]

Introduction - Rationale for the Development of Recommendations

The otherwise thoughtful discussion of the rationale behind the expert group's recommendations errs in one significant respect. The statement that "Data on effectiveness and safety cannot reliably be derived from data in adults" [lines 186-187] is not correct. On April 4, 2016 the EMA released a draft reflection paper outlining a framework for the extrapolation of clinical trial data from adults to children to support the authorization of new medicines for children([1]). Similarly, under the U.S Pediatric Research Equity Act, if the course of disease and the effect of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be extrapolated from adult data[2]. Accordingly, the statement regarding the inability to derive pediatric data from data in adults should be removed from the recommendations or revised to accurately reflect where such extrapolations are possible.

6. The Process of Informed Consent
6.1 Informed consent from the legally designated representative

The consultation document's recommendations provide that "as soon as" an adolescent is no longer a minor, or becomes an emancipated minor, "no trial related procedures may be performed until informed consent [from the participant] is provided." [lines 466-468] The consultation document acknowledges that the age at which a person is considered an adult is highly variable across Member States, and further that emancipation can take place as the result of certain actions, including marriage. As a result, the consultation recommendations will likely cause unintended serious GCP violations should a site not diligently police the personal status of their participants. The harm outweighs the benefits in this instance inasmuch as the population most likely in question here would have been solicited for agreement to participate at the outset of the trial as part of the process of obtaining consent from the parent/legal guardian and thus would have already been consulted regarding participating in the trial. Site investigators should obtain consent from participants who have reached majority, but this should be done promptly or as soon as practicable. This would correlate with the recommendation in section 6.4 of the consultation document where if a legally designated representative changes during the trial, informed consent should be sought again "as soon as possible" [lines 505-506]. As currently drafted the recommendation that the trial be halted with regard to a participant passing into majority or becoming emancipated sets a threshold that will result more in GCP violations by sites than offer any real protection for participants.

6.4 Consent at the beginning of a trial and continued consent during trial

Consent is an ongoing process, and taking the emotional temperature of participants at each study visit is an important part of the ethical conduct of the trial as well as a good way to promote optimal participant compliance. This is something that is best done through site processes and procedures where the expectations for each visit are pre-determined and followed as standard practice. Having established processes precludes the necessity of documenting every action taken every time. What is important is that there is individual interaction between the site staff and each participant at every visit, not that an entry is made on a checklist. Requiring documentation of consent at every visit is

[1] Reflection paper on extrapolation of efficacy and safety in paediatric medicine development. http://www.ema.europa.eu/docs/enGB/document library/Regulatory and procedural guideline/2016/04/WC500204187.pdf

[2] Section 505B(a)(2)(B) of the FD&C Act, 21 USC §355c(a)2(B)(i)

unrealistic and overly burdensome for the minimal benefit that might result.

8. Expertise Required for Assessment
8.3 Opinion on the application dossier/ Section 9.1 Design and Analysis

Considering that the impetus for the consultation document's recommendations was recognition of the urgent necessity for evidence based medicine for children, the wording of the requirement in lines 755-756 seems counter-intuitive. Rather than require that a justification be provided for the inclusion of children in a clinical trial, it would be more appropriate to require a justification for why children are not included in a study.

Section 8.3 also recommends that the protocol be designed and reviewed by parents and patients [lines 770-771]. This section implies that this is a requirement under the new clinical trials regulation [lines 746-747]. This is not the case. Annex I, section D.17 (e) of Regulation (EU) 536/2014 provides that "where patients were involved in the design of the clinical trial" the patient participation should be described in the protocol. Similarly, the recitals to the Regulation encourage Member States to consider involving laypersons, particularly patients or patient organizations, as part of the national review bodies (recital 18). The Regulation does not make this participation, in either the protocol development or national review, mandatory. However, sections 8.3 and 9.1 of the consultation document states as a requirement that pediatric patients suffering from the relevant condition to be studied, and their families, be involved in the design, analysis and conduct or the trials as well of the development of the patient materials [lines 800-803]. It is not typical to involve potential participants in the development of adult studies, singling out pediatric trials to impose this requirement is more likely to impede rather than progress pediatric research.

