

# NUFFIELD COUNCIL ON BIOETHICS

## Children and clinical research

### Summary of consultation responses

#### Contents

Introduction .....	1
How should children be recruited to clinical research?.....	2
What research proposals should be regarded as ethically acceptable?.....	38
How should research in children be encouraged? .....	53
Conclusion .....	69
Annex A: Call for evidence .....	70
Annex B: call for evidence GHRN network version .....	78
Annex C: Further responses to the GHRN blog and news posts .....	82
Annex D: Call for evidence – KEMRI version .....	86

#### Introduction

This document provides a summary of responses to the Nuffield Council on Bioethics' public evidence-gathering consultation.<sup>1</sup>

The consultation took two forms: the first was a 14-question consultation document (available at [Annex A](#)) aimed at professional organisations, stakeholders, and researchers. Modified versions of this document (with fewer questions) were drafted in order to capture responses from the international research community, with help from colleagues at the Global Health Research Network (GHRN) (see [Annex B](#) for the modified version of the call for evidence, and [Annex C](#) for further responses posted to

---

<sup>1</sup> The Working Party also published two questionnaires on the Survey Monkey website. One survey sought views from parents; the other from young people. Separate summaries of these surveys are available at: Nuffield Council on Bioethics (2015) *Children and clinical research*, available at: <http://nuffieldbioethics.org/project/children-research/>.

the Network's blog), and the KEMRI Wellcome Trust Research Unit in Kilifi, Kenya ([see Annex D](#)).<sup>2</sup>

Each of the 14 questions will be analysed in turn.

## How should children be recruited to clinical research?

### Question 1

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

Several obstacles to recruiting children to take part in clinical research were raised by respondents to the consultation, each of which can be categorised thematically. Where respondents suggested ways in which these obstacles might be overcome, they are also noted.

### Lack of awareness and information: the 'low profile' of paediatric research

Several respondents highlighted this obstacle, including:

*"I am dual trained nurse who worked on an acute paediatric ward for over 20 years and have moved to research in only the last 3 years. In my 20 years on an acute ward I haven't seen any research being undertaken or parents being approached."*

Anne Elmer

*"Recruiting children relies on children knowing that the study actually exists. This is a difficult one, families are faced with many challenges, and may be suitable to enter a number of studies, I believe here there is a role to have a portfolio of studies, making it clear to families which ones are open to them, so that they can see the range of studies available to them: so that we as professionals are open about the range of studies open and work with families in making their decision."*

Professor Faith Gibson

*"Clinicians may have had little exposure or involvement in research. If better informed they may be willing to partake or encourage families to become involved in research."*

<sup>2</sup> Some questions from the original document were re-worded or shortened. This analysis collates answers from all respondents, whether they answered the original, KEMRI, or GHRN document.

## Oxford Vaccine Group

*“... children do not appreciate yet the implication of research. We need to carefully bring this to their level of understanding and try to get the best out of them. Communication here is key.”*

Fasela Emmanuel from the NIMR in Lagos, Nigeria, responding to the GHRN document

Associated closely with the observation that paediatric research might be perceived as a ‘low profile’ area of clinical research is the suggestion that a further obstacle is a lack of *awareness* about its aims. This was a point that was raised in a response from the AMRC, which suggested that there is a “lack of awareness of opportunities to take part in research and information about what this involves”. An anonymous respondent also noted that, “for older children or young adults, I feel the greatest obstacle to recruitment is the lack of general information available to the public regarding clinical research.” This statement is supported by a response from the British Medical Association, who observed that “other barriers to parental consent can include a lack of understanding of the particular aims of individual studies and the often complex issues and technical aspects of research, such as randomisation and equipoise.” Fear of the unknown was raised as an obstacle by María del Carmen Díaz from the Facultad de Ciencias Médicas de la Universidad Nacional de Rosario in Argentina (responding to the GHRN document), and a lack of knowledge of clinical research and the associated processes involved was similarly cited, with one respondent to the GHRN document noting the “lack of familiarity with the idea of paediatric research amongst the public, but also healthcare professionals.”

Other respondents suggested that, in some quarters, there is low level awareness of the *positive* impact of paediatric clinical research, and consequently the negative effects of *not* encouraging research in this group. Iain Chalmers, for example, stated that there is an “insufficient acknowledgement by everyone – patients, parents, clinicians, research regulators and the public in general – that substantial harm has resulted when important uncertainties about the effects of treatments in children have not been addressed in reliable research.” Similarly, drawing particular attention to research in very young children, the Christian Medical Fellowship observed that “parents do not understand the significance of the research.” Muhammed Afolabi (based in The Gambia), responding to the KEMRI document, highlighted, in particular, that there can be “poor understanding of study rationale especially by the father, leading to marital disagreement or sometimes, forceful withdrawal of the child from the study.” A possible way of approaching this particular obstacle was suggested by Molline Timbwa, also in response to the KEMRI document: “Involve the ‘men’ during consent process, for example request them to spare time to come to hospital, call them where it is not possible for them to physically be available.”

Health, Ethics and Law, University of Southampton (HEAL UoS) also suggested that “difficulties that can arise when the ‘general public’ does not necessarily appreciate that

the medicines in question have not been previously tested on children; and accordingly may be unaware of the need for further trials on child subjects.” A similar suggestion was made by Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI), who argued that “greater recognition needs to be given to the specific health literacy, language and information needs of children and families. Current guidance on the production of children’s study information often acts as a disincentive and needs amending so that appropriate language and communication is used when conveying study information to children and parents and so that participation is presented positively, not defensively.” Professor Faith Gibson suggested further that for “young people in particular we need to be really creative in our approaches to recruitment, using all the formats/places young people visit to recruit. I know that Twitter/Facebook challenge some RECs, my view is we now need to build the processes and safety nets around these creative approaches, not just taking a blanket view of ‘not possible yet’.”

The NIHR Clinical Research Network: Children drew attention to the lack of awareness of *attitudes* to research as a potential obstacle: “...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.” Dr Daniel E Lumsden made a related observation:

*“Research in children is somehow still seen as remarkable, that only a small number of doctors and professionals will engage with, and that limited numbers of children will want to take place. A child’s participation in research is too often seen as “exceptional”, and to have overcome significant difficulties with ethics/R&D etc to have achieved that registration. This is erroneous.”*

### **How a lack of awareness and information might be overcome**

Several respondents commented on how a lack of awareness and information might be overcome. For example, the Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) noted:

*“Some paediatric specialties have established a successful research culture and others should learn from their experience. Infrastructure and capacity building within tertiary hospitals and visible university links are vital to raise the profile of research, and to ensure that academics remain engaged with the clinical community – this will allow the successful extension of research into all settings.”*

The Academy of Medical Sciences noted similarly that a “culture change” was necessary, “so that research is accepted as an essential part of care.” Dr Daniel E Lumsden also suggested that “research must be embedded in the curriculum and

training of healthcare professionals involved in the care of children, with evidence of active participation in research necessary for career progression.” The Health Research Authority also highlighted that “the provision of high quality professional education for all those involved in research involving children will be an important element in any approach to overcoming obstacles to undertaking research with children.” Moreover, the HRA added that “encouraging engagement and involvement of children, parents/carers and patient groups in the design and conduct of research will ensure that such research is more closely aligned to their needs of children and thus facilitate recruitment”, and the British Medical Association suggested that “encouraging confidence and addressing misconceptions regarding the purposes of clinical research more generally may be helped by publishing good practice or positive case examples.”

Publishing materials to support understanding of clinical research was also suggested by Muhammed Afolabi, responding to the KEMRI document:

*“Research information should target not only the mothers of infants/toddlers but also the fathers. Supporting materials like ‘Speaking Book’ has recently been used in a Gambian study to complement the informed consent document. Designed in two major Gambian languages, ‘Speaking Book’ narrates clear information about participation in vaccine studies. Mothers of study infants are encouraged to listen to it and share the information with their husbands at home.”*

The importance of communication was also raised by Molline Timbwa who suggested that information might be communicated “via frequent contact with participants throughout the extensive follow-up period and to offer clinical care where needed”, along with “monthly telephone calls to each participant to encourage adherence to visits and to monitor adverse events”, and “regular distribution of birthday and holiday cards to build a personal relationship and maintain communication.” María del Carmen Díaz, responding to the GHRN document, suggested that lack of knowledge about paediatric research “can only be overcome by a change in culture that includes patient-centred directed activities, and events and media impact, but also an organisational change.”

### **Workload pressures on healthcare professionals**

Recognition of health professionals’ heavy workload was raised by the Academy of Medical Sciences, and also an anonymous respondent who recounted that “in my experience a major difficulty lies with the need to delegate identification of the children to the healthcare team, which is usually a busy team with little time for such activities and at risk of forgetting about the various studies going on.” Professor Jane C. Davies highlighted further that “a lack of protected research time for most paediatric clinicians hinders their involvement and prevents their patients having access to clinical research.”

The AMRC also noted that staff might not have “the time nor the training to discuss research with their patients”, and the Paediatric Emergency Research in the United

Kingdom and Ireland (PERUKI) noted that obstacles were erected by the "...availability of resources, whether in the form of time, funding, or personnel." Dr Daniel E Lumsden similarly highlighted "... the limited capacity within the child health services to recruit children to studies and ultimately run those studies."

### **How workload pressures on healthcare professionals can be overcome**

No specific suggestions were made as to how this particular obstacle might be overcome.

### **The perception that paediatric clinical research is 'difficult'**

One anonymous response highlighted this obstacle, noting that "the principal 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." No specific remedy for this obstacle was suggested.

### **Protective attitudes to children and young people**

This obstacle was summarised in an observation by Felicity Shenton, Development Manager for Investing in Children, who noted that "adult gatekeepers are usually the biggest obstacle in recruitment and often make decisions about whether or not a child should participate and whether or not it is in the child's best interest without discussing with the child first."

#### **i) By professionals**

The Academy of Medical Sciences noted that clinicians might have general concerns about children's participation in research. This was echoed in a response from the University of Cambridge Department of Paediatrics, which observed that "some paediatricians and other health professionals are still reluctant to engage and some have a protective, negative response to research activity involving children." The Oxford Vaccine Group also felt that "clinicians may have had little exposure or involvement in research" and may be overprotective; "especially those who have worked with families of children with a chronic or life limiting condition."

The Health Research Authority similarly noted that obstacles could be found in "paternalistic attitudes towards children by clinicians who don't want to burden parents/children with research and don't ask." The Authority also suggested that there is an "assumption that children are incapable of making decisions, or may not have the altruistic approach that some adults have."

The AMRC also commented on this question, and noted that "risk aversion among clinicians, particularly those not personally involved in research, and the general public is felt to be the main obstacle to recruitment."

## ii) By parents

*“Sometimes parents are scared to allow their children participate in clinical trials where a new intervention is being tested. They would often have fears about safety of the product [...] Parents come in with very sick children [to the] ward set up, they are worried and anxious about the child’s wellbeing, and research may not be a priority to them.”*

Anonymous respondent to the KEMRI document

*“... although attitudes to research are generally positive amongst the general public, some parents may have pre-existing concerns or misconceptions about research in general, that their child would be used as a ‘guinea pig’...”*

British Medical Association

*“Caregivers will instinctively behave or react in as much [of] a protective way as possible whenever there is a perception of risk or danger to a child. So it makes for a tough case to convince parents/caregivers to expose a child to potential risks of research, even when that risk is often just a needle prick for blood draw.”*

Dr Roma Chilengi, Zambia, responding to the KEMRI document

*“The concept of research is new to most parents in poor resource countries, mostly familiar with clinical care, thus they may refuse to allow their children to participate.”*

Anonymous respondent to the KEMRI document

Parental concerns were also raised in a response from AstraZeneca: “parents may be reluctant to agree [to] participation of their child in a study, even more in the case of a placebo controlled study where their child could be receiving placebo”. The same respondent also noted that the “informed consent to be given by both parents is sometimes difficult to get”, and also noted a “mistrust of medical research.”

Attention was also drawn to the perceived vulnerabilities of very young children. For example, the Christian Medical Fellowship observed that “parents feel that the infant is very vulnerable and they feel responsible for allowing their infant to enter a study.”

### Addressing the obstacle of protective attitudes

NIHR Clinical Research: Children commented on the perception of paediatric research as ‘risky’ or ‘dangerous’:

*“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. While this may be true for some areas of research, it certainly isn’t necessarily the case that all paediatric research is “difficult” or “dangerous”.”*

The Oxford Vaccine Group also suggested that if clinicians are “better informed, they may be willing to partake or encourage families to become involved in research.”

In the context of the protective attitudes of parents, Molline Timbwa (responding to the KEMRI document) made the suggestion of having “a patient advocate, preferably from the local community, to help parents/ guardians overcome concerns by discussing in simple words what the study is about – the risks, the gains, and encourage and answer questions.”

