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

Main obstacles include:

Participant barriers:

- Study feasibility: a study agreed by a Paediatric Committee may be challenged by an Ethics Committee, or procedures judged too complex and too cumbersome for the parents who have to attend hospital visits as scheduled per study protocol; competition may be also a challenge, with too many studies targeting a limited patient population
- Patient recruitment and retention: parents may be reluctant to agree participation of their child in a study, even more in the case of a placebo controlled study where their child could be receiving placebo; informed consent to be given by both parents is sometimes difficult to get; time off work, transportation costs, out of pocket costs, concerns about medication side-effects, mistrust of medical research

Investigator barriers:

- Lack of/limited knowledge about the target population, limited guidance to study staff, recruitment based on convenience, ineffective informed consent process, limited knowledge of study conduct, GCPs and or appropriate retention method.

Regulators' barriers:

- The huge gap between Health Authorities' requirements and the actual daily life practice (e.g. insisting on minimum number of hospitalised days)
- The lack of clarity, of regulators' guidelines, dealing with pediatric population and most of the time trying to apply adults' guidelines.

How might this be overcome? Preparatory work is key, to identify key potential issues and solve misconceptions. There is a need to identify the right investigators, to train them appropriately where needed, and to prepare recruitment documents in line with the target patient population. Set realistic timelines and consider working with patients' organisations to improve informational materials, which could help enhancing recruitment and retention. Interacting with paediatric networks can also optimise recruitment and retention. Can some clinical trials be partly conducted from the home to help with logistics?

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.)**

The child's input should always be valued. This depends on child's age. It is expected that children as young as 2 or 3 won't be involved in the decision process. But when children get to 14 or 15, it is expected that for most of them, they can understand a lot about the process, even if some others may understand less or could focus on what is going to happen to them. In case of disagreement, it is

important that everyone including the child is comfortable with the research, otherwise, this could negatively impact the conduct of the study, and as a consequence, the data.

Any disagreement that could happen while the study is ongoing should be discussed appropriately to find whether there is a way forward. If agreement cannot be reached, patient's withdrawal from the study has to happen.

Parents and competent children should have the last say.

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

As per regulation, to recruit children into a study, parents have to give legal consent for their child to join a research study. Many people involved in treating young people believe that the child or adolescent should play a role in the decision to enter a research study. The process of assent is useful to understand how a child feels about being in a study. Children can be asked to give assent from as young as 6 or 7. However, in some cases this may be too young to put them under pressure, bearing in mind there is no legal requirement to obtain assent.

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?

Informed assent can lead to an ongoing, interactive conversation between the research team and the child or young adult. The research team may include doctors (who are often principal investigators and leading the study), nurses, social workers and other health care professionals. The process is not about getting the young person "to sign on the dotted line"; rather, it is about making sure they understand the study and what it means to participate. By engaging young people in understanding the research project, health care providers and young patients may become "partners" in the project. Children are likely to feel more in control and more involved in the trial as a result. This can help recruitment, retention and adherence to study protocol procedures.

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?

Regulation states that parents must participate in an informed consent process - just as they would do if they themselves were considering enrolling in a clinical trial - and give legal permission for their child to enrol. This process must follow the guidelines established for the general requirements of informed consent.

Although a child or adolescent may say that he or she understands that a choice exists, they may not be able to identify all the possible options and consequences. Similarly, this depends on the child's age and whether or not the parents are ready to

have their child participating in the decision process. It's a question of education and information (of parents and HCPs) probably, a specific guideline could help, but another regulation doesn't seem necessary. EFGCP recently published a guideline on ethical aspects of clinical trials performed in older people, which could similarly be used for paediatrics, another vulnerable patient population.

<http://www.efgcp.eu/Downloads/EFGCP%20GMWP%20Research%20Guidelines%20Final%20edited%202013-05-27.pdf>

- 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?**

In clinical research, only Healthy Volunteers involved in Phase 1 can receive money compensation. Phase 1 trials constitute "non-therapeutic" research as there is no benefit to the participant. For this reason alone, Phase 1 trials are not appropriate for children. Parents or guardians who incur expenses for travel, parking may receive compensation for those expenses. However, such compensation must not become an improper incentive to enrol the minor.

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

The 'best interests' of the child should be the guiding principle in all decisions that may affect them. Assessing a child's best interests should include what is clinically indicated in a particular case.

The following could also be considered:

- the views of the child, as far as they can express them, including any preferences they have given in the past
- the views of the parents
- the views of other people close to the child
- the cultural, religious or other beliefs and values of the child or their parents
- the views of other healthcare professionals involved in providing care to the child, and of any other professionals who have an interest in their welfare
- which choice, if there is more than one, will least restrict the child's future options
- Consideration of and adherence to any and all jurisdictional legalities that define what is considered to be 'in the best interests' of a child.

This is not a complete list. The importance one attaches to each point depends on the circumstances, and other relevant information. One should not make unjustified assumptions about a child's or young person's best interests based on irrelevant or discriminatory factors, such as their behaviour, appearance or disability.

