SIOP Europe
the European Society for Paediatric Oncology

Response to European Commission consultation on 'Ethical considerations for clinical trials on medicinal products conducted with minors'

31 August 2016 (updated and final)

SIOPE is the only pan-European organisation representing professionals in the field of childhood cancers, working together with parents, patients, survivors and their associations to advance more and better cure for childhood cancer across Europe. http://www.siope.eu

SIOPE generally supports the consultation document and would like to complement it with important considerations based on our core activities and expertise in childhood cancers and close cooperation with parents, patients and survivors.

7. Participation of minors in the informed consent process and agreement

Lines 599 – 611: *"It is important to note that "forming an opinion" should not be understood to only apply to children that have reached a certain age or level of maturity, as even young children are able to form and express their opinion in one way or another. Therefore, any objections raised by a child at any time during a trial should be analysed, including those of very young children. The child's will should be respected. The child does not have to provide reasons. The child should be informed of the possibility to freely withdraw from the trial, at any time for any reason, without any disadvantage or prejudice (cf. section 6.5). This also means that investigators should be able to recognize signs of resistance in children. They should evaluate whether these signs are part of the anticipated burden (e.g. distress or fear), consult with the parents/legally designated representative, and appropriately respond to the child's worries, e.g. by trying to decrease the burden. This behaviour may lead to the understanding that the child dissents, and that therefore the child should not be enrolled in or should be withdrawn from the trial."*

- **SIOPE comment**: A suggestion is where appropriate to have recourse to a multidisciplinary approach, including the child's psychologists, when the child expresses the will to refuse to participate/continue participating in a clinical trial. This approach would of course be applicable after the parent's consent. For instance, if a 4-year-old child expresses that he wants to stop, it is useful to understand exactly what is occurring. This is also true for § 7.2.2 and 7.2.3.

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7.2 Participation and agreement according to age groups and level of maturity

- 7.2.1 Newborns and infants (from birth to 2 years of age)

Lines 637 – 641: "*In this age group, it is not possible to obtain agreement, and understanding of research is not expected. Providing information to the child is mostly aimed at preparing the child for the procedures to come. Although these children are not able to raise verbal objections, any signs of resistance or protest should be identified and lead to a discussion with the parents/legally designated representative.*"

- **SIOPE comment**: The statement could be better adapted to the reality of patients in this age group when they find themselves in a clinical situation. Indeed, there are few medical interventions that such small children submit to willingly regardless of the fact that they are administered in a clinical trial.

- 7.2.2 Pre-schoolers (2-5 years of age)

Lines 650 – 656: "*Research on cognition shows that younger children have significant ability to provide agreement. It is recognised that children from the age of 3-4 years can express altruism and have an emerging capacity to form an opinion. At the same time, these children have significant ability to express fundamental resistance and protest, beyond the usual signs of discomfort during or after unpleasant procedures. These expressions should be taken seriously and discussed with both the child and the parents/legally designated representative. When it is evaluated that these are expressions of dissent, this should be respected."*

- **SIOPE comment**: A suggestion is where appropriate to have recourse to a multidisciplinary approach, including the child's psychologists, when the child expresses the will to refuse to participate/continue participating in a clinical trial. This approach would of course be applicable after the parent's consent. For instance, if a 4-year-old child expresses that he wants to stop, it is useful to understand exactly what is occurring.

- 7.2.3 Schoolers (6-9 years of age)

Lines 657 – 672: *"Within this age group there is a growing capacity to provide agreement, and this group is known to be able to express altruism. From the age of 7, children may be able to understand benefits and risks of research and start to understand conflicting or abstract information. This should be taken into consideration when developing information material and agreement forms (if applicable) aimed at children. Most children and parents are not familiar with the concept of randomisation, making it a complex notion to understand. However, it has been shown that children with chronic illness may have developed an increased capacity to make independent judgements based on previous life experience. These judgments and the child's point of view should be taken into account. The dissent should be respected, as these children are capable of forming an opinion of their own. In any case, it is of major importance to inform the child and obtain agreement as described above, preferably in writing, and to keep track of the procedures to seek agreement as well as of such agreement. Even though the child is of 'school age', i.e. able to read and write, proper understanding can be enhanced by making use of visuals such as videos, pictograms, cartoons and drawings."*

