32. NIHR Clinical Research Network: Children 311013

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

The National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN) has recruited over 45,000 children and young people to its portfolio of studies since it was established in 2005, and recruits in the region of 10,000 children on an annual basis. In addition, over 50,000 children were recruited to the NIHR Paediatric (non-medicines) Specialty Group (PSG) portfolio during 2012/13. Both these elements of the NIHR Clinical Research Network (CRN) work closely with researchers and clinicians, children and families, charities and funders, and the pharmaceutical industry in order to reduce or overcome the real or perceived obstacles to undertaking clinical research involving children.

Recruitment of patients to clinical research can often be problematic, regardless of whether the participants are children or adults, and many of the real and perceived obstacles have already been well described in the medical literature. Our response, submitted on behalf of the MCRN and PSG, will therefore focus on those obstacles specifically relating to the recruitment of children to clinical research.

There is concern amongst professionals, and in the wider public, that it is not reasonable or appropriate to discuss participation in a study with a sick child or their family at what may be an extremely stressful time. Whilst we recognize that these concerns are real, research has found that families are indeed happy to be approached in such situations, and are keen to be involved.[1],[2]

In contrast, clinicians are anxious about the process, citing the need for extra training to improve their understanding of the views of families on the recruitment process. There is therefore a need to further investigate patients' and families' attitudes to research and publicise or educate both professionals and the public of these views.

One obstacle often cited is a lack of appropriately trained clinicians with the necessary knowledge and experience of undertaking paediatric research[3]. Whilst we recognize that this can be a significant barrier to recruitment, we would suggest that changes introduced by the NIHR over the past 5-10 years have improved the situation significantly by increasing the level of training (in particular, Good Clinical Practice and Paediatric Consent training packages) and support available to

1 Shilling V, Williamson PR, Hickey H, Sowden E, Smyth RL, Young B. Processes in recruitment to randomised controlled trials of medicines for children (RECRUIT): a qualitative study. Health Technol Assess. 2011 Mar;15(15):1-116.

2 Abernethy LE, Paulsen EL, Monuteaux MC, Berry MP, Neuman MI. Parental perceptions of clinical research in the pediatric emergency department. Pediatr Emerg Care. 2013 Aug;29(8):897-902.

3 Modi N, Clark H, Wolfe I, Costello A, Budge H; writing group of the Royal College of Paediatrics and Child Health Commission on Child Health Research,Goodier R, Hyde MJ, Lumsden D, Prayle A, Roland D. A healthy nation: strengthening child health research in the UK.

clinicians to allow them to participate in clinical research, and provision of funding and mentoring opportunities to enable them to gain the necessary experience. Ongoing support by experienced research network teams contributes to this and helps to facilitate research by ensuring that investigators and research staff have access to training, information and a team of dedicated children's researchers, thus enabling them to focus on recruitment to the studies.

Another aspect of research involving children which is often seen as a barrier to recruitment is the perception that paediatric research is very complex, high risk and fraught with practical difficulties. Whilst this may be true for some areas of research, it certainly isn't necessarily the case that all paediatric research is "difficult" or "dangerous". It is important to distinguish between the risk inherent in the clinical situation and the risks introduced by a research project. Steps have been taken in the UK to introduce a "risk-based" approach to the regulation and monitoring of paediatric clinical trials which respect this distinction, will help to dispel the myth that all research is inherently risky, and reduce the bureaurocratic burden of undertaking paediatric studies. Publicity and training to highlight the benefits of and opportunities to undertake paediatric research will also have a positive impact. The importance of public awareness of the distinction between the risks of being sick and the risks introduced by a research project has been highlighted recently by the furore in the USA about the SUPPORT trial[4]. Similar trials were conducted in the UK and Australia. Better wording and greater clarity about the nature and source of the risks has meant that the problems encountered by American colleagues are less prominent in the UK.

We would like to comment on your statement: 'The very suggestion, by a trusted professional, that a child might consider participation, may be seen as an active endorsement of the project, and hence influence a parent's/child's decision.' We fully recognise the need for a non-directive approach to counselling a child and family about a study. However we do believe that the professional must truly believe in the value of the study, in other words to agree that it addresses an important clinical question and there is equipoise on the key study question. Different wording is clearly needed to distinguish belief in the study as a valid and relevant question rather than 'endorsement' as a sub-liminal pressure to participate. The danger here is that ethical discourse ignores the substantial risks arising from the inadequate evidence base that clinicians can use to guide discussion and decisions about treatment choices. The attending clinician is ideally placed to advise children, young people and families about the importance of evidence gaps and whether a particular study is relevant to an individual. If attending clinicians are to be prevented from telling children, young people and families about studies then there will need to be significant investment in doctors with sufficient clinical and research expertise if the