### **Age range in ‘child’ participants**

Recruitment difficulties were also highlighted in the context of the broad age spectrum encompassed by the group of ‘child’ participants.

*“For instance, communication material designed for a 12 year old might not work well for a 16 year old. One thing is common to all ages though, young people do not like to be told constantly about the potential consequences of their condition. They like to hear positive messages of hope. It is these that make them enthusiastic to try new treatments.”*

EMIG

### **Young people no longer living with their parents**

The Instituto Nacional de Salud del Niño del Peru, Instituto de Investigación Nutricional del Peru, Hospital Nacional Edgardo Rebagliatti Martins and US Naval Medical Research Unit No. 6, NAMRU-6 also drew attention to a specific set of circumstances in Peru where homogenous consent procedures for those at the older end of the age spectrum is problematic:

*“The need for the signature of both parents in the consent form is also an obstacle for research studies on sexually transmitted infections in 15-17 year-olds at risk and who no longer live with their parents. In cases such as these, the consent of a parent, as a step prior to the assent of the minor, could not be requested from the parents without placing the minor’s well being at risk.”<sup>3</sup>*

---

<sup>3</sup> Throughout the rest of this summary, this respondent will be referenced as ‘Instituto Nacional de Salud del Niño del Peru.’



## **Opportunity costs**

Opportunity costs to children and their families were also raised as a potential obstacle. For example, one respondent drew attention to the problem of taking time off school, and AstraZeneca noted the drawbacks of “time off work, transportation costs, out of pocket costs”. Muhammad Afolabi, responding to the KEMRI document, observed that “most Gambian children (those who could express views or those under 16) still rely solely on parent and guardian/carer’s decision before joining a study. The parents place higher premium on farming and schooling activities for the children than finding time to attend scheduled study visits. In many instances, these lead to protocol deviations and high drop-outs of the children from the study.”

### **Overcoming the obstacle of opportunity costs**

Several respondents made suggestions as to how this obstacle might be overcome. The University of Cambridge Department of Paediatrics, for example, suggested that this obstacle might be overcome by “making [it] more convenient for busy parents and children to participate in research studies.”

## **Uncomfortable procedures**

The EMIG noted that “operationally, one of the main obstacles for recruiting young children is the thought of blood sampling.” Muhammed Afolabi, responding to the KEMRI document, similarly observed that “in The Gambia, main obstacles against recruiting infants/toddlers to research include the parents’ concern about the frequency and volume of blood collected during the study visits”. Professor Jane C. Davies echoed this obstacle, noting that “concern over painful or uncomfortable procedures, many of which are technically more challenging in children such as venepuncture, and which are not required for clinical purposes.” No specific recommendations were made as to how this obstacle might be overcome.

## **Research proposals that do not focus on the participant**

This perceived obstacle included an observation by the AMRC that research should be “designed around the participant, and in consultation with them.”

### **Overcoming the obstacle of protocols that do not focus on the participant**

The British Medical Association suggested that such an obstacle might be addressed “...through balanced and age-appropriate communication of what a study involves.” The EMIG argued that “the challenge of recruitment could also be reduced by taking every appropriate opportunity to involve children in the process of identifying their needs and wishes in relation to research.” Further, EMIG added that “children should also be members of development programme/individual study advisory panels, wherever practical and appropriate.” The British Medical Association echoed this suggestion,

noting that “involving parents and children in the design of studies, wherever possible and relevant, could also help to encourage recruitment and retention.”

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) added further that this obstacle could be overcome by developing “consent procedures which are not primarily oriented towards meeting formal legal requirements but towards fitting the needs and realities of overwhelmed parents facing high-risk situations for their child”.

Professor Faith Gibson also highlighted the importance of engaging with children and young people, and observed that “engagement is about talking, reading, showing children what it means to participate to say yes or no. Many of our studies involve children ‘doing things’ so showing them pictures, using fuzzy felts, board games to help them see this and ask questions about it is important. There are now a few examples of creative techniques to help children; these can be used in addition to a well-written age/developmentally appropriate information leaflet.”

### **Burdensome and unclear approval procedures**

Several respondents referred to the role of approval procedures in creating difficulties for recruitment of participants. For example, the AMRC referenced “delays in obtaining NHS R&D permissions holding up research”. A lack of clarity of “regulators’ guidelines, dealing with paediatric population and most of the time trying to apply adults’ guidelines.” Similarly, an anonymous respondent addressed the “lack of campaigns and understanding about the rules, regulations about clinical research to inform parents and lay population.”

A lack of clarity was also raised in a response from Health, Ethics and Law, University of Southampton (HEAL UoS), which noted that “researchers find it an obstacle to have different ages of consent in operation, dependent on the precise context, and a lack of clarity as to whether a *Gillick* standard of competence applies in different scenarios.”

From the perspective of a country with different consent procedures from the UK, the Instituto Nacional de Salud del Niño del Perú drew attention to the practical difficulties of fulfilling consent requirements for clinical research with children:

*“The current Peruvian regulation states that “the consent form requires the signature of both parents.” At the Peruvian National Cancer Institute, almost 50% of the patients come from the provinces and are accompanied only by one single parent. Because of this, these minors cannot participate in the clinical research studies being conducted. In general, the rate of households ran by a single parent in Peru is between 25% and 27% in urban areas. Children are excluded from clinical research because they only have one parent present to sign the informed consent.”*

The University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) also focused on difference between nations in approving research, but focused on how different countries interact; in highlighting obstacles that undermine the efficiency of recruiting children to take part in research, UCL and ENCCA noted that "... international cooperation is necessary but sensitive to localisms and time-consuming."

### **Overcoming the obstacle of burdensome and unclear approval procedures**

Professor Jo Bridgeman addressed this obstacle by suggesting that "as clear as possible a statement about what is legally established alongside guidance which offers a route through the legal and ethical issues which need to be addressed would, I think, be of most use in overcoming the obstacle of uncertainty about legality."

The University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) called for a harmonisation of "review procedures of protocols by ethics committees, locally as well as in Europe, in a view of maximizing both children's protection and consistency (thus predictability) of decisions".

Approaching this obstacle from the perspective of developing countries, Dr Roma Chilengi (based in Zambia, responding to the KEMRI document) observed that "public education and literacy on what research is and its benefit is a major problem. This is also reflected at the highest policy decision-making level whereby, prevailing laws were adapted from the colonial system within a real appreciation of what research is. Many developing countries have not had real due diligence given to articulation of laws governing research in their countries and as such, there is lack of depth and breadth in articulating the laws that should govern research."

### **Lack of 'joined-up' services**

A further administrative obstacle was noted by other respondents. The University of Cambridge Department of Paediatrics, for example, stated that "currently research is not embedded in general paediatric practice with the possible exception of paediatric oncology."

### **The proposal of research participation in emotional or traumatic circumstances**

A response from Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group highlighted obstacles that can arise in very sensitive areas of clinical research: "There are particular difficulties in carrying out research in neonatal palliative care, largely because parents of newborns may not have had time to come to terms with their baby's poor prognosis and the introduction of a palliative care approach, let alone considering participation in research studies."

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA), commenting on recruiting participants appropriately “(to recruiting children in the proper ethical way)”, highlighted the role of “psychological distress, especially if inclusion occurs near the time of diagnosis or relapse...”

### **Addressing the obstacle of inviting research participation in the context of traumatic circumstances**

The Academy of Medical Sciences suggested how this obstacle might be overcome:

*“Another area to consider is ways of communicating the research. Families may be asked to provide consent to participate when they are under psychological distress, for instance during the time of diagnosis or when a relapse is identified. Consent procedures should be orientated towards the needs and realities of the parents and children, to allow accurate assessment of the child’s chances of benefiting from research.”*

### **General approaches to overcoming obstacles**

A number of other general comments were submitted by respondents on approached to overcoming obstacles.

*“...potential obstacles can only be overcome through an attitudinal and cultural shift, underpinned by the recognition of need for a strong evidence base in our clinical practice. This must be supported by a robust funding structure which translates directly to those who wish to deliver and develop high quality research.”*

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

*“It may also be valuable to consider tailoring approaches to different research participants.”*

AMRC

*“In the past we have had difficulties recruiting children from black and minority ethnic groups although this obstacle has been overcome by involving researchers from black and minority ethnic groups, making participation more convenient, worthwhile for families and offering a range of participatory data collection activities.”*

British Society of Paediatric Dentistry

## No obstacles/exaggerated obstacles

Very few respondents expressed the view that there are *no* obstacles to recruiting children and young people to take part in clinical research. A positive approach to recruitment was, however, highlighted by NIHR Clinical Research: Children:

*“One obstacle often cited is a lack of appropriately trained clinicians with the necessary knowledge and experience of undertaking paediatric research.<sup>4</sup> Whilst we recognise 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 clinicians to allow them to participate in clinical research, and provision of funding and mentoring opportunities to enable them to gain the necessary experience.”*

Dr Eleonora Espinoza from the Comité de Ética de Investigación Biomédica, Facultad de Ciencias Médicas, Universidad Nacional Autónoma de Honduras, Tegucigalpa Honduras (responding to the GHRN document) observed that “in general in Honduras there are no obstacles to recruit children as research subjects.” Expanding on this observation, Dr Espinoza observed that “there is usually consent by the parents, probably due to ignorance of what it means to participate in scientific research.”

### Question 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.)

### Who should make the final decision where there are disagreements?

#### The role of children and young people

Several respondents expressed the view that the child or young person should make the final decision where disagreements arise, with many respondents attaching caveats to this approach. For example, Professor Jo Bridgeman suggested that “... if the child, after being provided with age-appropriate information, advice and discussion does not want to participate, that decision must be respected. But a decision can only be reached after the

---

provision of age-appropriate, child-focused, information, discussion and advice”. Professor Bridgeman further noted that “guidelines offer a route to arriving at a decision about the participation of children in clinical research which requires an assessment of the child’s views, parental views and their views together as a family unit and which stresses the importance of respect for the contributions and roles of the entire professional team.”

The British Medical Association made a suggestion about how a situation involving a child refusing to participate might be approached: “...in cases where disagreement arises because a parent gives his or her consent for a competent child’s participation but the child refuses, arguably this refusal should be respected and the child or young person should have the final say in the decision, unless this would clearly be significantly detrimental to the child interests.” The BMA also commented on a scenario where a child might want to take part in clinical research, but their parent(s) disagree: “In cases where children who lack competence wish to participate in research but their parents object, a child’s assent alone would not provide sufficient basis for enrolment on a study and parental consent would be required. Although in theory a competent child’s decision to participate could be determinative, much would depend on the type of study and the risks and benefits involved.”

Anne Elmer observed that “the fundamental issue with children’s nursing is to respect the child’s wishes and treat them as an active participant in their care.” A similar view was taken by the Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI), who observed that “health care professionals should always take children seriously, and make sure that they have a voice (which is listened to), even in the case where children are not the final decision-makers. Even in young children, it is important that dissent is considered, even if it is not respected.” María del Carmen Díaz from the Facultad de Ciencias Médicas de la Universidad Nacional de Rosario, Argentina (responding to the GHRN document) also took the view that “though the persons in charge (persons or tutors) must give the assent, the children (human free beings) must give their assent if they’re of the age of understanding. Only in the case of risk of his life might they not be consulted.” Similarly, Fasela Emmanuel from NIMR in Lagos, Nigeria (also responding to the GHRN survey) suggested that “the child should be made to make these final decisions after carefully assuring him/her of his safety and benefits as well as the minimal risks. If the child says no, then there should be no research conducted on them.”

The Health Research Authority noted its “agreement with the UN Convention on the Rights of the Child which *“affirms that children are full-fledged persons who have the right to express their views in all matters affecting them and requires that those views be heard and given due weight in accordance with the child’s age and maturity”*. Thus, increasing weight will be given to the views of the child shifting the balance of decision making from parents/carers to the child until the point at which the child attains sufficient maturity and understanding (“Gillick competence”) to give valid consent for themselves.”

Other respondents suggested that the age of children and young people had an impact on the level to which they might be involved in decision-making.