- 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)?**

Current regulation helps to ensure that the rights, safety and well-being of subjects involved in clinical research are protected. Clinical trials are conducted in the hope of finding new, and more effective treatments. The most compelling benefit of a clinical trial is the potential for a more effective treatment and better outcome for the child involved - and ultimately a cure for the illness, which will benefit many more children in the future. In addition to potential benefits, being a trial participant could bring some risks (potential safety risks, negative outcome) and imply commitments such as frequent visits to the doctors, complex procedures to be followed, which could adversely impact the child and family (but can be minimised by a comprehensive and appropriate information).

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.**

Phase 1 clinical trials constitute “non-therapeutic” research as there is no direct benefit to the participant. For this reason alone Phase I trials are not appropriate for children.

There are situations where it is acceptable for a child to be invited to participate in clinical research when there will not be *any* personal benefit. In some Phase 2 or 3 clinical trials, children can be randomised to the placebo group. Placebo is then used as a control, only if the lack of treatment is short (perhaps a few days) and poses minimal risks, or if the tested therapy is used to only treat uncomfortable symptoms (like watery eyes) and not a severe illness. In more severe situations, rescue medication would need to be considered.

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?**

Such a situation is unlikely to happen since prior to Ethics approval, a research whether or not performed in children, has to be approved by Health Authorities, and even by PDCO if part of an approved PIP.

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?**

The Clinical Trials directive that should be replaced soon by a Clinical Trials regulation, and other related directives have helped to ensure that the rights, safety and well-being of clinical trial subjects are protected by requiring sponsors of trials to be responsible for designing, conducting, recording and reporting clinical trials according to internationally recognised principles of Good Clinical Practice (GCP). In addition, the regulations further protect public health by helping to ensure that the results of clinical trials are collected, recorded and analysed in accordance with those principles so that they can be audited and verified before being used to impact

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on public health, for example through a publication that changes medical prescribing practice or as evidence to support applications to place medicines on the market.

In addition, there is the paediatric regulation which main objective is to improve the health of children in Europe without subjecting children to unnecessary trials, or delaying the authorisation of medicinal products for use in adults. Since 2007, when the regulation came into force, one could question what has been delivered and whether the objective has been achieved.

A regulation can always be revisited but it takes time e.g. revision of the paediatric regulation is not planned until 2017.

Despite regulations in place, patients' recruitment remains an issue in EU; the EU commission can only encourage the Member States to promote clinical research among people at the national level.

Some amendments would be beneficial:

- More flexibility for when to submit a paediatric plan: submitting a PIP after POC would avoid the need to withdraw a PIP when a project is terminated prior to Phase 2;
- A less detailed PIP would probably limit the number of PIP modifications while product knowledge based on adult data has increased;
- Better use of pediatric networks;
- Better information of the public by Health Authorities/member states to encourage patients' recruitment in CTs.

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?

This should be a medical decision based on drug mechanism of action and high unmet patients' needs. Those involved in decision-making should include Pharma and academia experts, also regulators and patients' organisations.

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

Working together, building trust and confidence, and transparently sharing expertise should help encouraging research (which is an approach not specific to children).

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

Clinical trials must be conducted in line with GCPs and according to Regulation in force in the different regions/countries, including Declaration of Helsinki.

Investigational products' availability beyond clinical trials: in some instances (oncology, infection), AZ has provided drug if the patient (children or adult studies) continues to demonstrate benefit, Access to a new drugs not already registered is also possible via compassionate use (can benefit adults as well).

Researchers can no longer ignore the situation:

- Patients' organisations will be more and more involved in drug evaluation by regulatory Health authorities (e.g. EMA, FDA) and Ethics committees;
- Patients' organisations are also actively involved in Private-Public Partnerships (e.g. the European Union (EU) IMI U-Biopred consortium);
- EU PDCO concept paper on the involvement of children and young people in PDCO Activities - Listening to children/youth opinions before making decisions may help increase their adherence and people awareness of the need to conduct clinical research;
- Free access to databases: e.g. <http://clinicaltrials.gov/>, <https://www.clinicaltrialsregister.eu/> provides current information about clinical research studies to patients, their families, their friends and caregivers, and the public; the EU Clinical Trials Register website allows EU citizen to search for information on clinical trials in EU member states and the European Economic Area (EEA) and clinical trials which are conducted outside the EU/EEA if they form part of a pediatric investigation plan (PIP);
- Patients more and more value being treated as partner in research, it is thus, important to release information when the study they participated in is completed.

As a company involved in clinical research, AstraZeneca (AZ) is fulfilling any legally required actions in place; additionally, AZ has a specific website that publicly provides clinical trial data, results and other information from or regarding AZ-sponsored clinical trials. Results are posted, irrespective of whether they are favourable or unfavourable, of marketed medicines, medicines in development, and discontinued medicines as mandated by law and AZ Policy. Disclosure requirements and timeframes are found on the AZ website under 'our commitment to transparency' section. Compliance is mandatory across the AZ Group of Companies. From February 2013, AZ has voluntarily disclosed clinical trials research protocols on its company owned website once a manuscript relating to an investigational or approved product is published in a peer-reviewed journal.