[4] How not to reduce uncertainties in care US Office for Human Research Protections messes up Neena Modi *BMJ* 2013;346:f3786.

gap in research evidence is to be filled. A principled approach to avoiding undue influence on the grounds of reducing autonomy would need to balance the threat to equable access to research. An informed clinician may not reduce autonomy, rather enhance it by providing a view that balances the research need with the research opportunities and the burdens of a specific project. Clearly this position requires safeguards. These safeguards are feasible and include training, supervision and monitoring. An insistence on an approach about research from independent professionals would render many studies unfeasible. There are no safeguards against ignorance arising from lack of 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.)**

The decision of whether a child participates in clinical research should ideally be a joint one supported by all parties, including the child. Clearly for younger children and those incapable of taking a meaningful involvement in making a decision, parents or carers will need to decide on behalf of their child. We believe that the age of informed consent (16 years) should remain unchanged for research, not least to remain consistent with clinical care. Less experienced clinical researchers undertaking studies frequently need support and guidance to achieve the necessary and appropriate standards of research governance and any disparity in age of consent would add to the confusion between clinical and research governance.

Even if a child lacks the capacity for formal consent, researchers should still seek their assent (a positive agreement). Many children express very altruistic behaviour through their feedback to researchers or other professionals. Nevertheless, there are occasions, such as venepuncture when a child can suddenly become upset and/or refuse participation. Some such episodes are temporary and with careful support, the study can proceed. However, research teams need to be very sensitive and vigilant to ‘the burden of research’ for instance in studies with repeated visits sometimes over many months (or years). The ongoing consent should be sought (informally) at each research visit.

If children actively say they don't want to take part in research, then it would be inappropriate to enrol them. The only circumstances in which it might be appropriate do so would be if it was possible to clearly define that it was in the child’s best interest to participate.

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

Consultation with members of the national MCRN Young Person's Group revealed that they generally agreed with the concept of assent, however they queried the definition of "competent" in relation to assent and questioned how this would be assessed in an individual child.

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?**

We would support this statement but emphasize the absolute right of the child (if competent) or their parent/carer, as legally defined, to be the final arbiter. This view was also expressed by the members of the national MCRN Young Person's Group when we sought their perspective on this issue. In addition there may be practical difficulties in a 'shared' approach, e.g. how to cope with differences of opinion, weighting of one member's view over another etc, coping with 'split' families. There are also circumstances such as research in newborns, especially preterm babies or in other emergency situations, where a 'shared' approach isn't feasible. In all situations where the 'standard' informed consent process is unsuitable, we would like to see a careful discussion and justification of the proposed option(s) for recruitment and consent described in the protocol.

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?**

The underlying principle is the child's right to make a decision, when he/she is both competent to do so and the research setting is conducive to that. As described above, different approaches are needed in different research settings or when the child is not competent to make an informed decision. There are broader issues inherent in the question that relate to different cultural/ethic attitudes to research and these need further research (as the burden of some diseases is disproportionate in some of those groups with particular cultural concerns about research). It would be preferable for a standard approach to be taken but always taking into account the parent perspective.

Ethical guidelines need to recognize this diversity. Guidelines should distinguish between what is preferable for a particular group and what is tolerable for society in

general. Care should be taken that vocal concerns form one group do not distort the overall possibilities.

This is particularly important at the European level. Binding European law (European Regulations) should not aim to impose limitations that are specific to one or more Member States on the whole Union. Subsidiarity allows Member States to retain appropriate competences in the ethical sphere that allow national specificities.

It is also important to remember that some aspects of paediatric research can only be conducted at a global level (particularly rare diseases). This means that guidelines that apply globally must be permissive rather than limiting. National and supranational governance arrangements can be used to provide safeguards for specific populations. However, as noted at multiple points in this document any safeguards must ensure that the voices of children, young people and families with experience of relevant clinical conditions and research are at the centre of all discussions.

There is a large number of guidelines for the conduct of clinical studies and many of them are relevant to children[5],[6]. There is a high degree of concordance between these guidelines: Kolman et al. found 15 significant conflicts in a thematic analysis of more than 6000 guidelines. Some guidelines contain statements that are clearly outliers. The element of the Oviedo Convention referred to above is one example of a statement that is clearly unrepresentative of other guidelines. Work to harmonise guidelines needs to focus on facilitating interoperability among coalitions of the willing supplemented by local safeguards rather than complete alignment of all aspects of all guidelines.