*“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.”*

AstraZeneca

*“Children aged 8-18 years should themselves make the decision to participate through the informed assent. In infants, for instances studies on vaccines in two-month olds or older children, parents and guardians should take the decision through informed consent”.*

Dr Eleonora Espinoza, Comité de Ética de Investigación Biomedica, Facultad de Ciencias Medicas, Universidad Nacional Autonoma de Honduras, Tegucigalpa Honduras (responding to the GHRN document)

*“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.”*

NIHR Clinical Research: Children

*“For babies: the parent should have the final say... For young children: where a young child clearly does not want to have blood drawn or other form of procedure, I feel it is the health professional’s responsibility to ensure that the child is not put under any unnecessary stress or trauma. Ultimately, however, it is the parent’s decision... When the child is able to communicate clearly, one would hope that both parent and child can come to an agreement before the health professional seeks consent and/or assent.”*

Anonymous consultation respondent

*“The child should be involved in the decision as much as possible, given their age, and if they are capable of refusing to take part, this should be honoured.”*

Professor Caroline H.D. Fall

*“As the child herself is the research participant the final decision should rest with the child. The concept of Gillick competence is important. Where a child has sufficient understanding she should be able to make an informed decision about whether or not to participate or continue to participate in a research project. Good practice suggests that wherever possible parental/carer’s consent should also be obtained.”*

Felicity Shenton, Development Manger, Investing in Children

The Christian Medical Fellowship also made a distinction in cases involving older children:

*“Among older children, dialogue between child, parent and researcher should involve a joined up decision by parent and older child. Among older children, researchers have a great responsibility for ensuring that both children and parents are equally informed about all aspects and potential discomfort of the research, including the knowledge that the research may not actually benefit themselves necessarily.”*

Similarly, the Oxford Vaccine Group noted that “we should apply ‘Gillick’ approach for under 16s in research decisions as well as in decisions about treatment... [it is] easy for young children and teenagers, but difficult when a child is in a transition age, i.e. over two years of age.” However, an anonymous respondent observed that age is perhaps not a key factor in circumstances where disagreements occur, stating that “if minors truly disagree with the objectives/aims/content (e.g. risks) of the research: minors. Such dissent implies true understanding, and there is no reason to disrespect dissent merely because one has a certain age.”

A further comment on the age of participants was raised by the Instituto Nacional de Salud del Niño del Peru:

*“In Chile, Argentina and Colombia, the legal stand of a ‘mature minor’ allows a 16- or 17-year old to assent to research studies of, for instance, sexual behaviour, without the consent of their parents. In Peru, the legal stand of a “mature minor” does not exist. In Peru, even mothers who are under 18 years old cannot consent for their children to be enrolled in a clinical trial. The parents of the underage mother need to consent for their grandchild to participate and this, in many circumstances, impedes their participation in research.”*



Further comment on approaches to this question outside a UK context was raised by University College London and the European Network for Cancer research in Children and Adolescents (ENCCA), who noted that "... in Europe, legal requirements can explicitly preclude to overriding a child's refusal to participate in research. French law states this way that: "In any event, their refusal or revocation of acceptance cannot be ignored..." Obviously, such legal dispositions are open to interpretation, at least according to a child's age and maturity; moreover it does not prevent intra-familial disputes about research participation to occur."

### Parents or guardians

Other respondents felt that parents were the key decision-makers in cases of disagreement.

*"In all cases involving minors under 16 years of age, the decision shall be made by the parents or duly appointed guardian, and the assent of the minor. In case of parental discrepancy, the decision shall be not to intervene."*

Hector Verlade

*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).*

Anonymous consultation respondent

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) emphasised that "while it is desirable not to arbitrate intra-familial disputes solely on a case-by-case basis, it is of paramount importance to take the specifics of each situation into consideration and to maintain good communication, or "shuttle diplomacy", with patients and parents." Although addressing the first question of the call for evidence, an anonymous respondent to the KEMRI document highlighted that decision making can be affected by family structures:

*"Children more often are brought to hospital by mothers/grandmothers who do not regard themselves in-charge of making decision to allow the child to participate in research in the absence of the father. In most African cultures the father is regarded as the "mwenye" (owner) hence mothers feel incapable of making decisions regarding the child participation in research and clinical care at times."*

A similar observation was made by Molline Timbwa, again in response to the KEMRI document: "In the African culture the man is the decision maker yet most times it can be

extremely difficult to get them on board to discuss issues of the research.” The role of parents in decision-making was observed further by Dr Roma Chilengi, Zambia (KEMRI respondent):

*“Generally the developing world setting has a long historical culture of children being dependent on their parents/guardians until very late in life. This is changing slowly as some affluence is coming in. But it is difficult to imagine a 16 year old having so much appreciation of what may be [the] scientific benefits of research, and [making] independent decision to bear what risks that may pose to themselves; especially in the absence of some direct benefits... real consenting should be left to legal guardians and the practice of obtaining assent above a locally determined age threshold is appropriate.”*

The role of parents and the place of a child or young person in family dynamics, in a context outside the UK, were points also raised by Muhammed Afolabi (a respondent to the KEMRI document):

*“When parent and child disagree, the most pragmatic approach is NOT to enroll or involve the child in the study. This is because, in most sub-Saharan African countries, children (even beyond age of 18) are still considered a dependant who needs the approval of parents to take any major decision, including research participation. A child who deliberately exercises his/her rights of competence is seen as disobedient and disrespectful to the parent, which has grave social, cultural and religious implications on the child.”*

### **Arbitrator or legal professionals**

A small number of responses highlighted the role that legal professionals could have in cases of disagreement. For example, one respondent observed that “In the case of a very promising experimental therapy not yet registered and considered to be superior than the best standard of care available based on the actual knowledge, most likely the attending physician should seek for judicial advice if the gap between the initiation of the treatment and decision will not interfere with the patient’s treatment.”

The University of Cambridge Department of Paediatrics also noted the potential role of a neutral third party: “Where there is a disagreement between a child under the age of sixteen and parents as to whether he or she should be involved in a clinical study, this can usually be resolved through discussion or the involvement of a neutral third party. There may be rare examples where the conflict cannot be resolved and in these cases, which we suspect only involve early phase clinical trials, an additional form of mediation may be required.”

## **Schoolteachers**

The Christian Medical Fellowship drew attention to the potential role of schoolteachers in decision-making, noting that “in certain cultures, schoolteachers of boarding schools may take responsibility for giving permission for research on children on behalf of parents, but this should only be accepted if there is clear evidence that the children themselves have an opportunity of leaving the study or not entering it in the first place.”

## **The responsibilities of health professionals and researchers in cases of disagreement**

### **Responsibility to inform**

The Oxford Vaccine Group highlighted a responsibility “for professionals [to] always... take the child and parents along with them, especially in sensitive situations. Unless life threatening [we] would not want to overrule anyone.”

### **Responsibility to mediate**

A response from the Academy of Medical Sciences also suggested that researchers might have a mediation role where disagreements occur, stating that “efforts should be made at all times to try and reach a position that all parties are comfortable with. Appropriate clinical input may be required to reach this position.”

An anonymous respondent suggested that “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).”

### **Responsibility to support and advise**

The British Medical Association suggested that “Researchers have a responsibility to ensure children and young people and their parents have the support and advice they need about their options, including explanations of the purposes, risks, and expected benefits of the research, and that they understand the consequences of agreeing or refusing to take part in a study.” Professor Andrew Tomkins also noted that “Researchers have responsibility for ensuring that parents understand all the implications of research for infants and young children, taking responsibility for assisting in the study despite some apparent discomfort.”

Similarly, the Christian Medical Fellowship felt that “researchers clearly have responsibility for ensuring that parents understand all the implications of research for infants and young children...”

## Responsibility to protect the child or young person

Several respondents felt that health professionals and researchers had a responsibility to protect the (potential) participant. One respondent, for example, suggested that “the health professional and the researcher have a duty to protect the child and may have to mediate on behalf of the child where there is disagreement.”

## Other comments

Respondents also addressed other issues. For example, Professor Andrew Tomkins instead engaged with the question of what constitutes ‘disagreement’. Professor Tomkins observed that “...there are many ways of responding to “disagreement”. Does this mean that a child who cries when he has a blood spot taken for a biochemical measurement is a child who disagrees? Does this mean that a child who is in a trial of a nutritional supplement among school age children and decides that he does not like the taste of the tablet is actually disagreeing?”

### Question 3

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

Responses to this question can be categorised broadly into those who thought the concept of assent was useful, and those who thought the opposite. More respondents subscribed to the former category.

### **It is helpful to distinguish between consent and assent: assent as ‘useful’**

## Distinguishing the role of parent and child/young person

An anonymous respondent highlighted the role of assent in distinguishing between the responsibilities of parents and young people: “Assent is a useful concept. It is good to distinguish between the responsibilities of a parent and the responsibilities a young person has for making their own decisions.” Muhammed Afolabi, responding to the KEMRI document, noted that “in Africa, the concept of ‘assent’ is useful and relevant as long as the parents do not have concern/reservation to the child’s participation.”

Professor Andrew Tomkins also raised the role of assent in making distinctions between the role of parents and their children: “It is important to distinguish between the two however, because consent can only occur if the child fully understands and agrees whereas assent can occur if the parent/carer fully understands and the child assents by agreeing to trust the researcher and the parent.”

## **The role of assent as a safety mechanism**

EMIG, for example, noted that “the advantage of assent forms is that they help to ensure that the nature of the clinical trial has been well explained to the child.” Felicity Shenton, Development Manager, Investing in Children similarly noted that “the concept of assent is very useful in understanding the importance of the child’s understanding of what they are being asked to agree to and what the implications/consequences of this may be.”

## **Assent’s role in engaging children and young people in clinical research**

The role of assent in engagement was highlighted in a response from Molline Timbwa, responding to the KEMRI document: “Children do want to have a say in what happens to them and they want to ask questions and have them answered. When children are asked if they want to join a study, it shows respect for them. And they will feel good about being in the study and more committed to doing what the study requires.” Anne Elmer also commented on the impact assent can have on effective engagement: “Having used assent forms with children on a research ward I found them invaluable. The children were engaged, found a sense of empowerment and were fully aware of what was involved with the study. Having appropriate assent forms for the variety of ages involved is paramount however you occasionally see studies involving children without any assent forms which I feel is a poor reflection on the PI and his understanding of children.”

EMIG also observed that “opinions do vary on the objectivity of assent, but overall, when asking parents for written consent, it is recommended that children with the capacity to understand should be involved and at least provide verbal assent.” The British Medical Association also saw a further way that assent is helpful: “babies and very young children will have very little if any understanding of research whereas some children will have sufficient understanding to be deemed competent to provide full and valid consent. The concept of assent may help to formalise the decision-making capacity of children whose level of understanding lies between these extremes. It recognises that this level of competence is a relevant consideration in research decisions and should be sought by researchers, whilst still distinguishing it from full consent to take part.”

Dr Roma Chilengi, responding to the KEMRI document, argued that “the concept of assent is extremely important. The difficulty we have is finding that line-demarkating assent from consent. We assume that a parent with understanding, can make a decision on behalf of their child and particularly in the context of research causing some pain through invasive procedures, any reluctance from the child come more from the fear of pain. However, at some point that child should be allowed to say “I don’t want this”. In a sense children always express that when they see a needle stick, but they do that even when it clearly is for their benefit in case of treatment or therapeutic research. The strange thing is that we allow adults to refuse participation in the trials even when clearly they are only afraid of the needle; but we insist on children on grounds that the parent has agreed. I do not have an answer as to where that shade changes colour.”

## Concerns about introducing alternative concepts

Professor Jo Bridgeman argued that "... I would favour its employment given the dominance of the concept within the law regulating modern medicine. The potential misreading of a decision to employ an alternative – for example, the impression that informed permission is not an essential requirement to good practice in this area - leads me to the conclusion that this is not the context in which to employ an alternative concept."

The Instituto Nacional de Salud del Niño del Peru also observed that "if the name changes from "consent for minors", it may lead to documents that are harder to understand and this would deny the true purpose of the assent form." The Instituto concluded that "We find this distinction between assent and consent useful. Assent is for minors and as such, it uses simple, easy to understand language. A minor's assent is required for his/her participation in a research trial and thus, his/her cooperation with the study procedures."

## Other comments on the usefulness of assent

Other substantive support of assent included the following observations:

*"The concept of assent is considered to be useful. It provides the child with information, and includes them in the research process, before the research begins. It also identifies questions the child may have about the research which may not be obvious to the researcher/parents, and provides an opportunity to address these at an early stage. It ensures that the important voice of the child is heard alongside the consent required from the parent/carer."*

Health Research Authority

*"... as children grow in autonomy and in maturity, to fully respect their dignity involves to take their assent into consideration in a correlatively increasing degree."*

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA)

*"These are useful distinguishing terms. The word 'consent' implies a full understanding of all the rationale for doing the research and a full understanding of the benefits or lack of benefits of entering a study. The word 'assent' implies an agreement to enter a study, trusting in the integrity of researcher and parent/carer alike, without necessarily understanding the full benefits, lack of benefits or risks of entering a study... It is important to distinguish between the two however, because consent can only occur if the child fully*

*understands and agrees whereas assent can occur if the parent/carer fully understands and the child assents by agreeing to trust the researcher and the parent.”*

Christian Medical Fellowship

*“Generally we felt that the current parent’s full consent and children’s assent procedures work well. They encourage researchers to provide appropriate information for the children as well as more extensive information for the parents. This means that the children can be involved in the decision as to whether they are involved in the clinical study or trial.”*

University of Cambridge Department of Paediatrics

*“The process of assent is useful to understand how a child feels about being in a study.”*

AstraZeneca

*“...it reminds professionals that minors do have a voice that is of key importance and because it is truly respectful to children.*

Anonymous consultation respondent

However, the same anonymous respondent added further that “for mature minors, it may underestimate their decisional abilities, certainly in specific types of research.” Other respondents also qualified their subscription to the usefulness of assent. For example, NIHR Clinical Research: Children noted that “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.”

