

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

The principle obstacles to increased and better clinical research involving children are the collective perception that it is difficult or 'impossible' and the greater prevalence of a view that established clinical practice is already effective or at least effective enough. In both cases the beliefs are erroneous and in particular given that the truth of our understanding is often less secure in paediatrics there is a greater need to define and develop effective interventions. This reluctance has contributed to the relative lack of funding particularly in areas of non-medical paediatric disorders and therapy (my anecdotal impression would be that 'cancer' and 'vaccine' research are disproportionately well supported compared to other areas in paediatrics). In addition to material support in many disciplines a culture of 'comprehensive observational research' or audit is much needed to define current practice and ultimately inform further developments in a more methodical fashion.

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 final decision will generally lie with the responsible adult (who has parental responsibility) though not always (there are several examples of parents refusing treatment against medical advice where the withdrawal of consent has been overruled by the courts in the child's best interests and similar situations could arise in a trial setting although are less likely). Ideally a disagreement between parent and child does not arise and the law is reasonably clear depending on where the disagreement lies with respect to the medical opinion. Clinicians should challenge parental and professional efforts to avoid appropriate disclosure to the child in an age and development appropriate and sensitive manner. Generally speaking the clinicians and researchers in such situations should seek a professional consensus first if possible (and ask why not? if not able to) before challenging the responsible parent or competent older child). A wider opinion from outside the clinical/research team such as from a local ethics committee/forum can be beneficial. In difficult situations where the 'parent', child and clinical/research team disagree legal clarification may be necessary with ultimate recourse to the courts though this does not necessarily determine what is 'right' so much as what is legal.

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

On reflection, assent is probably a much less useful concept in paediatrics than in adults (and indeed truly informed consent, even among adults, is unfortunately much less prevalent than we clinicians would wish to believe). For example a common example of assent is the holding out of an arm for venesection/cannulation. In a competent adult this is often taken as assent as would allowing a subsequent infusion. A cooperative pre-schooler may display the same behavior but has limited

understanding of the reason for the procedure much less the effect of the infusion particularly if it has no apparently noxious effect. This 'assent' is not indicative of much on the part of the child whereas an older child or adult might more (though arguably again may not appreciate the full implications depending on their level of understanding). It is probably more helpful to consider three ideal elements to undertaking a course of action: the rationale (a clinical justification), the authority to undertake an action (the 'consent') and the agreement/cooperation (which may not always be forthcoming from the paediatric patient and may need to be overridden).

- 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?**

This would seem to be an ideal to aspire to however is dependent on the exact clinical context and it could be argued that in some situations non-participation should be the exception (the experience in paediatric oncology demonstrates the power of this approach). This does begin to stray in potentially ethically dubious territory which in children must be closely appraised as unlike competent adults who can act to their detriment children are treated differently 'in their best interests' a concept that is not fixed and could conceivably (and has) led to unethical actions in the past. Alternative approaches might be more appropriate in the context of certain research settings

Problems should first be recognised and where there is time addressed in a careful multilateral manner. Indeed problems in decision making are an opportunity to address uncertainties and define the current view on 'best interests' and other issues.

- 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?**

It is reasonably well established that children often are aware of more than the adults around them may be aware or wish to believe both with regards to their own health matters and more broadly to the emotional context in which they exist. Whilst there must be respect for the family context of each individual child consideration must also be made for the potential deleterious effects (or opportunity costs) of compliance with parental views on the amount of disclosure and involvement with decision making appropriate for their child. Again this will be age and development dependent and there may be a professional disagreement with parental wishes which clinicians should not shy away from treating it as any intervention with a series of increasingly formal processes (discussion, consultation, mediation, legal proceedings) until there is a resolution in the child's best interests.

- 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?

These can be reasonable and/or pragmatic in some settings and are usually justified by those expecting poor recruitment and/or high dropout rates. In general they should be discouraged particularly as children are liable to be even more susceptible to distorted perceptions/behavior as a result.

Indirect inducement by ensuring minimal/no detriment as a result of the research, a pleasant environment in which research is undertaken, zero material cost to the family and refinement of the study and techniques to minimise inefficiency. Of course a well-researched study design and well conducted study are prerequisites.

Finally a written expression of gratitude to both the child and family should reinforce positive verbal feedback throughout the study.