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?**

The issue of rewards and incentives is a contentious one and we would not advocate the use of any reward that could be perceived either by the child or their family, or externally, as incentivizing involvement in research. We have found that one of the burdens of research is the extra hospital visits, which often take longer than standard care visits and may involve more family members. We fully support reimbursement of appropriate travel fares and a reasonable subsistence allowance. This view was

[5] Kolman 2012; Conflicts among Multinational Ethical and Scientific Standards for Clinical Trials of Therapeutic Interventions.

[6] Jacob M. Kolman, Nelda P. Wray, Carol M. Ashton, Danielle M. Wenner, Anna F. Jarman, and Baruch A. Brody journal of law, medicine & ethics spring 2012; 99-121.

expressed by the MCRN Young People who felt that small, age-appropriate token (for example toy, vouchers) would be acceptable and should be mentioned in the patient information leaflet. The use of small tokens of gratitude to a participant at the end of their involvement in a study, may be appropriate but often causes difficulties as recruitment is rarely undertaken at a sole time point so that 'finishers' may mention a reward to potential 'starters', raising the concern of inducement.

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

The question of best interests is a reflection of the risk/benefit balance of the study. We advocate that users of research be involved in the discussion of risk/benefit and that this process be clearly documented in the study application (e.g. for Ethics review). For instance, a discussion with a volunteer parent group who had experience of preterm babies on intensive care, would be useful if conducting a study of an antibiotic in newborns where extra blood samples (or volumes) were necessary (e.g. for pharmacokinetics). A study of a new agent for Duchenne Muscular Dystrophy (DMD) might be reasonably discussed with the parent and child support groups (and indeed this is the practice for current EU and commercial studies in that disorder, where such groups are co-applicants). In DMD, families and specifically, affected boys are consenting to studies involving muscle biopsies to enable efficacy and safety data to be gathered for new therapies of very little likely benefit to themselves. As several boys said in their feedback: 'I am doing this to help other boys'. This is a sentiment expressed by a number of children in studies, who then question the rights of adults to make those decisions for them. Several of our young people, speaking through the MCRN Young Persons' Groups, have questioned whether Ethics committees are adequately resourced or informed to deal with some children's studies. It has been suggested that a presentation from potential participants or their representatives might assist an REC. Thus the definition of best interests needs to account for people expressing altruism.

By contrast, a study of an intervention in an otherwise healthy child who develops an acute (but limiting illness), such as acute tonsillitis or bone fracture, would need a different risk/benefit balance and the feasibility – perception of the risk/benefit balance by individual participants may be as important and the overall perception by ethics committees etc. Again, discussion with those who have experienced the disorder (or related illnesses) can yield an acceptable approach. Our experience has taught us to pay attention to feasibility. While studies may be scientifically and ethically justifiable, the proportion of eligible participants who give consent may be the rate-limiting step to timely completion of the study. We believe that real and meaningful involvement of potential participants in the research design and set-up, will enable those bodies charged with approving the study, to be reassured of the risk/benefit balance. Although this may seem an extra burden to the research team,

we strongly believe that the research itself will be better, with more relevant outcome measures and a higher chance of successful completion.

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)?**

We believe the approach documented above provides a way forward. A key principle is that the individual child or their parent/carer (if underage) retains the absolute right to agree or not for that child's participation. The interests of the individual child should take precedence over the rights and interests of the children to whom the results of the research will be applied, as clearly specified in the Declaration of Helsinki.

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.**

It is an ethical imperative to offer children (and their parents) the opportunity to contribute to the development of useful knowledge, even if there is no personal benefit to the individual, if the study is well-founded. By well-founded we mean: needs to be conducted in children / young people; meets an important need for understanding of mechanism or treatment; appears proportionate to informed children/young people and families with relevant experience; has been approved by an appropriate ethics committee following independent scientific peer review by clinicians and scientists with appropriate experience.

We are happy to work within the framework for non-beneficial research in children laid out by the European Medicines Agency and endorsed by the European Commission. We are also happy to work within the framework incorporated in US Federal law relating to research regulated by the FDA as described by Skip Nelson Chapter 9 “Additional Protections for Children Enrolled in Clinical Investigations” in A.E. Mulberg, S.A. Silber, J.N. Van den Anker, Pediatric drug development : concepts and applications, John Wiley, Hoboken, N.J., 2009.

Our preferred guidance is that issued by the US Office for Human Research Protections (OHRP) in their 1993 Guidebook for IRBs which states: “In research where no direct benefits to the subject are anticipated, the IRB must evaluate whether the risks presented by procedures performed solely to obtain generalizable knowledge are ethically acceptable. There should be a limit to the risks society (through the government and research institutions) asks individuals to accept for the benefit of others, but IRBs should not be overprotective.”