- **SIOPE comment**: A suggestion is where appropriate to have recourse to a multidisciplinary approach, including the child's psychologists, when the child expresses the will to refuse to

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participate/continue participating in a clinical trial. This approach would of course be applicable after the parent's consent. For instance, if a 4-year-old child expresses that he wants to stop, it is useful to understand exactly what is occurring.

7.3 Difference of opinion between the child and the parents/legally designated representative

Lines 701 – 710: "*This means that the investigator should aim to reconcile the differences of opinion, in order to do justice to the (growing) capacity of children to make adult-like decisions. If the child and parents/legally designated representative are not able to come to a consensus, the dissent of either party is decisive."*

- **SIOPE comment**: It is not clear from the statement what exactly should happen if there is dissent between child/adolescent patient and his/her parents.

8. Expertise required for assessment

- 8.3 Opinion on the application dossier

All section (Lines 744 – 794)

- **SIOPE comment**: For early clinical trials in oncology, the lack of validated treatment option should be documented and validated.

9. Design of clinical trials conducted with the paediatric population

- 9.1 Design and analysis

Lines 800 – 803:*"To ensure feasibility of trials to be performed, 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*."

- **SIOPE comment**: It may not always be possible to have a patient suffering from the disease involved such as in the case of cancer, due to factors such as availability during the treatment periods, prospect for some patients to also take part in the trial, and limited number of patients in some pathologies. The requirement to involve actual patients, if too strong and narrowly construed, may lead to increase demands on patients as well as inequalities in rare conditions.

Trained/expert patient representatives including survivors and parent groups can effectively ensure representation as well. As the design, analysis and conduct of trials usually need expert knowledge and experience, it is important to make efforts to identify patients or representatives who are able to contribute significantly and correctly.

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Lines 810 – 812: *"To this end, it is in any case suggested to use "smart" trial designs, and advanced statistical techniques for analysis of paediatric data. Examples of designs are adaptive designs and proof of concept in combination with a randomized controlled trial (seamless approach)."*

- SIOPE comment: SIOPE strongly supports this point and suggests that the following considerations are taken into account in particular:

- Limited value of repeating dose finding studies in "older" children
- Recommendation of decreasing lower age for inclusion in early clinical trials of drugs with strong rationale to use them also in children/adolescents
- Specific and limited studies including specific PK studies in the very young children

11. Identifying, minimising and monitoring risks and burden

- 11.1 Assessment of risk

All section (Lines 1002 – 1034)

- **SIOPE comment**: The issue of long-term risk and long-term follow-up should be inserted.

- 11.2 Assessment of burden

Lines 1090 – 1093: *"Age-appropriate explanation should be given to the child prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might lead to humiliation of the child (such as undressing), therefore causing emotional pain, should be avoided or explained."*

- SIOPE comment 1: What kind of and how explanations are given should be determined on a case by case basis.

- SIOPE comment 2: SIOPE proposes to delete lines 1092-1093 – "*Any procedures that might lead to humiliation of the child (such as undressing), therefore causing emotional pain, should be avoided or explained*" – as the sentence suggests negative implications of clinical trial circumstances which rarely apply in practice.

Lines 1112 – 1115: *"At the sign of distress and/or dissent the trial procedure should be stopped; a short pause to allow the child to feel in control, further explanation and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure and perhaps even withdraw from the trial."*

- SIOPE comment 1: The statement as it currently stands may imply the suggestion to stop every time a child objects or becomes distressed, which is not appropriate. An alternative and more fitting suggestion is to ensure that experienced medical staff undertakes procedures to limit attempts on children. Parents will know when to put a stop to a procedure if there are concerns or undue distress of their child.