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

'Best interests' as a principle underpins the bulk of ethical and legal thinking on the practice of medicine in children as well as adults lacking capacity (although the increasing implementation of advance directives and recognition of limited capacity maintain the distinction in children below a certain age and level of development). It would appear that this is the best option at present for handling situations where the correct course of action is not agreed by patient, parent, doctor, institution and society (both in terms of the law and general acceptance). A definition of 'best interests' is actually difficult as a variety of philosophical traditions could be invoked. I would acknowledge the imperfection/limitations of the concept and determine best interests as a composite of the factors outlined above with precedence given to the evidence for clinical efficacy and family preference (the balance of which depends on the specific situation). The other factors (organizational, professional opinion as opposed to professional knowledge, law, societal views) generally take secondary precedence. For a situation of clinical uncertainty whether there is equipoise or not the question is more difficult and I am not sure it is always clear what to do (this is the arena of genuinely collaborative decision making. It could be argued that if the best treatment is unknown or all treatments are of limited or uncertain effectiveness that participation in planned research or at least a well structured n=1 trial (difficult in surgery and other effectively irreversible interventions). This verges on coercion and can only really be suggested in because of the accepted position of children's limited (indeed for a large part of childhood absent) capacity to consent.

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)?

It is a generally accepted principle that the rights of the individual should not be sacrificed for the collective benefit of the society as a whole. This is more difficult in children as they cannot express an opinion and even if the parents agree this is not necessarily the ethically correct course of action. If we define ethics (which to a

large extent we do and in the absence of any religious or metaphysical basis we do entirely) then we can imagine a society where the experimentation on citizens is mandatory accepted (perhaps not even a source of contention for the majority). In such a setting parents will of course accede to the de facto professional enrollment of children in research studies on the basis of collective good. I feel this would go too far, certainly any additional detriment of participating in research should be minimal or at least minimized. It must be proportionate to their clinical problem (and if they are healthy and participating in research there really must be (almost) no detriment or they must be free and willing competent participants.....again being mindful that children (and indeed adults) can be coerced or conditioned into involvement in unethical and unacceptable processes. It is therefore difficult to have absolute protection from harm but for research into the treatment of medical disorders the first prerequisite is a better understanding of current knowledge.

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.

Yes, indeed there are many examples where clinical/physiological research is conducted on healthy children who are unlikely to directly benefit (well constructed survey/quality of life control studies). Again the acceptability and ethical status of such participation will depend on the nature of the research and potential ill-effects. Such research may also be conducted on children with health problems with the same caveats and the initial risk that they may misconstrue the purpose of the study again a developmental stage appropriate consideration of these issues should be made in the study design as a potential psychological detriment.

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?

Yes, there are situations where this may be appropriate and indeed some involvement in prospective evaluation of the proposed high risk intervention in the situation where there is no less risky alternative and the committee are satisfied that there is a clear understanding by the family of the balance of risk and benefit. In the absence of effective interventions there should also be an explicit consideration of 'palliative' treatment in the broadest sense. These situations will generally arise in life threatening conditions or with the prospect of severe handicap. In this last consideration there will be a tension in the decision making group (patient, family, professional) between the effect on the patient of all outcomes vs the effect on the family and how this may influence what they consider the child's 'best interests'.

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?

My familiarity with this area as a medical professional is poorer than perhaps should be the case. It is interesting that there is so much off-label use which tacitly

reinforces the dearth of research in children. There is quite rightly a concern that without the greater acceptability of off label prescribing (a situation that does not arise in non-drug therapy to the same extent) there would potentially be major harm inflicted on children not able to receive what are clearly effective therapies. The deficiency probably lies in the implication that because off label use is accepted that there is no need to apply the same rigour to children and young people's medical care. This will require development of the regulatory framework to ensure children are protected but also to encourage confirmation of assumptions of generalisability of adult trials to paediatric patients. There is also the option that the small population under consideration though a disadvantage in terms of commercial interests lends itself well to post-regulatory monitoring and evaluation. This is some distance from the gold-standard randomized trials but alternative approaches may nonetheless give practically useful information on generalizability on the more rigorous trials in adults. There is of course no reason that trials cannot be conducted in children but a lack of funding and commercial interest are likely to be rate-limiting as is the present experience. This is an area that again could be addressed through greater allocation of government funding for more niche areas including some areas of paediatrics as the big name diseases and commercially attractive avenues of inquiry will likely continue unabated with funding from other sources. The net benefit in poorly funded areas will almost certainly be greater if studies are conducted to the high standards.

