1. **What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?**

Lack of campaigns and understanding about the rules, regulations about clinical research to inform parents and lay population. All institutions involved with clinical trials should participate in national, regional or local programs to inform / train the population as well health professionals about the ethics and rules about clinical research.

2. **Who should make the final decision as to whether a child participates, or continues to participate, in clinical research when parent and child disagree? What responsibilities do health professionals or researchers have in such cases? (You may wish to distinguish between children at different stages of development and/or the different ways in which disagreement may arise or be expressed.)**

After being explained about the clinical research, it will be the parents and a capable of expressing a view child final decision for not consenting to participate in the clinical research. In the case of a very promising experimental therapy not yet registered and considered to be superior than the best stand of care available based on the actual knowledge, most likely the attending physician should seek for judge advice if the gap between the initiation of the treatment and decision will not interfere with the patient's treatment.

3. **How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?**

It is clear the division between consent and assent. The concept of assent should be a collaborative' or 'shared' decision-making, as mentioned. In case the attneidng physician or health professionals detected a conflicting situation between parents and a capable of expressing a view child final decision, probably the most adequate way would be seeking for a counseling meeting with the parties.

4. **A 'shared' or 'collaborative' decision-making model is often advocated for decisions about a child's research involvement, involving the child, relevant family members and professionals. Is this a helpful approach? How might any problems arising in this model be overcome?**

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5. **Parents' views on whether (and how) children should be involved in decisions vary enormously both within and beyond the UK. How should the law and professionals take account of such different parenting approaches?**

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6. **Rewards (such as vouchers) for children participating in research may be welcomed as an appropriate way of saying 'thank you', or criticised as a form of undue incentive (to either child or parent). What forms of**

compensation/reward/expression of gratitude for research involvement do you think acceptable, and why?

Acknowledge their participation in study newsletter, hospital and advocacy groups, interviews and advertisement with the solely purpose of delivering a unbiased scientific and ethical information.

7. **How helpful is the notion of the best interests of the child participant? How would you define 'best interests'?**

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8. **How can the rights and interests of individual children (potential participants in research) be balanced against the rights and interests of all children (potential beneficiaries of the knowledge gained by the research)?**

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9. **Are there any situations in which you think it would be acceptable for a child to be invited to participate in clinical research when there will not be *any* personal benefit to them? If so, please give examples.**

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10. **Are there any circumstances where it would be right for a research ethics committee to approve research involving risks they would usually regard as too high, if parents and young people had clearly expressed their willingness to accept these?**

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11. **Do you think the current regulations strike the right balance between promoting clinical research in children, protecting child participants, and involving children in decisions about their own participation? What (if anything) would you like to change?**

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12. **With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions?**

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13. **What responsibilities do funders, researchers and stakeholder groups have to encourage the coordination of children's clinical research?**

Unmeet need diseases in children are frequently related to rare populations and can be considered one the most challenging aspects in clinical research development. This is a recruitment limiting factor that potentially prevents collecting enough interpretable data. Many protocols are being submitted to test different drugs in the same population as a EMA PDCO requirement, and consequently protocols compete with the same population impacting the trial performance with consequent delays and compromising the statistics analysis to draw any conclusion. This has the potential to miss a true efficacy therapy effect already proven in adults due to the lack of sample

size. The lack of coordination between researches funders who are exploring similar childhood conditions can also lead to unnecessary duplication of research effort should be addressed by regulatory agencies to reach a common agreement between sponsors to avoid unnecessary burden on research participants. This poses also a crucial question about the ethical aspects of allowing multiple studies testing different drugs in the same disease population. One way of addressing this issue, would add to regulators (e.g. EMA, FDA) the duty of care ask, that have a clear view about all Pediatric Investigational Plans submitted in a particular disease setting that before approving the plans, to compare them and engage sponsors to define priorities and suggest a master study, e.g., where different compounds would be added as new arm compared with standard of care. This will allow the evaluation of safety and efficacy signals. Such trials have been already designed to address the same question in adults clinical oncology development. One example is the I-SPY 2 study. *"This is an investigation of serial studies to predict your therapeutic response with imaging and molecular analysis targeting the rapid, focused clinical development of paired oncologic therapies and biomarkers. It is a collaborative effort among academic investigators, the National Cancer Institute, the US Food and Drug Administration, and the pharmaceutical and biotechnology industries under the auspices of the Foundation for the National Institutes of Health Biomarkers Consortium. SPY 2 will compare the efficacy of novel drugs in combination with standard chemotherapy with the efficacy of standard therapy alone. The goal is to identify improved treatment regimens for patient subsets on the basis of molecular characteristics (biomarker signatures) of their disease. Regimens will be dropped if they show a low probability of improved efficacy with any biomarker signature. New drugs will enter as those that have undergone testing are graduated or dropped. The overall trial design for I-SPY 2 will feature two arms of a standard regimen, starting with standard of care in one arm, and in the other arms, multiple new drugs will be tested simultaneously, each being added to standard therapy. There are 3 reasons why investigational drugs may leave this type of trial design: (1) An investigational drug can leave the trial because it has been shown to be beneficial and will likely be successful in a specific larger trial. (2)An investigational drug can leave the trial because it has not been shown to be significantly more beneficial to patients. (3)An investigational drug may be removed from the trial if patients have serious side effects to the drug*. (*http://www.ispy2.org/*).

14. **What responsibilities do researchers have towards child participants and parents when the study is over?**

If the patient is receiving benefit from the experimental treatment, sponsors should keep providing the experimental drug until it becomes commercially available and consequently supplied by the local health authorities *(Post study termination drug assess – Based on the 2000 Helsinki declaration - At the end of the study subjects will receive the best therapeutic methods identified by the study) http://www.wma.net/en/30publications/10policies/b3/).*