In this context we need to draw attention to paragraph 2.ii of Article 17 in Chapter V of the Oviedo Convention (1997) which clearly fails to respect the autonomy of children, young people and their families. This paragraph relates to when non-therapeutic research can be conducted and states “ii. the research entails only minimal risk and minimal burden for the individual concerned; and *any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden*” (our italics). The italicized text disregards the ability and rights of children, young people and families to weigh up research projects. We note that the Convention has not been signed by Belgium, Germany, Ireland and the UK. The Convention been signed by, but has not entered into force in, Italy, Netherlands, Poland and Sweden. Fortunately the impact of the Oviedo Convention is minimal and needs to remain limited. Paragraph 2.ii of Article 17 in Chapter V of the Oviedo Convention (1997) has no relevance to the practice of research in the UK, or other research-active countries in Europe, and this should be emphasized in the Committee’s recommendations.

There are situations (see Q8) in which children will volunteer and/or their parents will consent for research without any obvious direct personal benefit. Besides DMD, examples include pharmacokinetic studies in newborns, natural history studies to develop biomarkers for possible new treatments in life-limiting conditions (e.g. mucopolysaccharidoses). Recruitment to such a study may be much lower (as a proportion of the eligible participants) and there is some evidence that parents with very young children are less likely to agree than those considering participation of an older child. An example was the global challenge in recruiting children with hypertension to a single dose pharmacokinetic study of a new anti-hypertensive agent (a potential once daily agent in a class of very well established medicines). Recruitment to the older cohorts (7-16y and adults) was relatively straightforward but the study was stopped due to lack of global recruitment in the 6 months to 6 year old cohort. There were certainly less eligible young children but parents consistently didn't want to 'subject' their children to this study for very limited benefit. This suggests that families are able to make judgments about the extent of risk, burden and benefit. To improve evidence in this situation, a different approach/methodology should be considered in recognition of the extra challenges in this age group.

The protective instincts of ethics committees need to be balanced against the autonomy of altruistic children, young people and families and against the harms that arise from lack of knowledge.

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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Yes. It is an ethical imperative to respect the views of parents and young people in these situations, if there is a well-founded research question that will have a useful impact on the understanding or treatment of a condition. For example, if there is a well-founded research study it would be appropriate in severe and life threatening conditions to allow research considered to be of high risk to the individual participant to be undertaken, irrespective of the benefit accruing to the individual. Children suffering from conditions such as DMD where no/limited treatments are available, and their families, may be willing to participate in studies if it offers them the opportunity to potentially benefit from a new treatment where otherwise options are limited or non-existent. However in such circumstances it is essential that the full risks of participation are clearly explained before a child is recruited to the study so that s/he and their family can assess the true risks and potentially negligible benefits of taking part prior to making a decision. In addition, the vulnerability of children in such circumstances must be recognized and taken into account. We would recommend that research ethics committees are provided with clear guidance on these issues to ensure a consistent approach to such circumstances, and that this guidance is informed by the views of children and families as well as by the medical professions. A consistent approach to this issue should be fostered either by clear guidelines, or the development of specialist ethics committees (which should not delay the study in any way) or a dedicated panel of advisors who could be co-opted to RECs if a large number of RECs continue to be involved in these studies.

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?**

No. The regulations for obtaining marketing authorization in Europe have shifted the balance towards protecting children from ignorance but more work is needed. The changes to the regulatory environment over the past 5-10 years have brought great benefits in terms of new paediatric product development. With respect to medicines which are regulated through marketing authorization, this has been exemplified by the significant growth of the MCRN commercial portfolio which has seen an increase from a handful of commercial studies in 2006 to current levels of 250 studies in 2013 (representing 56% of the MCRN portfolio). Reviews of the regulatory framework for marketing authorization EU and drug registration in the US have shown that research is driven by conditions that are found in adults and children[7],[8],[9]. The

[7] European Medicines Agency, General Report on the Experience Acquired as a Result of the Application of the Paediatric Regulation, 2012. http://ec.europa.eu/health/files/paediatrics/2012-09_publicconsultation_en.pdf.

[8] Responses to the Public Consultation on the Experience Acquired With the Paediatric Regulation, 2012.http://ec.europa.eu/health/human-use/paediatric-medicines/developments/2013_paediatric_pc_en.htm.

specific therapeutic needs of children have been relatively neglected in research planned by pharmaceutical companies over the past 5 years. We need to refocus this effort on the needs of children. We recommend that work is undertaken with the pharmaceutical industry to develop paediatric investigation plans to match disease in children rather than for products with adult indications.