- SIOPE comment 2: SIOPE furthermore suggests modifying the wording to read as follows: ***"At the sign of distress and/or dissent, the trial procedure should be halted to allow the child to feel in control and to allow further explanation. Sometimes, an assessment…"***

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13. Assays in relation to age/bodyweight and blood sampling

13.2 Volume of blood

Lines 1311 – 1319:"*The following blood volume limits for sampling are recommended (although are not evidence-based). Per individual, the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1% at any single time. In the rare case of simultaneous trials, the recommendation of 3% remains the maximum. The total volume of blood is estimated at 80 to 90 ml/kg body weight; 3% is 2.4 ml blood per kg body weight. When blood sampling is also needed for normal health care, these indicated trial-related blood volumes may be too high, especially in (preterm newborn) infants. Trial-related blood sampling should always be justified.*"

- **SIOPE comment**: It should be made clear whether the intention is for these limit indicators to apply when routine blood samples are added to research sample volume. It is written in a way that suggests that they only apply to additional research samples.

18. Individual Data protection

Lines 1383 – 1393: "*The specificity of data protection in children also relates to future (unknown) use of data obtained in children. The use of the data beyond the protocol, e.g. for the purpose of future research, should be subject to informed consent, and conform with Article 28(2) of the Clinical Trials Regulation. Biobank samples retention and the need for consenting to such use should be discussed in the protocol. It may be difficult to reach a minor participant of a trial after several years to obtain consent after the participant has reached the age of consent. In such cases, yearly check-ups regarding the contact data of the patient and his/her parents are advisable. The law of Member States determines how to act when the participant who has reached the age of consent, cannot be contacted, e.g. samples may have to be destroyed. 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).*"

- **SIOPE comment**: There is the need to clarify if the statement applies to anonymised trial data. It should be possible to use anonymous data for trials in the future even if consent cannot be obtained at that time from the child. In the area of rare diseases - such as virtually all forms of childhood cancer, such data use is indeed essential for knowledge and development of new agents. In the case of non-anonymised data, it has been a clear conclusion of meetings with patients/parents representatives conducted during the EU FP7 ENCCA project (European Network for Cancer Research in Children and Adolescents) that re-consent at the majority was necessary for any new biological study on collected tumour samples (including during a clinical trial).

19. Unnecessary replication of trials

- 19.1 Publication of paediatric trials and results

Lines 1417 – 1418: "*In case of paediatric trials, the summary should be understandable by the children that have participated in the trial.*"

- **SIOPE comment**: It should be included in the statement that the nature of such understanding is dependent on the age of the participating population. The summary of the

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results should be made available in an age-appropriate manner, while recognising that very young patients may need to wait long enough to understand the summary. A lay perspective could be sufficient for a parent or young person to understand and explain the contents to a child.

22. Insurance issues

Lines 1456 – 1459: "*Obtaining insurance for trials performed in children, in particular those in neonates, may be difficult, for example, because insurance companies invoke issues of long-term liability. Insurance companies' contracts should not waive liabilities regarding long-term effects, or limit the liability period,… "*

- **SIOPE comment**: This is an important point – we need to ensure that the costs of clinical trial insurance for trials involving children are not prohibitive because of a perceived risk of long term liability.

25. ANNEX 1: List of issues to be considered in a clinical trial involving minors

Point 14, p. 38: *Inclusion and exclusion criteria*

- **SIOPE comment**: The wording 'exclusion criteria', although classical, is not logical: to be excluded, the patients would have first to be included; here we are talking about '**non-inclusion**' criteria.

Point 17, p. 38: *Safety measures including the set-up of a Data Safety and Monitoring Board (DSMB)*

- **SIOPE comment**: Suggest adding '**when relevant**'.