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 is always a difficult issue and there will never be enough resources to do everything we would wish to do. The first step is of course to use all funds as efficiently as possible, avoid unnecessary duplication and ensure that the findings are important (this is often construed as implying an immediate practical outcome is necessary however this is not always the case). To draw a financial analogy, the portfolio of research activities should be diverse to minimise risk (wastage of resources in ineffective areas of research) however there must also be consideration of potential benefits per unit resource and this is likely to be greater in neglected areas. The decisions should be made by representative bodies/individuals of the source of the funds however consideration should also be made for levies on the largest funders of research to support research in niche areas/rare disorders, where there is a limited commercial interest and where academic interest is for whatever reason limited despite a need for high quality research.

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

The funders, researchers and stakeholder groups will have different emphasis and attitudes towards their role in the coordination of research activity. Funders will have an interest in the quantity and quality of research delivered for the material support provided. I hope they have feel there is an ethical duty to do this however funders of research are diverse with many and sometimes mixed motivations, not all positive. There are also in some cases conflicts of interest and vested interests in terms of the nature of research supported and the way in which the funders operate.

Researchers and stakeholder groups also have potential conflicts in their motivations for conducting/supporting research activity and should be honour bound to guard against undue inappropriate personal or external influences. The balance can be difficult to maintain and it is the collective duty of all involved parties to avoid collusion in inappropriate practices. Funders should work with other funders to ensure equitable distribution of spending, researchers should engage in collaborative work where this facilitates research and should ensure that their work is not redundant or unnecessarily duplicated and this can only come through good communication. The stakeholders can be the stimulus to the others by highlighting areas of weakness and maintaining the focus of other involved groups on the core problem which should be the effort to alleviate suffering in priority to their other interests (which may be necessary goals but should not usually be preminent).

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

This can be a tricky problem particularly where the interventions are costly or have yet to be subjected to an economic analysis that will persuade the health service to implement a change in practice. In many ways, paediatric patients can benefit from the general goodwill society has towards children and the relatively small numbers involved making the absolute costs almost insignificant next to spending on health and social care as a whole. This is not an excuse to be wasteful but that should not stop the absolute costs being a positive argument for prioritising funding of some treatments for children that are more difficult to provide for adults.

By analogy one of the difficulties for children requiring medical care is the transition to adult services which can be an abrupt change in the environment and atmosphere in which they receive their care. The same is true of the transition from a research environment when there may be extra attention to the patient experience and the minimisation of harm as discussed above (if not outright positive inducements in some cases). The researchers clearly must factor the post research impact of the research study as well as any opportunity costs of the return to 'standard' care. There are also the negative outcomes which should be dealt with promptly, sympathetically and by restitution as close to the premorbid state as possible.

Finally the ultimate expression of gratitude for participation is the communication of the outcomes of the research in a patient orientated fashion whatever the outcome....indeed the importance of 'negative' results should be as carefully explained as the trial protocols during the consent process.

Please highlight any relevant areas you think we have omitted, or any other views you would like to express about the ethical issues arising in clinical research involving children.

My only other comments which have been partly alluded to are the unfortunate lack obvious focus on non-drug/medical trials. As a paediatric surgeon in training and one interested both in research and the ethics of modern medical practice I am aware of the neglected place of surgery in general in the provision of research and within surgery the even smaller profile of paediatric surgical subspecialties which are among the smallest medical specialties in the UK.

The result of this is research in surgery and paediatric surgery in particular being often of a much lower standard than we are led to expect in our training as doctors and scientists. This I see as a collective deficiency of the institutions supporting research and the same applies to other areas of specialist intervention/imaging/diagnostics for children. Undoubtedly this leaves much of the current medical practice for children being based on less than solid grounds but nonetheless carried out to the highest standards possible in the circumstances by dedicated clinicians. I would have one caution and that is greater involvement and scrutiny research organisations should not stifle innovation which is one of the positives in the perhaps under-regulated paediatric arena. Novel approaches are taken in some areas to permit step-wise evolution of techniques with institutional support and ethical review without some of the more bureaucratic process of the research ethics process. This is perhaps an area where debate on the ethics of this more limited (and potentially useful) form of oversight.