### **It is not helpful to distinguish between consent and assent: assent has no, or limited, use**

A number of respondents took the view that assent was not a useful concept, including:

*“In the absence of a right to express dissent, assent is a meaningless concept.”*

Anonymous consultation respondent

*“It probably isn’t very helpful to distinguish between consent and assent for young people: assent is consent, in so far as the child is able to understand the full implications, even if they are under the age of 16.”*

Academy of Medical Science

*“Assent is not the answer. Nonsensical term... No one understands the difference between consent and assent, mainly a term used in research, less so in medical practice... Asking a child to sign something (that is not recognised legally) undermines the process... Assent is, in effect, a process of communication in research: how could this be put in[to] some sort of framework?”*

Oxford Vaccine Group

*“The concept of assent is not particularly useful as we feel children should have the right to decide for themselves about their participation in research.”*

British Society of Paediatric Dentistry

The Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) observed that the usefulness of assent depended on the group it referred to, stating that “the concept of assent is felt to be helpful for patients, though less so for clinicians or researchers. It explains objectively and overtly why the reasons they are being invited to participate, and what the study is about. Empowering children from a young age to participate in their healthcare gives them a sense of autonomy and control.”

Further caveat was raised by Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group, who argued that “... assent or any other similarly situated principle should not be watered down or ‘babyfied’ consent.” An anonymous respondent also drew attention to how assent might be categorised in paediatric research when compared to adult research:

*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.*

Nigel Monaghan felt that the concept of assent should be replaced, recounting that “As someone who organises surveys of young children in schools I would avoid the use of assent for young children and use cooperating. We ask parents to consent to their child to be examined, but indicate to parents that we will not examine an uncooperative child.”

An anonymous respondent argued a different point: “I have observed minors who do not wish to be involved in decisions at all, notwithstanding their age, their excellent



capabilities of understanding information and making decisions. They might consider assent as a burden, and just wish to be cared for without having to make decisions at all...”

### **Other observations on assent**

Respondents also made further comments, and raised other issues, in relation to the question of assent.

*“Assent essentially describes the process of absence of dissent that I have described above. It is not dissimilar to the way in which decisions are made every day within families. EG Mummy has decided that you will go to nursery and that you will go to this nursery, a child may not be involved in these decisions explicitly but implicitly they may be asked OK/ Ready to go?”*

Anonymous consultation respondent

*“Consent procedures should be considered on a case-by-case basis. Considerations include carrying out all necessary discussions with a parent or other legal guardian, as well as the child participant to the extent appropriate. An important issue of consideration is re-consenting procedures when the child reaches the age of 18.”*

Wellcome Trust

*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).*

Anonymous consultation respondent

### **Question 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?

Again, responses were split broadly into two categories in response to this question; those which felt collaborative decision making models were helpful, and those who felt them to be unhelpful.

## Shared or collaborative decision making models are helpful

Several respondents indicated that these models of decision making were helpful.

*“This is a helpful approach... it is important to try and get to a position that everybody is comfortable with.”*

Academy of Medical Sciences

*“It is important to ensure that everybody is informed and happy with what will be taking place.”*

Anonymous consultation respondent

*“Taking a collaborative approach allows all parties to feel as if they have had a chance to have their views heard in relation to the study in question. It is likely to ensure better data through full participation to completion of follow up in any study, and allows any seemingly unreasonable stances to be explored.”*

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

*“I feel all research carried out with children should be a shared decision as the norm.”*

Anne Elmer

*“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.”*

AstraZeneca

*“It recalls the necessity and the value of maintaining a good communication between all parties.”*

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA)

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) suggested further that these models of decision-making are unavoidable: “...research participation has to be free and consensual between parents, patients and professionals. Shared decision-making in such settings is unavoidable; there is a matter of rights and of principled thinking, much more than a matter of utility and of consequential thinking.”

The Christian Medical Fellowship also noted that collaborative models could involve other parties: “In certain cultures, the involvement of community leaders and schoolteachers might also be considered in the shared model.” The relevance of cultural context was also raised by Professor Andrew Tomkins: “A key question of integrity is important, particularly in those cultures where children’s rights are not emphasised and there may be unduly and inappropriate pressure on a child from parent or community leader to become a participant in a study. It is important in shared models of decision-making to ensure that the child’s rights are respected at all times, even when these are counter-cultural.”

Other respondents urged an element of caution when using collaborative decision-making models. For example, Professor Jo Bridgeman noted that “‘collaborative’ decision-making should not be employed as a shorthand for a careful decision-making process which needs to be detailed.” The Health Research Authority also highlighted the question of resources needed for these models to operate: “...it may require quite intensive work from the professionals involved. They should be properly trained in communicating with children and young people, using a range of techniques. It may not be helpful to try to achieve a decision in a single meeting.” Anne Elmer echoed this view, noting that “any model of shared decision making also requires a great deal of time spent explaining all the issues and this may hinder some research which is time sensitive”, as did the Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI), which stated that the approach was “resource intense”.

An anonymous respondent argued that the helpfulness of the models depended “on what is pre-existing. Within the family, cultures of shared decision making may exist, and if these work well and entail sufficient respect for the minor, this shared decision making culture of families could to a large extent be used/respected in the setting of clinical trial participation. To introduce completely novel ways of making decisions may not always be feasible or workable.”

Health, Ethics and Law, University of Southampton (HEAL UoS) also highlighted that problems might arise where research was particularly sensitive: “... research into the use of drugs or sexual relationships, where involvement of the parents or other family members may be problematic; or in CRTs, where it may be inappropriate. In short, it should not be the only approach for research involving children as research participants.”

NIHR Clinical Research: Children also raised the point that “there are also circumstances such as research in newborns, especially preterm babies or in other emergency situations, where a ‘shared’ approach isn’t feasible.”

### **Shared or collaborative decision making models are unhelpful**

Flaws in these decision making models were raised by a number of respondents. For example, the British Medical Association noted that “Problems may arise where there is

misunderstanding or a failure to communicate the specifics of the study clearly, problems which can then often be difficult to overcome.”

The Academy of Medical Sciences also highlighted that “problems in achieving agreement may arise when children are in care or when the child’s parents are separated. It is important for researchers to know which adults to approach when making decisions.” Muhammed Afolabi approached the question of collaborative decision-making from the perspective of African families: “... shared or collaborative decision-making is not very likely to be effective in African settings. African social system does not give room for a parent and child to negotiate on important life decisions and this could extend to research participation.”

Similar concerns were Dr Roma Chilengi, also raised concerns about this approach from the perspective of developing countries: “I still think the option where local ethics committees make a determination of what is appropriate is the best. The mechanisms of a shared decision-making approach would in my view make research, especially in developing country settings, impossible.”

Practical issues were addressed by Instituto Nacional de Salud del Niño del Peru, noting that “sometimes the ‘collaborative’ decision-making model is somewhat difficult logistically speaking. Its feasibility varies with each situation, and it should not be a requirement. It is good to promote communication between parents, children and researchers, and the latter should be available for any additional information.”

Caution was also urged by one anonymous respondent, who suggested that “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).”

### **How could problems with these models be overcome?**

These caveats led to respondents making a number of suggestions for how potential problems with these decision-making models might be overcome.

#### **Adopting a multilateral approach**

An anonymous respondent suggested that “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.”

#### **Comprehensive explanations of the research protocol**

The British Medical Association suggested that “full explanation of what the research will entail, any possible side effects and the expected or predicted outcomes must all be

made as clear as possible. Sometimes, a cooling off period for a decision is needed and further meetings also required.”

### **Strong facilitation or mediation**

Other respondents suggested that problems might be overcome through the use of a strong mediator. For example, Dr Ayesha Ahmad stated that “the problems that this model might encounter such as differing of perspectives and monopolization of a central voice can be aided by a strong facilitator who is neutral from the group.”

One anonymous consultation respondent similarly observed that this model “sounds good but could just end up as coercion by one of the parties. Could there be a role for an outside mediator? That begs a further question – who?” Dr Daniel E Lumsden noted that “shared or collaborative decision making is a potentially useful model, but it is important in these models that a clear, unbiased advocate for the child is identified... It is also important to determine if decision making is through a unanimous consensus of the group, or if the group is to inform the decision of a smaller number of people.” Instituto Nacional de Salud del Niño del Peru added further that “it is critical for the investigators to understand how far they can go so as not to cross the line and unduly influence the parents’ decision, and to ensure that the investigators’ input is objective.”

#### **Question 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?

Responses to this question were limited in number, although several suggestions were received that addressed how the law and professionals might take account of differences in approaches to parenting.

A perspective beyond the UK context was given by Dr Roma Chilengi, based in Zambia:

*“This is broader than both parents and professionals; I think it is a societal issue and how we deal with it should not be left to the parent or the professional. In fact this is why the concept of an ethics committee that is well represented is probably the best shot we have at making objective decisions on how we involve children in research. Unfortunately, many of our laws are archaic and desperately need updating; and professionals are in this case in a difficult and conflicted position. A broader decision making mechanism is called for. Something akin to the “shared decision making”, but that decision making should not be at the point of actual consenting/assenting.”*

Dr Ayesha Ahmad argued that “rather than the emphasis being placed on the outcomes of the approaches, greater understanding is required in how the development of these approaches is related to a wider spectrum of narratives such as culture and religion.”

Dr Daniel E Lumsden, for example, suggested that “comparable to the situation around clinical care, the opinions of families must be respected to a large degree, and differences (culturally and personally) in parenting style acknowledged.” Professor Jo Bridgeman adopted a similar approach, and argued that “If the parent wants the child to be involved in the research then the child must be able to participate in that decision. If the child wants to entrust the matter to their parents they should be entitled to do so.” The variability highlighted in Professor Bridgeman’s response was also acknowledged by EMIG, which noted that “This variability is unavoidable. However, the use of assent forms can help ensure that, even if the individual child cannot have the final say in terms of consent, he/she understands what is involved in the trial.” NIHR Clinical Research: Children also highlighted the role of diversity: “Ethical guidelines need to recognize... 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 from one group do not distort the overall possibilities.”

A different approach was taken by the Christian Medical Fellowship, which highlighted the importance of the role of parents: “Respect for the rights and interests of parents means that we must accept that attitudes to research will vary widely and hence we should not recruit children into clinical research against the wishes of the parents.” A similar argument was made by Health, Ethics and Law, University of Southampton (HEAL UoS), who stated that “We would prefer to respect diversity, and seek only to overrule parental views when good reasons for so doing could be shown.” Conversely, University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) argued that “the first role of the law and of professionals in this respect should be not to preclude the possibility for the child to grow in autonomy, by deferring too much to parental preferences.” Kingsley Victor Y. Kayan (based in Ghana, responding to the KEMRI document) argued that “parents are directly responsible for their children’s upkeep and are directly affected by any consequences; therefore their views about children’s involvement in research should be well regarded and respected by researchers and health professionals.” The Oxford Vaccine Group suggested that “both parents and child should agree. Need to respect the family context as this is long-term”, however they also added that one “should not have a battle unless [the situation] is life threatening.”

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) focused on the role of the law, and argued that “the current stance should be maintained. The law should neither force people into research, nor prevent them from participating should they wish to do so. Creating or changing a legal framework generates the possibility for mis-interpretation, and we may be accused of making the process unethical by making it too difficult for children to participate.”

The facilitative role of professionals in dealing with different approaches to parenting was highlighted by an anonymous respondent, who noted that “In the first instance professionals often need to work with parents to explain why it may help to start to provide more information to their child over time.”

A general comment was also made by an anonymous respondent who observed that “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.” Further, Felicity Shenton, Development Manger, Investing in Children noted that “there will be local variations that are affected by culture, faith, class, age etc. and which impact on approached to parenting. The conflict between parental rights and children’s rights is a complex one.”

### Question 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?

Respondents put forward several overarching comments as to why rewards may be appropriate in a general sense.