Point 18, p. 38: *The option of sperm and oocyte cryopreservation if the child's fertility has the potential to be affected by participation in the trial*

- **SIOPE comment**: Suggest adding condition at the end of the statement as follows **'and the risk is increased by the trial intervention**'.
Indeed, for many paediatric oncology treatments, the impact on fertility is often due to the standard treatments, and provisions for fertility should be part of the institution's normal clinical practice and therefore not a trial-related requirement.

Point 23, p. 38: *Study burden for participants (including pain, fear discomfort, time investment and logistical aspects)*

- **SIOPE comment**: Suggest adding '**assessed in the context of the burden of disease and current standard treatment or alternatives**'.

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26. ANNEX 2: Information for informed consent

p. 40, para 2: "*The number of age-specific variations of sets of information material should be kept to a minimum number required to include substantially different wording or presentation. In addition, information sheets should not cause unnecessary distress. They should be designed with input from participants, affected children or parents."*

- **SIOPE comment**: This is a very welcome point. Many parents deal with raised concerns about giving the children too much information causing them distress. A possible recommendation is to use age categories in line with the PDF document para 5.1 including for instance preschool age, school age, 10-17 year-olds, etc., with no information document foreseen for infants. In addition, patient representatives may also play a role and may be better placed to do so in certain circumstances. Peers may also help to assess whether information is plain and understandable according to age.

Point 3 (List of items recommended to be covered in the information sheets), p. 40:

Will I have the same doctor or investigator from start to finish?

- **SIOPE comment**: This would be difficult to commit to as people do change jobs, retire etc. Perhaps the same research team could be referred to instead?

Point 7 (List of items recommended to be covered in the information sheets), p. 40:

What are the compensations?

- **SIOPE comment**: SIOPE suggests clarifying the wording depending of what is implied exactly. Is the statement about the benefits of participating? Or is it a question on whether or not expenses will be compensated?

Point 18 (List of items recommended to be covered in the information sheets), p. 41:

Will my taking part in the trial be kept confidential?

- **SIOPE comment**: SIOPE suggests making the reference to personal data protection more explicit and rephrase in a manner such as '**Will my personal data be protected?**'

27. ANNEX 3: Examples for levels of risks and burden

p. 42, para 5 (last para on page – Definition of minimal risks and burden): *"…In general, minimal risks and burden can be defined as the probability and magnitude of harm or discomfort similar to risks and burden ordinarily encountered in daily life. "*

- **SIOPE comment**: This definition can be complemented with those risks and burden '**encountered in the normal treatment of the condition outside a trial**'. For example, the risks of a new intervention should be assessed in the context of the risks of the standard treatment. In oncology, the standard treatment may have high 'risks' due to the side effects of chemotherapy drugs, but these are necessary to treat a life threatening disease. The side effects of the new intervention should be assessed in this context.

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Table: 3 Categories of Procedures - Ethical considerations for clinical trials on medicinal products conducted with minors (p. 43)

Feedback requested Q1. Is the proposed categorisation of these procedures still adequate?

- **SIOPE comment**: broadly yes with the exception of PET scanning placement in Category 3 (More than minimal risks and burden, regardless of the standard treatment). Indeed, PET is increasingly being used to assess paediatric conditions as standard care. SIOPE therefore suggests moving PET scanning to Category 2 (Risks and burden that might be regarded minimal, dependent on the standard treatment).

Feedback requested Q2. Which insights may lead to changes in categorisations (in particular those indicated in yellow)?

- **SIOPE comment**: The key point for all mentioned procedures is assessment compared to current standard care and the burden/seriousness of the disease concerned. All risk assessments need to take these aspects into account. Thus, a bone marrow aspirate is not an increased burden if it is to assess response to a new trial treatment for leukaemia, but extra bone marrow aspirates just for biological sample collection would be an additional burden that would need to be fully justified.

28. References

- Research and clinical trials in children

SIOPE suggests including the following ENCCA project reference:

- Ethical issues of clinical trials in paediatric oncology: a systematic review over 10 year developments (2003-2013). Dupont JCK, Pritchard-Jones K, Doz F. Lancet Oncol 2016, 17(5): e187-197

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