In both EU and US there have been efforts to support research into off-patent medicines which are used in children with an inadequate evidence base. In the EU this has been through the mechanism of the Paediatric Use Marketing Authorisation (PUMA). There is general agreement that the PUMA initiative has not been successful whilst it could have provided very significant increases in information and thus benefit to children (and health services). We would not wish to see this initiative lost, rather advocate review of the incentives that might be provided to companies successfully delivering a PUMA. One suggestion is to increase patent rights on one of the companies' products and not necessarily the agent studied through the PUMA.

Concern has been expressed that the financial implications of taking a new product through the development process has deterred some companies from pushing through potential new products, however it is unclear whether there is evidence to support this concern.

Research has been consistently hampered by paternalistic attitudes among ethics committees and clinicians. Educational campaigns must be launched to ensure that all those involved in decision-making about research are aware of the risks and harms arising from the lack of research in children and the true magnitude of harms arising from research. Our view is that the risks of ignorance considerably outweigh the risks of almost all conceivable research designs. NHS research practice needs to be informed by a presumption that research should be done rather than a need to prove the worth of every project.

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?**

Priority setting for children's research is currently undertaken by a diverse group of organizations including disease-specific and generic charities and funders, patient support groups and the pharmaceutical industry, each operating from a different perspective and utilizing a range of approaches and methodologies. Within paediatrics this can be problematic, particularly given the varied nature of childhood

[9] M.J. Field, T.F. Boat, Institute of Medicine (U.S.), National Research Council (U.S.), Safe and effective medicines for children : pediatric studies conducted under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act.

disease, and the rarity of many paediatric conditions. Within both the MCRN and PSG, we have endeavoured to bring together the key organizations associated with paediatric research to encourage a collaborative approach to priority setting and to facilitate use of robust, systematic methodologies for the identification of key areas to address. Whilst there are some areas in which this work has been effective, the differing perspectives and requirements of the organizations involved has precluded a fully "joined-up" approach. We would suggest that work is required to facilitate more effective partnership working in order to maximize impact and make best use of limited resources. In addition, guidance on approaches to take and methodologies to employ would be helpful. We would strongly advocate that methods to capture the views of children, young people and families forms a key element of any priority setting exercise.

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

Coordination of the delivery of children's clinical research within the NHS falls within the remit of the NIHR Clinical Research Network, and the introduction of a specific theme focused on children's research (NIHR Clinical Research Network: Children) within the network which is to be introduced from April 2014 will further enhance the coordination of this activity. This builds on the improvements that have been realised since the establishment of the NIHR MCRN and PSG, and the alignment of all children's (apart from paediatric oncology and child mental health, which fall within other themes) research within one theme will bring further benefits. However, more work is required to better link funders, charities and other stakeholder organisations into a more joined up approach to coordination of the delivery of children's research. In addition, questions remain on the most appropriate way to facilitate effective partnership working in relation to the development of paediatric research. Again we would advocate that the active involvement of children, young people and families is essential to improve the development and delivery of children's research, and we would recommend that consideration is given to how best to achieve this. Clinical Studies Groups which are well established within NIHR Clinical Research Network are best-placed to act as convening bodies to link the research community in specific areas. Links between AMRC, other funders and a group for the NIHR Clinical Research Network: Children (advisory board or similar) will be the best way to link funders and the research community.

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

Consideration on what arrangements are put in place when a participant ceases to be involved in a research study needs to be given during the development of the study protocol, and such arrangements need to be clearly outlined to prospective participants prior to recruitment. It is the joint responsibility of the investigator, the

funder and sponsor to ensure that this issue is appropriately and adequately addressed prior to commencing a study.

We strongly feel that researchers have a responsibility to provide study participants with feedback, in the form of a lay summary, on the findings of the research in which they have taken part. Our young people recently highlighted transparent and full dissemination of research findings as one of their key messages to founders of research. Any such summary should use the appropriate language and content for the intended audience, and we would recommend that children, young people and families are consulted on the proposed methods and content of any such feedback. Further updates may be required as the results of the research impact on clinical practice and policy. However we recognise that this may prove difficult to achieve if study personnel move on to new projects, and would recommend that ways in which provision of appropriate feedback is handled is considered up front rather than as an after thought. Funders and study sponsors have a role in ensuring that appropriate arrangements are put in place.

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.

We believe that these issues are relevant not only for health professionals and patients/families but that there is an additional need to educate not only the adult public but also children through incorporation into the school curriculum. This concept of educating the next generation in the importance of research and its conduct was a key issue for our national Young Persons Group and the title of their recent meeting: Generation R, the Generation for Research, was testament to this.