*“Rewards reinforce the sense that children have done the right thing by participating this might contribute to their social education.”*

Anonymous consultation respondent

*“... the framing of ‘reward’ or ‘compensation’ is significant.”*  
*“What is essential in thinking about the potential impermissibility of using rewards or incentives for participating in research is to identify exactly what purports to be the source of wrongness in offering money, goods or services. Is it that such provisions would constitute exploitation, commodification, objectification, coercion, something else?”*

Health, Ethics and Law, University of Southampton (HEAL UoS)

*“Payment/rewards should always be offered to participants in order to recognise and value their time and expertise.”*

Felicity Shenton, Development Manger, Investing in Children

*“The balancing between appreciation and coercion must be strictly managed...”*

Dr Ayesha Ahmad

*“A risk analysis should be performed for all “rewards” that are given in any study, assessing the risk to the child and to the study itself.”*

Professor Andrew Tomkins

*“Some investigators believe that the compensation should not be announced at the start of the study so as not to influence what should be a voluntary decision to participate. Others believe that it should be disclosed at the very beginning of the study so that participants may not think that compensation is provided because something has gone wrong in the study.”*

Instituto Nacional de Salud del Niño del Peru

*“Adults are reimbursed so children should be.”*

Oxford Vaccine Group (

*“... we need to know what children and families see as appropriate recognition for taking part in various types of research studies.”*

Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group

*“The underlying principle should be that we avoid the use of rewards which are in any way coercive or manipulative and which are in danger of overwhelming or compromising judgement and rationality. The essence of clinical research is that it should be freely entered into as an expression of altruism and solidarity with the rest of suffering humankind.”*

Christian Medical Fellowship

*“Compensation for minors undergoing a clinical research procedure must be the same as compensation offered to adults in the same situation.”*

Hector Verlade

A range of suggestions for acceptable forms of compensation/reward/expression were made by respondents, including:

*“Where children are required to do drawings or writing diaries etc it is nice to give them a good selection of pens/pencils/stationary to use and keep as a thank you.”*

British Society of Paediatric Dentistry



*“I think a small gift or voucher is appropriate as a token of thanks/memento as long as the receipt of such a gift is not the reason for taking part. So, for example, if the child and family did not know in advance that they would receive anything, this would be acceptable.”*

Anonymous consultation respondent

*“... fun things specifically for children to do while undergoing trials, for example educational games/apps/tools/ activity books etc, could offer real value without raising ethical concerns.”*

EMIG

*“Participating in research is an extra burden for parents and the child. Some form of compensation is necessary. Probably the type of compensation can be chosen by the family.”*

Oxford Vaccine Group

*“I do think ‘thank you’s are acceptable. They need to be of relatively small monetary value, but something that is appreciated by the child e.g. I-tunes vouchers, but not a new iPad. Certificates and badges can make children feel proud to be involved and are less likely to attract criticism.”*

Professor Jane C. Davies

*“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.”*

Anonymous consultation respondent

*“Often in Paediatric studies certificates and other acknowledgements of involvement in studies can be very useful to young people in preparing their CVs for applications to university, etc.”*

University of Cambridge Department of Paediatrics

Suggestions from respondents to the KEMRI document offered alternative ideas for other forms of reward, compensation, or gratitude that might be appropriate.

*“Rewards such as malaria insecticide treated nets, cleaning agents like soap, beverages for children or health insurance packages for children could be used to say “thank you”*

*because they directly benefit the children instead of monetary rewards which could be of more interest to parents.”*

Kingsley Victor Y. Kayan, Ghana, responding to the KEMRI document

*“Reward should be context-specific so as not to set unrealistic precedents. Re-imbusement of transport fares to and fro the study site and giving of nutritious food to mother/child could be considered appropriate compensations in most low-income countries where malnutrition is a major problem.”*

Muhammed Afolabi, responding to the KEMRI document

Dr Roma Chilengi (responding to the KEMRI document), however, suggested, more generally, that “there can be no global standard for what incentive is appropriate. If researchers have access to funds and are able to give something to their participants, it is principally a good thing.”

Most respondents addressed this question by observing that rewards were not ‘bad’ *per se*, but that some levels of reward were more acceptable than others, or that some rewards should not be offered at all. A range of views were received as to which rewards fitted into the latter category.

*“The reward... should never reach the level of monetary incentive and it is acknowledged that judging the boundaries so that they do not become an inducement can be difficult.”*

Academy of Medical Sciences

*“... a small thank you in the way of a voucher is perfectly acceptable approximately £10-30. I do not agree (which I have seen) a sliding scale of reward depending what activities the child was involved with.”*

Anne Elmer

*“In low or middle income countries such as Ghana, giving money or vouchers to participants could unduly influence participants to participate in research and should be avoided. Our culture is such that people fill satisfaction when they know that they are involved in something good. Therefore, giving something of value that parents/participants could afford under normal circumstances is regarded as a sign of respect and gratitude. I will therefore suggest soap, Milo, milk, Child’s food, treated bed nets, etc as acceptable rewards.”*

Fred Kanyoke, responding to the KEMRI document

*“Participating in research should not result in a financial burden for parents or families. Transport, parking and catering costs incurred directly from research study participation should be covered. However, prospective rewards are viewed as an undue incentive.”*

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

*“... whatever is put in place, it is important for children to be protected from manipulation, increased risk or unnecessary harm due to the incentive to adults.”*

Anonymous consultation respondent

PERUKI's view that prospective rewards are an undue incentive was supported by other respondents. For example, the British Medical Association observed that “offering a non-financial reward to a child as recognition of his or her involvement would not constitute an incentive or inducement to participation, provided it is given after a study has completed and is not a part of the consent process (although this may become problematic if potential study participants become aware before enrolment that rewards are given).” A timing consideration was also raised by NIHR Clinical Research: Children: “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.”

Instituto Nacional de Salud del Niño del Peru, however, indicated that rewards for participation in paediatric research should not be given: “Other researchers of our working group do not agree with compensations of any type for research volunteers, they believe that these compensations distort the voluntary nature of the informed consent process, placing a focus on the economic interest, which may include gifts. Even if there is no mention of compensation, all potential participants eventually find out and this changes their perception of the study.” A cautionary note was added by an anonymous respondent who observed that rewards “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.” However, an anonymous respondent to the KEMRI study argued that “I feel giving the parents vouchers for their child participation in research is appropriate as long as this is done at an appropriate time (I would consider at the end of the study). If done at entry to the study, yes it may influence their participation as may be considered an incentive.”

Suggestions were also made as to other means by which researchers might continue to include participants in their work once the research is completed. For example, Professor Jo Bridgeman noted that “in addition to expenses and rewards for participation, as a matter of good practice children and their parents should be asked if they wish to be informed of the findings of the study: which should then be provided in an accessible

form.” Similarly, another anonymous respondent urged researchers to “acknowledge their participation in study newsletter, hospital and advocacy groups, interviews and advertisement with the solely purpose of delivering an unbiased scientific and ethical information.”

### **Supplementary question (KEMRI document)**

Concerns are sometimes expressed that families agree to take part in research for other reasons e.g. because they think they will then get access to better healthcare, or because rewards have been offered. What responsibilities do researchers have in this regard?

The KEMRI and GHRN documents posed a further question around the motivations of families to take part in research, focusing particularly on the possibility of accessing better healthcare via research participation.

Before suggesting ways of approaching the question of researchers’ responsibilities in this situation, respondents first acknowledged the problem, and cited examples of its occurrence.

*“It’s true that families agree to take part in research for other reasons. An example: “we had a mother who was admitted in the ward and her child got recruited into one of the studies. She used to receive fare for follow up visits and this was good money to her. One day her 2<sup>nd</sup> sibling fell ill and was admitted to the ward. Apparently the child was not eligible to any of the studies but the mother demanded that her child be recruited into a study and it was later found out that, the mother felt she will not receive any money if the child is not in a study”.”*

*Anonymous respondent to the KEMRI document*

*“It is... difficult for the researchers (especially those who happen to be physicians as well) to deal with some unspoken potential reward. The mere attention rendered to the patient in a research setting can be said to be a great privilege for a lot of people.”*

*Dr Roma Chilengi (based in Zambia), responding to the KEMRI document*

The difficulty of approaching these types of motivations was highlighted by an anonymous respondent to the KEMRI survey who observed that “I feel this matter is not an easy one for researchers to deal with especially where studies are conducted in poverty afflicted settings.” A further respondent to the GHRN document noted that such

expectations were “possible and it is hard to get around this.” The socioeconomic context was raised further by Dr Roma Chilengi:

*“Part of this phenomenon has been termed “therapeutic misconception” and it is a real issue. It is particularly discussed in context of developing world settings, but I think it is a general issue. First because rewards for participation are widely advertised in developed countries; but also because the typical participants even in those context can generally be considered as ones less endowed with resources.”*

A range of suggestions were made as to the responsibilities of researchers in these circumstances, and how they might approach responding to families’ perceptions of benefit. The role of information provision was especially prevalent in respondents’ answers:

*“... researchers should give clear information about differences between medical care and research participation.”*  
Muhammed Afolabi, responding to the KEMRI document

*“... it’s the researchers’ moral responsibility to abide to what is laid down in the protocol/consent information, and not to use the rewards/benefits specified in the protocol as a means to attract/convince parents into participation. Researchers should give parents the necessary information they need to know about the study and explain reasons why they are receiving fares/rewards during their participation.”*  
Anonymous respondent to the KEMRI document

*“... researchers are obliged to provide as much information as possible to potential participants including benefits and risks involved. But the fact that the researcher’s interest is to recruit, one can argue whether they are best placed to determine whether a fair information exchange has happened.”*  
Dr Roma Chilengi, responding to the KEMRI document

*“Researchers’ responsibilities will be to explain to potential participants that what will be done is research and that their involvement is voluntary. In certain situations, it is better when rewards or compensations are not disclosed to participants at the onset of the study.”*  
Anonymous respondent to the KEMRI document

An example from personal experience in addressing such concerns was raised by Dr Eleonora Espinoza: “The regulations of our IRB include [the requirement] to ensure that

stipends or compensations for time or transport are just that; a compensation or stipend, and not a way of inducing participation in the study. This is especially critical because of the precarious economic situation of a large part of the population who participate in these studies. Also, when in a study it is guaranteed that children will have specialised medical [attention] it should not be seen as an inducement to participate.” However, Morenike O. Folayan adopted a different approach: “families can take part in research for whatever reason they like.”

## What research proposals should be regarded as ethically acceptable?

### Question 7

How helpful is the notion of the best interests of the child participant? How would you define ‘best interests’?

### How helpful is the notion of best interests?

#### ‘Best interests’ is a helpful notion

Several positive comments about the role of best interests were made by respondents. These included:

*“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.”*

AstraZeneca

*“Best interests are helpful when a child has an obvious need. Does a particular child ‘need’ to participate in research? Certainly all children need research to be done. In many ways considering children’s best interests against a backdrop of research is more informative than considering interests in the context of therapeutic intervention.”*

Anonymous consultation respondent

*“The concept that the child’s best interests should be of paramount consideration are set out explicitly. What is complicated is who defines ‘best interests’? is it parents, professionals etc. and what about the child’s own perspective? Is the child recognised as having an idea of what is in her won best interests?”*

Felicity Shenton, Development Manger, Investing in Children

*“The notion of the “best interests” is helpful for it elicits an objective standard for the fair handling of sick children and adolescents.”*

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA)

*“Very helpful. This is where children are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. The best interests and rights of the child should be the primary consideration when conducting research with children and/or young people.”*

Molline Timbwa, responding to the KEMRI document

*“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).”*

Anonymous consultation respondent

*“The notion of best interest of the child is helpful in the sense that parents are assumed to be protective of their wards and will only agree for their wards to participate in research if they have every reason to believe that the research will enhance the welfare and safety of the child.”*

Fred Kanyoke, responding to the KEMRI document

Respondents also suggested how the framing of ‘best interests’ might impact on what research in children should be supported. One respondent, for example, observed that “The concept of best interests of the child is helpful in thinking about what study designs to exclude. In my opinion this concept renders a placebo-controlled trial problematic as it is not usually in the child’s best interests to receive placebo.”

The British Medical Association suggested that best interests might be helpful to different degrees, depending on the party who sought to use it. The BMA observed that “the term “best interests” is embedded in medical case law and medical practice. Its familiarity to health professionals and the fact that it can be used to encapsulate the different and sometimes competing factors at stake in the decision-making process, mean that, in some circumstances, it may be a helpful concept in relation to decisions about a child’s participation in research. The general public however may not have a well-developed understanding of the term and there is a responsibility on medical professionals to ensure that its meaning and application is communicated effectively to patients or research participants whenever it is used.”

Professor Jo Bridgeman further observed that “it has the benefit of being easily and widely understood. It also offers flexibility in that there can be a number of legitimate views as to what is in the best interests of a child.”

### **The notion of ‘best interests’ is unhelpful**

Some respondents highlighted the positive and negative aspects of the conception of ‘best interests’; Professor Jo Bridgeman, for example, while emphasising the benefits of it being easily and widely understood (see above), also observed that “it may, however, be that the best interests of the child is not the most appropriate basis upon which to justify the decision to involve a child in research or to secure consent from child or parent. Whilst it is necessary to identify the circumstances in which involvement can be justified in an individual case, there is no reason to be limited by existing concepts which are not directly applicable.”

Instituto Nacional de Salud del Niño del Peru commented that ‘best interests’ “is a very ambiguous concept.” An anonymous respondent to the GHRN document also observed that the term was unhelpful because “this might be interpreted as ‘best interest’ for the child to take part in the research. However, it might not be the case since the findings of the study may only be implemented after the results of the study are available to the decision makers.” A further illustration of the suggestion of ambiguity was observed by an anonymous respondent:

*“This terms is not very helpful as it can be taken to mean the best interests of the child taking part in research (in the here and now) or it could mean the best interests of future generations of children who may benefit from the research. These may very well not be synonymous.”*

In contrast with the view of ‘best interests’ as objective, an anonymous respondent commented that “the concept of ‘best interests’ is subjective and will depend on your personal value system.”