We agree that community outreach is important and can have a real and positive impact on participant enrollment and retention; however, having parent and patient input on study design and protocol review is an impractical requirement to impose as a part of a clinical study application review. The research group here at [redacted] has the distinct advantage of being comprised of practicing clinicians. The investigators heading up our research efforts are involved with patients and parents as a matter of course. This experience informs our view of those areas in which research is most needed. We have also engaged an independent patient advocate to serve as a reviewer of our protocols and have reached out to [redacted] for projects on which we can collaborate. By initiating community engagement activities in this stepwise fashion, we can improve our studies while continuing to effectively conserve limited study resources. We anticipate that as experience on both sides grows, we can collaboratively grow our efforts. Making participant engagement in the research planning stages a requirement to application review risks making the effort an exercise to be got through rather than the conduct of meaningful outreach.

9. Design of clinical trials conducted with the paediatric population
9.2 Paediatric control groups

In addition to the control groups discussed in the consultation document, in studies where use of an active placebo control group is impossible or unethical, consideration of natural history data for the condition studied for use as a comparator group may be provide value. Although not typical in studies here, this has been suggested by our regulatory authority as an alternative design.

Box 1. Guide to assessing acceptable levels of risk and burden in relation to the benefit [lines 1198-1243]
We had difficulty understanding the intended flow of this graphic. If intended as a decision tree, the first two boxes have no decision function associated with them, apparently assuming that the answer

to all 5 questions must be “yes” or the only alternative in each instance is “don’t do the trial.” Similarly, it appears that the right side of the chart is intended to be the “yes” side for all questions asked in the boxes on the right side, whereas the left side is the “no” side. The illustration requires some additional work to be an effective tool to “guarantee appropriate protection” for children in research.

12. Assessment of relationship between benefit, risk and burden
12.2.1 Standard treatment
Lines 1247-1249 recommend that “Since in paediatric medicine the level of evidence may be poor, in those cases best practices qualify as standard treatment.” If the expert recommendation is to be reliance on best practices, some additional guidance on what would be considered reliable “best practices” in these situations would be merited. As noted earlier in the consultation document, definitions of standard or care may vary; similarly, what is considered “best practices” under any given circumstances can also vary widely.

12.2.2 Assessment of risks and burden for individual children
There is a typographical error in line 1273.

18. Individual Data Protection
The recommendation to conduct yearly check-ups regarding the contact data of “the patient and his/her parents” appears to be connected to obtaining consent “several years” after the initial trial to use data or specimens for other research purposes. This recommendation is directly contrary to the overall requirement that confidentiality and data be protected. Keeping contact information from a clinical trial after the trial is concluded and periodical checking and refreshing that information is an open invitation to a security breach. It is far better to recommend that the original consent comprehensively address exactly what uses will be made of participant data and samples now and in the future and all future activity be governed by that consent. Alternatively, the initial consent can provide for the removal of all identifying information or a statisticians de-identification of personal information in support of a broader future research use.

It is an unfortunate requirement of Regulation (EU) 536/2014 that investigator records must be saved for 25 years. This extended retention period exacerbates the difficultly of protecting participant confidentiality as well as increasing the cost of conducting a clinical trial through the extended secure storage requirement. The practical implications of trying to adhere to this requirement while complying with the higher duty of protecting the “Anonymity of the data, as well as confidentiality of personal information related to the child involved in the research, and to his/her family” [Annex 1 : line 28] have yet to tested. We do not recommend adding to these potential problems by requiring periodic updating of participant contact information.

19. Unnecessary replication of trials
19.1 Publication of paediatric trials and results
Protocols should not restrict publication by the investigators; however, there is no reason why timelines for publications should be specified in a protocol. This puts an additional burden on participating investigators with no corresponding benefit. Trial results are already required to be posted in both the U.S and EU clinical trials registries within specified timeframes so participants and the general public will have access to trial results. Putting manuscript deadlines in protocols benefits no one and makes protocol deviations in this one instance almost a certainty.

27. ANNEX 3: Examples for levels of risks and burden
We have no comment on the current allocation but question the completeness of the list. Where does drug administration fall on this? If lumbar puncture, arterial puncture, IV placement, bone marrow aspiration, CT scans, contrast media, and punch biopsies are minimal risk, does

administration of an authorized medication, when used as an investigational or comparator product, also comprise minimal risk?