Further, the Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) observed that “this is a vague term which often carries no real benefit to any party as it is poorly understood, and remains a nebulous term which is difficult (impossible) to define in the current climate. In some cases it may be used to prevent rather than facilitate research, and ideally should only be used if the child is willing to participate and not in the opposite context.” A similar opinion was expressed by Muhammed Afolabi, who responded to the KEMRI survey. He noted that “the notion of ‘best interest’ is viewed from the parents’ perspectives which are driven mainly from societal and cultural norms, and not the legal or internationally agreed guidelines for child participation in research. In most situations, conflict exists between the parents’ social values and international guidelines; making ‘best interest’ a subject of varied interpretations and not very helpful for child participant in Africa.”



The University of Cambridge Department of Paediatrics commented on the role that best interests might play, noting “the notion of the ‘best interests to the child participant’ is not particularly helpful. As with all research projects, the best interest of the patient is paramount and research must balance risk/benefit and should be carried out in a way which leads to robust conclusions which can be used in informing treatment in future generations.” Health, Ethics and Law, University of Southampton (HEAL UoS) also noted that there “are conceptual difficulties in defining ‘best interests’ in the context of clinical research, as it would operate in rather different circumstances than those usually found in Family Law decisions relating to the child’s upbringing or property”.

Limitations of the concept in research-specific scenarios were also raised by the Health Research Authority: “Best interests’ in the research context are difficult to define given that the inherent nature of research, and the rationale for undertaking it, will inherently mean that outcomes are difficult to predict.”

### **Alternative terminologies or concepts**

Some respondents felt that the ‘best interests’ might be replaced by different terminology. The British Society of Paediatric Dentistry suggested that “the terminology ‘best interests’ is not particularly useful in the context of children and parents’ understanding – we should look for a more participant-friendly and modern phrasing. It could be defined as what psychosocial or health benefits may be gained directly by child as a result of participating in the research.”

### **How might ‘best interests’ be defined?**

Respondents also commented on how ‘best interests’ might be defined.

### **Exclusionary criteria**

Some respondents chose to highlight how best interests should *not* be defined. For example, the Academy of Medical Sciences noted that it “should not become a paternalistic concept. Children – as far as possible and especially if old enough – should be brought into the discussions about what is in their best interest.” AstraZeneca observed further that “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.”

### **Current definitions**

Several respondents referred to *current* descriptions of best interests. The British Medical Association, for example, noted that “‘best interests’ stands as an objective a test as is possible of what would be in the actual best interests of a child and encompasses the full range of factors relevant to a decision.” The Christian Medical Fellowship suggested that “legally and operationally, the definition provided by the UK Mental Capacity Act is helpful.”

## Suggestions for how the concept might be framed

Respondents made several suggestions as to how best interests might be framed.

*“In conditions of uncertainty about the effects of treatments for children, their best interests are served by addressing and reducing the uncertainties in properly controlled research, rather than by acquiescing in insufficiently informed practice, with the real possibility that harm will be done by clinicians practising with the best of intentions.”*

Iain Chalmers

*“Best interest of the children is when there is no possibility of benefit for the child who is a research subject, and this child will die anyway, but his/her participation may enable the identification of treatment for future siblings or children with the same condition.”*

Hector Verlade

*“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 factors... with precedence given to the evidence for clinical efficacy and family preference (the balance of which depends on the specific situation).”*

Anonymous consultation respondent

*“The best interest of a child entering a study involves ensuring that the health (physical and mental and psychological) nutrition and development of the child is not compromised by the study.”*

Professor Andrew Tomkins

*“Only a broad definition of “best interests” can be proposed, as including everything that is susceptible to promote a child’s health and self-realisation in a given situation... Accordingly, a child’s best interest in participating in clinical research can be determined using two criteria, namely whether participation could benefit the child’s health directly or indirectly, and whether it could constitute a valuable achievement in his/her life.”*

University College London and the European Network for Cancer research in Children and Adolescents (ENCCA)

## Other observations

Some respondents chose to highlight other factors associated with the concept of best interests, other than its usefulness. Dr Daniel E Lumsden, for example, noted that “in paediatric practice, particularly around rare conditions, “best” clinical care may often be experimental. Mechanisms should exist for third party reviews of situations regarding a child’s involvement in a given trial to ensure that best interests are in mind.”

NIHR Clinical Research: Children suggested that “the question of best interests is a reflection of the risk/benefit balance of the study [...] 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.”

A separate observation was made by Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group, who suggested that “...ethics committees should be looking to see if all potential ethical issues have been addressed in the proposal rather than looking for reasons not to do the research.”

### Question 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)?

Relatively few respondents addressed this question, but most who replied took the view that the rights and interests of individual children should take precedence over the rights and interests of all children. For example, University College London and the European Network for Cancer research in Children and Adolescents (ENCCA) argued that “the rights of the former come first, it means inasmuch the rights and interests of those children currently in treatment and involved in clinical investigations remain in the forefront of ethical reasoning.” An anonymous respondent noted further that “there is no duty to participate in research whatsoever, it is truly voluntary. So ‘all children’ cannot claim anything of the individual. The individual is free to contribute to the welfare of ‘all children’, although there are clearly limits to for example the risks that can be reasonably taken in this process (which does not automatically imply rigorous risks thresholds).” Other respondents adopted similar views:

*“Few children are enrolled in research studies and face their risks for the benefit of others in other countries and without a direct benefit. This is not a fair distribution of burdens and benefits.”*

Instituto Nacional de Salud del Niño del Peru

*“This is a difficult question to answer as the rights of the individual are paramount however society has a duty to all. I believe that ultimately the individual rights will take precedence as they have the final say whether they wish to be involved with the project.”*

Anne Elmer

*“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.”*

Anonymous consultation respondent

*“Rights and interests of children participating in a study are always more important than the potential beneficiaries of the knowledge gained by research.”*

Malick Ndiaye, responding to the KEMRI document

*“... retaining a sense of the ‘best interests’ for the individual child is of critical importance. Only when this has been ascertained, can the interests of the wider society be considered.”*

EMIG

Substantive approaches to the issue of balancing rights and interests included:

*“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.”*

Anonymous consultation respondent

*“... it’s safety that determines this balance. As long as the study is considered safe and the participant is informed about all benefits and risks and is making a truly informed decision, there should be no objection to the conduct of a study.”*

Anonymous respondent to the GHRN document

*“The sacrifice of individual children benefits all children, which may even be future children. The issue is really to ensure that the risks involved are brought to a minimum possible. Learning is the principle thing; benefits can be put in context case by case. So if there is merit in the questions to be*

*answered, and risks are reasonably mitigated, then the balance exists.”*

Dr Roma Chilengi, responding to the KEMRI document

*“... asking a child to participate in research is to ask a child to be altruistic. Children may choose to participate in the interests of other, including future, children. But I think that should be recognised as an act of care for others and not be considered as something to which others, whether it is treating doctors, other children with similar conditions or future beneficiaries of the research, are entitled to.”*

Professor Jo Bridgeman

*“In this context, I think the use of the word ‘balance’ is wrong. It implied some sort of equality between the two groups which may be far from the reality. It should be more about ‘protection’ of the two groups from untoward risks/outcomes.”*

Anonymous consultation respondent

*“I find it easiest to balance rights in terms of a best interests model i.e. if there is no personal gain only minimal risk research is permissible.”*

Anonymous consultation respondent

The practicality of these rights and interests might be balanced was summarised by the Health Research Authority, who observed that “the balancing and protection of the rights and interests of participants and the rights of those who may stand to benefit from the knowledge gained in the research is central to the review carried out by research ethics committees.”

Other suggestions were made as to how the relationship between these two groups of children might interact if research were to go ahead; the British Society of Paediatric Dentistry observed that “it would be nice for children to have future interactions/engagement with those children who have directly benefited from their research participation.” Instituto Nacional de Salud del Niño del Peru also suggested that “it is also very important to spread the word when the benefits of research finally reach the communities and the way in which they do. For example, in case of vaccines, their inclusion in national vaccination plans needs to be widely disseminated, particularly in the communities where studies were conducted, to ensure they enjoy the benefit, as well.” The importance of communication was also highlighted by María del Carmen Díaz (responding to the GHRN document), who suggested that “it is necessary to explain to them that... they, as boys of the future, are important; and that the children of the future can be their own children.”

## Question 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.

A summary comment in response to this question was made by Felicity Shenton, Development Manager, Investing in Children: “Children are often very realistic about the outcomes of research and fully aware that there may be no improvements for them personally but that things might improve for other young people or future generations.”

### **Situations where child participation is acceptable, without personal benefit to them**

Respondents who felt that participation without personal benefit was acceptable put forward a wide range of circumstances in which they felt this might be the case.

*“Healthy volunteers. For example, questionnaires or surveys, measurement of physiological parameters, or establishment of a set of normative values where no invasive testing is required.”*

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

*“There are many areas of research where there may not be any personal benefit to the participant, for instance observational and cohort studies, where children already take part willingly.”*

Academy of Medical Science

*“Research solely involving additional scans or other non-invasive procedures involving minimal risk and minimal burden which is not against the interests of the child is acceptable.”*

Health Research Authority

*“Some types of research, such as notes-based studies, do not provide a direct benefit to the child but also involve no obvious harms to children. Provided appropriate consent has been obtained and the protocol has been approved by a research ethics committee, studies of this kind do not raise obvious concerns regarding acceptability.”*

British Medical Association

*“... children may be invited to participate in descriptive and exploratory research. More often the children in these studies may not get direct benefits from participation but act as key stakeholders in helping researchers gain insights into the health subject of interest, to clarify and define problems.”*

Anonymous respondent to the KEMRI study

*“Under extraordinary circumstances, research posing additional risk may be ethically permissible; in the case of pre-event pediatric MCM [paediatric medical countermeasures] research, the Bioethics Commission recommended that such risk be limited to a minor increase over minimal – a level that is still very limited and poses no substantial risk to participants’ health or well-being.”*

US Presidential Commission for the Study of Bioethical Issues

*“It is perfectly acceptable for parents and children to engage in clinical research where they may be no personal benefits to them. This is true for all the randomised placebo control clinical trials, or for that matter, comparisons of active drugs where one may prove to be superior to another. If these trials cannot be carried out in children we will forever be condemned to off licence use of drugs that have been evaluated in adults.”*

University of Cambridge Department of Paediatrics

*“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.”*

Anonymous consultation respondent

*“Yes, there are situations in which it is ethically acceptable to involve child[ren] in research without any personal benefit. Such situations include phase I trials to evaluate safety and immunogenicity of new medicines, vaccines etc.”*

Muhammed Afolabi – The Gambia

*“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.”*

AstraZeneca

*“For example many paediatric oncology trials may not be of any personal benefit. There are benefits of being on a clinical trial, but this is a slightly separate issue. The way the treatment for leukaemia has improved over the years is by clinical trials.”*

Paediatric Oncology Reference Team (PORT)

*“We believe that said situations do exist. For example: a phase I trial which could be conducted in healthy pediatric population would be done in the population affected by the disease to which the drug is directed.”*

Instituto Nacional de Salud del Niño del Peru

*“There are situations (see Q8) in which children will volunteer and/or their parents will consent for research without any obvious direct personal benefit... examples include pharmacokinetic studies in newborns, natural history studies to develop biomarkers for possible new treatments in life-limiting conditions (e.g. mucopolysaccharidoses).”*

NIHR Clinical Research: Children

Respondents also suggested that acceptable situations depended on the young person's capacity choose.

*“Like adults, children can see the value of medical research and be altruistic. If a study has received ethical approval and the child has the maturity and information to enable them to make an informed decision to participate we believe they should be allowed to do so.”*

AMRC

*“Participation in non-beneficial paediatric research is irreducibly a matter of individual choice (mostly mediated by parental consent), but not a matter of supererogatory behaviour or self-sacrifice (since participation can concur to fulfil some identifiable basic needs of young patients and since it is subjected to objective risk-ceiling and public order measures to prevent unethical agreements...”*



### **Other factors**

Other respondents felt that acceptability was defined by different criteria. For example, the British Society of Paediatric Dentistry felt that acceptability might occur "...in situations where child participants experience minimal discomfort and/or risk."

### **The participation of children in clinical research without personal benefit is not acceptable**

This was a view that very few respondents subscribed to. However, Hector Verlade responded: "No, there are not. No minor should be exposed to risks to their health without the prospect of benefit to their health."

### **Other observations**

The question of what constitutes 'personal benefit' was also addressed. The AMRC, for example, observed that "though they may not benefit in terms of their personal medical condition, knowing that they are helping others can have a huge positive effect on their mental wellbeing."

Respondents also suggested other factors that might be taken into account in making an assessment as to whether a child might take part in clinical research without personal benefit. NIHR Clinical Research: Children, for example, suggested that "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." A similar point was made by the Health Research Authority: "... children may hold altruistic views and wish to participate in research that, whilst it may not benefit them directly, will provide knowledge that may benefit others."

NIHR Clinical Research: Children noted further that "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."

## Question 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?

### Circumstances where RECs should give their approval

Respondents gave several reasons supporting the argument that RECs should approve high risk research, where young people and their parents express support for participation.

#### **It is unethical *not* to approve research where parents and young people understand risks**

A response from the AMRC adopted this view, starting: “Where risks have been fully explained to participants and their parents, and accepted by them, it could even be considered unethical not to allow participation in trials where they stand to gain life-enhancing benefit.”

NIHR Clinical Research: Children took a similar view:

*“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.”*

In addition, Felicity Shenton, Development Manger, Investing in Children argued that “the role of the ethics committee should be to ascertain that there are no unnecessary or unreasonable risks or consequences. If the possible risks have been identified and every effort has been made to predict, address or reduce these and both parents and the child have been fully informed, the child should be able to agree to participate.”

### Conditions for approval

Respondents also submitted conditions under which it would be right for a REC to approve high-risk research with willing young people (with willing parents).

## **Composition of the REC**

The AMRC, for example, felt that “it is important for research ethics committees to contain paediatric specialists or experts in research involving children to help them consider the different viewpoints that parents and children may have.” Felicity Shenton, Development Manager, Investing in Children also suggested that “having patients/service users on the ethics committee may help to generate informed discussions and debates about how to manage the process to allow innovate research to take place.”

## **Beneficial and non-beneficial clinical research**

The British Medical Association observed that “It is important to distinguish between research studies which would and would not offer any potential benefits to participant children in the type of situation described. Exposing a child to high risk in a study which offered the participant child no benefit at all would be unacceptable, particularly if the research could instead be carried out on others with a more favourable risk-benefit profile.”

## **Where the child or young person has a life-limiting condition**

One anonymous respondent argued that “for children with debilitating life-limiting conditions for which there is currently no known treatment, it may be appropriate to try an experimental treatment. However, this requires extreme caution and constant consideration of the individual’s risk benefit ratio.” Another anonymous respondent alluded to a similar scenario: “Potentially in a very poor prognosis situation where a new treatment is being developed it would seem unfair to restrict a perhaps Gillick competent mature child the chance for participation if under similar circumstances this would be allowed of adults...”, and Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI) suggested that “there may be some scope for this to possible. We feel that some areas in which this may be the case are in situations where patients may have a terminal condition or one for which no conventional treatment already exists. Such an approach could only ever be taken after full consultation with parents and families who have previously been in this situation to examine their views on this approach. Were a trial with these circumstances to approved, it would have to be approached very sensitively on a case by case basis.”

An anonymous respondent also commented that “in the case where (parents of) sick children express their willingness to take these risks, especially where there is no viable alternative treatment, or quality of life/life expectancy is so poor, then perhaps a higher risk is acceptable in the hope of finding treatment for current and/or future patients.” The University of Cambridge Department of Paediatrics asked: “Just as an adult may agree to participate in an early phase study of potentially life extending drug in a terminal condition; can we really prevent parents make the same decision for their terminally ill child? Perhaps in these rare circumstances involvement of a third party may be important.” A similar view was taken by an anonymous respondent: “Yes, there are situations where this may be appropriate and indeed some involvement in prospective

evaluation of the proposed high risk intervention [...] 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'."

### **RECs should not give their approval to higher risk research, even if young people and parents agree**

Other respondents felt that RECs should not approve higher risk research at all, regardless of the young person/their parents' willingness. Anne Elmer, for example, responded, "Definitely not! The purpose of the ethics committee is to look at all aspects of a trial and to protect patients and participants even if it means protecting themselves from themselves!" Muhammed Afolabi, responding to the KEMRI survey similarly stated that "I do not think ethical approval of a study depends on the opinion and assessment of parents and young people. The ethical committee must balance the risk and benefits of child participation in research and the safety/well-being of the child participant remains the paramount priority."

The Christian Medical Fellowship also added a note of caution: "Parents are more likely to 'over-volunteer' their children in order to please medical staff or get access to regular surveillance. Children need to be protected against over enthusiasm of parents to enter their children into studies, particularly where there are very limited medical resources available locally." The CMF added that, "In principle, we consider that only adults are sufficiently mature to agree willingly to risk their own health or well-being for altruistic reasons. Children are too vulnerable to all forms of coercion, especially emotional coercion." Professor Caroline H.D. Fall adopted a similar position, and stated that "unless the research is of direct benefit to the child, any procedures included should carry minimal risk – I do not think studies that carry higher risk can be ethical, even if parents and children appear willing to take part."

These views were supported by a response from the Health Research Authority:

*"Not in normal circumstances. One of the roles of research ethics committees in protecting participants is to provide an objective, independent assessment of the risk/benefit ratio involved in the research and to take a view of its ethical acceptability. In doing so RECs take into account the likely prognosis of the potential participants... However, whilst the "willingness" of the potential participants will be taken into account by RECs in such circumstances it will not be determinative. Other factors will always be in play and the 'strength of feeling' or 'desire' to take part exhibited by the potential participants will rarely outweigh other more objective factors considered by RECs."*

The Health Research Authority's observation was echoed in part by a response from Instituto Nacional de Salud del Niño del Peru, which noted that "We believe that it is very unlikely for a REC to approve a high-risk study in the circumstances presented in this question. Clinical research is first approved by the REC and then presented to the parents and high-risk studies would most likely not be approved by RECs."

## How should research in children be encouraged?

### Question 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?

A significant proportion of respondents addressed these two questions. Responses to each are analysed separately.

### Do regulations strike the right balance?

#### Yes

AstraZeneca offered a positive take on upcoming changes to regulations:

*"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)."*

Dr Daniel E Lumsden observed that "I do not see the regulations as the key issue. Barriers around regulation are, to my mind, more perceived than real. The real barrier is the competency and mindset of the workforce and the empowerment of CAYP to feel the right to demand to be involved in research."

An anonymous respondent took the view that "there's regulation and there's practice. I think regulation is sufficient. But there is few to no support in implementing the regulations in practice, and cultivating good practice in these matters."

#### No

The Christian Medical Fellowship commented on the effectiveness of some international regulations, noting that "there are currently considerable problems in ethical committees

in a number of developing countries. In some universities and ministries of health, for instance, there are several layers of ethical committees. Some, usually unpaid, committees have members with very little understanding of the nature of research and they sometimes object to studies being formed on non-rational bases. Others have committees which have paid members, requiring investigators to submit large fees.”

The Instituto Nacional de Salud del Niño del Peru also commented from an international perspective: “In Peru, the current Regulation of Clinical Trials is extremely protective of research subjects, which leads to selection bias in the case of the requirement of the signature of both parents in the consent form. This also leads to the exclusion of minors due to their inability to meet the parental signature requirement. Another requirement that precludes paediatric research due to the Regulation is the mandate to have a hospital infrastructure at the study site, which greatly limits the conduction of community based, low risk studies.”

NIHR Clinical Research: Children commented that “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.”

An anonymous respondent drew attention to the view that “current regulations are weighted far too heavily in view of clinical drug trials and as such reflect a reliance on parental consent and do not adequately address the question of the child’s voice and how it should be heard.” A similar observation as to how regulations address other areas of clinical research was made by an anonymous respondent:

*“Research related to wellbeing and service provision of children with complex needs – learning difficulties, mental health issues, from excluded families, or looked after children – can easily be hampered by research restrictions designed for research into potentially harmful drugs etc. These barriers can make what could be very inclusive, empowering research aimed at finding answers to complex service problems, expensive and difficult to carry out in a cost-effective way.”*

The NIHR Clinical Research: Children also noted that “the regulations for obtaining marketing authorization in Europe have shifted the balance towards protecting children from ignorance but more work is needed.” A similar response was submitted by Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI), who noted that “At the minute they often appear balanced towards making clinical research in children difficult, with multiple layers of overlapping bureaucracy.” Delays were also raised as an issue by the University of Cambridge Department of Paediatrics, who observed that “generally the regulatory framework for research in children has improved with more rapid responses from REC and MHRA but local R&D risk assessments and approvals can still lead to major delays in study initiation.”

The Teenage Cancer Trust commented on its own area of research, noting that “there are significant arbitrary, commercial and legislative barriers which mean that only 20% of teenagers and young adults with cancer in the UK have access to clinical trials. Although legislation does not restrict access for this age group, the practice of trial protocol setting is often leaving them out.” The Oxford Vaccine Group also highlighted the role of cancer research, noting that regulations should be extended further to encompass an “assumption that a child will be taking part in research, unless they actively opt-out. In oncology [this is] generally what happens and has transformed treatment.”

The role of off-label prescriptions was also highlighted by an anonymous respondent who observed that “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.”

### **What, if anything, should be changed?**

Respondents made several suggestions for how regulations might be changed.

#### **Further mechanisms to hear children and young people’s perspectives**

The Academy of Medical Sciences argued that “there should be more widespread inclusion of children’s perspectives by the various organisations that regulate this area, for instance the research ethics committees, Medicines and Healthcare Products Regulatory Agency, and the European Medicines Agency.” This view – that regulations should encourage further participation from young people – was common among respondents who addressed this question.

*“There is scope to increase involvement of young people in decisions about their own participation.”*

*Anonymous consultation respondent*

*“... much more could be done to involve young children in decisions about their participation.”*

*Anonymous consultation respondent*

*“The information that children have access to on clinical trials - what is involved, what might be the consequences – is currently inadequate. This has been highlighted in a number of studies, some which suggest a different approach to delivering such information, for example in a graphic novel format.”*

## EMIG

*“It would help our research if there was less variation between research ethics committees in their views on involving children in research, for example the content and format of participant information sheets.”*

British Society of Paediatric Dentistry

The Oxford Vaccine Group also suggested that reference to age in regulations should be removed.

### **Increased specialist knowledge on RECs**

This view was adopted by Professor Faith Gibson, who made the following observation:

*“My final comment here is about the various levels of approval and where expertise that relates to children lies. This is a particular challenge for researchers that attend an NHS Ethics review where they feel their views as ‘experts’ with this population are not being taken into consideration, so changing odd words to suit a committee even where it is known children do not understand that word is less than helpful. We might want to consider going back to named RECs that have this expertise, or have expertise on each REC, offering enhanced advice to what is there on the NRES website. I am concerned that if this does not improve, we will see less research with children rather than more, researchers will avoid RECs, and in particular those working with children at end of life.”*

### **Further encouragement of inter-country cooperation**

Professor Andrew Tomkins encouraged “a critical review of ethical committees in developing countries and to develop some guidelines which would be accepted through international organisations such as the International paediatric Association or others.”

### **The role of pharmaceutical companies**

A suggestion was made by NIHR Clinical Research: Children that highlighted the fact that “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."

In a different context, the role of companies was also raised by Kingsley Victor Y. Kayan, responding to the KEMRI document: "Yes, the regulations strike a good balance, but a change of directing funds to research organisations to be financially independent could be providing a more independent research work than the researchers depending on funding from manufacturers."

### **The role of trust**

Professor Caroline H.D. Fall urged that regulations should "generate trust – trust that research is needed, trust that their wellbeing is paramount and that the research will not harm them, trust that data will be handled confidentially."

### **A more consistent approach throughout all types of clinical research**

One respondent to the GHRN survey observed that "although there are supporting frameworks and legislation, they are still very prone to subjective interpretation. Some aspects of good clinical practice are taken more seriously in clinical trials than in non-experimental studies. This should change. The definitions of 'ethical' do not change depending on the type of study so the quality demands and the degree of monitoring should be exactly the same."

#### **Question 12**

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

These two questions generated a significant amount of response. Respondents acknowledged, for example, that "this is always a difficult issue and there will never be enough resources to do everything we would wish to do."

#### **How would you decide priorities for research into childhood conditions, with limited resources?**

Several factors were listed by respondents, including:

- High prevalence
- High burden/the severity of the condition being researched
- High unmet patient need/existence of other treatment options
- Diseases that are high cost
- Communicable diseases
- Ensure that the findings are/will be important

- Risk of mortality or disability to the child
- Current state of scientific knowledge about a particular condition
- Where adult research suggests that data on younger groups would be helpful
- Research that alleviates the greatest suffering
- Likely improvement in child development
- Research based on disability-adjusted life years
- Research that offers the greatest gains in benefits to future children
- Limiting research to questions that can only be answered in the population in question

Further general comments included:

*“A coordinated approach to funding can help to ensure key problems are addressed, encourage collaborative working, and to avoid duplication.”*

Dr Daniel E Lumsden

*“The priorities would need similar assessment to those made by NICE. The HRA would support the identification and prioritisation of research into diseases that could offer improvements to the majority of children.”*

Health Research Authority

*“...work is required to facilitate more effective partnership working in order to maximize impact and make best use of limited resources.”*

NIHR Clinical Research: Children

*“Emotional and mediatized claims should be strongly avoided.”*

Anonymous consultation respondent

*“As paediatricians we believe that the condition in childhood should always be given priority for research as it has implications over a lifetime. Increasingly the childhood origins of adult disease have been identified and early prevention may be critical.”*

University of Cambridge Department for Paediatrics

*“The list of research priorities should not be restrictive nor impede research in other topics that are novel and promising, but not well known yet.”*

Instituto Nacional de Salud del Niño del Peru

*“... research should be prioritised to the need of the country or population where the resources are to be invested... A*

*second layer of decision-making is to determine, based on available evidence, where the research would make the most impact.”*

Morenike O. Folayan, responding to the GHRN document

Dr Roma Chilengi, responding to the KEMRI survey, noted, however, that “this is [the] wrong question. “He who feels it knows it most.” Any illness, no matter how small it may be seen by another person, as long as it causes discomfort as a medical condition requires our efforts to learn how to deal with it. All conditions should be researched, as long as the research is done properly.”

### **Types of research that should *not* be prioritised**

An anonymous respondent highlighted a factor that should be avoided when prioritising research, noting that “the most promising research to alleviate the greatest suffering should be supported. That does not mean that the decision should be purely economic as there is room for consultation with parents and children regarding what is the greatest suffering.”

Another anonymous respondent also observed that “rare conditions should not be excluded just on the grounds of being rare as this excludes them in the long term from advances in treatment.”

### **Overlooked research needs**

One comment from the British Society of Paediatric Dentistry argued that “there is a tendency for high profile conditions such as cancer to have disproportionately high funding, but it is important that conditions which are common to all children, such as tooth decay, are not overlooked.”

### **Who should be involved in making decisions about priorities?**

This question also elicited a number of responses, which can be sorted into four categories.

#### **Professional decision-makers**

EMIG suggested that “people who are on the front line (e.g. paediatric doctors and nurses) should be involved in making decisions about which conditions should take priority in research.” In addition, another respondent noted:

*“A professional panel, with the participation of all groups involved, should discuss, prioritize and encourage pediatric research as befitting the needs of the country.”*

Instituto Nacional de Salud del Niño del Peru

## Public decision-makers

Respondents also suggested that the public might be involved. Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group, for example, argued that “the voices of children, parents and families need to be part of lobbying for funding.”

An anonymous respondent argued that “the public should be more involved than they currently are, but this is most helpful only where the public are adequately informed by an unbiased source.”

Further public involvement was suggested by EMIG, who argued that “the groups of patients that really understand the need to research in children are those that have life-long diseases, often inherited. Parents are frequently very well informed – although they may, as a result, also have very strong opinions.”

## A joint enterprise

Respondents suggested that making decisions might also be a joint enterprise between a number of parties.

*“Those involved in decision-making should include Pharma and academia experts, also regulators and patients’ organisations.”*

AstraZeneca

*“... a consensus process should be developed among the key stakeholders to identify priority areas.”*

Anonymous respondent to the GHRN document

*“If decisions do need to be made around priorities they should be taken by parent groups, professional organisations and charities representing these young people, and cannot be left to the pharmaceutical industry where they may see the profit margins as being very slim.”*

University of Cambridge Department for Paediatrics

*“All stakeholders including researchers, funders, policy-makers and communities who are end-users of the interventions should be involved in making these decisions.”*

Muhammed Afolabi, responding to the KEMRI document

The notion of shared responsibility for making decisions about research priorities in developing countries was raised by Professor Andrew Tomkins:

*“Decisions on priorities of research in developing countries require very close interaction with colleagues in universities, research units and ministries of health, together with other cognate ministries such as education and community development. A key task of investigators is to make relevant and strong cases to donors and grant giving bodies for an increase in support of key areas for research.”*

### **Role of charities and private philanthropy**

Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group observed that “in harsh economic times other private philanthropy is needed to fund research alongside government funding. Governments should further incentivise research funding (for example through tax breaks or match funding).”

A note of caution in relation to the role of charities was raised by EMIG, however: “While charities and advocacy are important to furthering research, sometimes the attention they bring is unbalanced when one disease is compared to another.”

#### **Question 13**

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

Several responsibilities were raised by respondents, including a responsibility:

- To produce outputs from high quality, ethically sound studies
- To avoid duplication of previous clinical research
- To promote collaborative research
- To produce websites for participants
- To make all research results available, for example via a central coordinating body
- To ensure that children and young people are not ‘over-researched’
- To do no harm
- To be fully aware of the research that is happening in their field
- To encourage involvement from patient and public groups, perhaps making it a condition of funding that this type of engagement is carried out
- To develop networks that provide training and support to researchers
- To ensure that studies are large enough and sufficiently well-organised to provide robust outcomes
- To make information on current research studies accessible to the public
- To use research networks, such as those provided by the NIHR
- To identify research sites that are cost-effective and well-organised
- To ensure that the minimum number of children are involved

- To work with other funders so that distribution of funds is equitable
- To forge better links with charities and stakeholder organisations
- To engage actively with children, young people, and their families

Other general comments submitted by respondents include:

*“Key activities such as communication and collaboration are probably more important than cooperation.”*

Professor Andrew Tomkins

*“Funders and investigators are responsible to include pediatric populations in their study designs for new drugs, vaccines, devices and others.”*

Instituto Nacional de Salud del Niño del Peru

*“Funds should be made available to develop networks, with training and support available to researchers working in many centres. Academics should not be encouraged to “go it alone”, unless it can be clearly demonstrated that the research question they wish to answer can definitively be answered by a single centre.”*

Dr Daniel E Lumsden

*“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.”*

Anonymous consultation respondent

*“Funders have a responsibility to ensure proper use of the funds. They also assure the quality of a study and establish that the research proposal is worthwhile, of high scientific quality, and represents good value for money. They ensure appropriate research infrastructure for the study: for example, management and governance, access to potential participants, equipment, materials or support staff.”*

Molline Timbwa, responding to the KEMRI document

*“Consideration should be given to developing the concept of the academic hospice/hospital/service/organisation, whereby on entering the service children and their families give their consent to receive information on appropriate research studies so that children and families can themselves decide if they would like to find out more about a study.”*

#### Question 14

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

A range of suggestions were made by those who chose to respond to this question.

#### To provide feedback once the research is concluded

Several respondents suggested that researchers had a responsibility to provide feedback following the conclusion of the clinical research. Substantive comments received to support this view included:

*“At a minimum, parents and children should be told the results of the research in general terms.”*

Professor Caroline H.D. Fall

*“Dissemination to those who have participated is just so important. So often I hear, from young people in particular, that they often participate in research but they never hear back about what happened. Depending on the length and nature of a study I would suggest that there is often a role for newsletters (paper/and E version), throughout a study, just letting children (and family members) know what is happening is beneficial. But certainly at the end, a brief study report, written for a range of formats, that is age appropriate...”*

Professor Faith Gibson

*Ongoing provision of information and feedback is desirable. For most studies no additional resource will be available once the grant finishes, so the activity is likely to be confined to website updates, sending e-mail alerts and provisions of newsletters.”*

Academy of Medical Sciences

*“Researchers should disseminate the results of the research to the children who have been involved and to other children and young people more generally.”*

British Society of Paediatric Dentistry

*“Providing study participants and/or their parents or guardians with an overall summary of the findings is important.”*

Christian Medical Fellowship

*“... the opportunity of a one-off debrief/follow-up, after study completion. This was considered particularly important in the context of longitudinal studies.”*

Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group

*“... 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.”*

Anonymous consultation respondent

### **To provide ongoing access to drugs that have a positive effect on the participant’s health**

The issue of ongoing access to drugs following the completion of a clinical drug trial was raised by several respondents:

*“Any responsibility for providing any continuing access to new medicine should fall upon the research funders, not the research body or the NHS. Trials cannot become an alternative gateway to NHS funded care bypassing the main decision making process.”*

Dr Janice Allister

*“... if the participant has benefited from a medicine provided during a clinical trial, is there provision made for continued access after the study ends? Where there is a lag between the trial and marketing, is there an obligation to provide the drug in the interim period?”*

Health, Ethics and Law, University of Southampton (HEAL UoS)

*“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.”*

Anonymous consultation respondent



## **To provide ongoing support to research participants, even after the research is complete**

*“... 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.”*

Anonymous consultation respondent

*“Let participants know of any adverse outcomes of the therapies that they may have been exposed to.”*

University of Cambridge Department of Paediatrics

## **To publish the results of clinical research**

*“Researchers have a moral duty to ensure research is disseminated and benefits others by being taken up into clinical practice. Maintaining a connection with research participants after a project is complete can also be hugely useful if follow-up is ever needed in the future.”*

AMRC

*“Researchers and sponsors of research also have a responsibility to ensure that the results of research are published or otherwise made available such that they are open to public and scientific scrutiny. Individuals consent to take part, or give their consent for the participation of others, in medical research on the understanding that the risks they undertake will help to advance medical science and benefit future patients. Selective publication of research results betrays this altruistic motivation and, more generally, it distorts the scientific record and threatens the likelihood of people being willing to take part in research in the future.”*

BMA

*“Research findings... must remain accessible even after the study is complete to answer any potential questions, perhaps via email.”*

Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI)

## **To maintain ongoing high levels of confidentiality**

*“Confidentiality is vital, particularly where there are links between child health and maternal health, such as HIV.”*

Christian Medical Fellowship

*“Where personal information on a child is collected, stored, accessed, used or disposed of, a researcher should ensure that the privacy, confidentiality and cultural sensitivities of the subject are protected, subject to the usual exemptions (such as where there is a statutory duty to disclose or a public interest in doing so).”*

BMA

*“Researchers need to be mindful that individual information gathered on children at one age might cause distress at a later date. This might be particularly so in the use of photographs.”*

Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group

*“Researchers have a responsibility to maintain accurate records that should be available to participants/GPs (e.g. where a new vaccination has been administered)... They should also be considerate about providing publications of results.”*

Anonymous consultation respondent

### **To thank the participants**

*“Expressing gratitude for their participation.”*

University of Cambridge Department of Paediatrics

### **Other comments**

Respondents used this section to raise any further comments about children, young people and clinical research that they had not had cause to address through answering other questions raised by the consultation document.

### **The general role and importance of (various types of) clinical research with children**

*“Without research to continually drive innovation and advance medical practice there is a danger that paediatric medicine will stagnate leading to the continuation of medical treatment*

*based on untested and possibly suboptimal interventions, with the inherent risks that entails.”*

British Medical Association

*“As a clinician, some of my child patients suffered and sometimes died because I did not have ready access to reliable research evidence to inform my clinical management decisions. Avoidable harm continues to be done to child patients because of longstanding reticence about encouraging research to inform treatment decisions in children.”*

Iain Chalmers

*“Although it may be challenging, we need research involving children. Disease and disorders in children may differ fundamentally from those encountered in adults and have to be understood in terms of the growing and developing child. We cannot assume that children are “small adults” and the pharmacological properties of drugs and their effectiveness may relate to physiological changes during childhood and are not always directly related to body size. Increasingly, early childhood origins of adult disease are being recognised and successful prevention of many adult diseases may need to start in childhood [...] While our instinct may be to protect children, their participation in research is essential to refine the treatments they receive and reduce harm from dangerous or ineffective drugs or other interventions.”*

University of Cambridge Department of Paediatrics

*“My only other comments which have been partly alluded to are the unfortunate lack of 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.”*

Anonymous consultation respondent

## **The importance of involving children and young people in decision-making**

*“Child protection is very important; their decision should be respected.”*

Fasela Emmanuel, responding to the GHRN document

*“In the last years, the cognitive structure of the minors was organised in forms different to ours. It would be necessary to explore more the levels of comprehension that they really possess to adapt our explanations. In addition, the dialogue with the minor participants must be constant during the process of investigation.”*

María del Carmen Díaz, responding to the GHRN document

### **The importance of language**

*“The language used in the guidance is very important. For example, it is not uncommon for children, particularly younger children, to be spoken of as particularly vulnerable in relation to participation in research. Portrayal of children as vulnerable presents the danger of children being presented as other to adults, as ‘non-adult’ or ‘not-yet adult, as lacking the qualities that the adult is considered to possess. Often professional guidance is written for adults with a section which considers the issues in application to children. Child-centred guidance which does not seek to draw comparisons with adults needs to be attentive to the specific vulnerabilities of children and not rely upon constructions of children’s vulnerabilities.”*

Professor Jo Bridgeman

### **How researchers might be better guided**

*“... perhaps something akin to the intervention ladder used in the NCOB (2009) Public Health: ethical issues report about how to approach public health interventions would be useful to researchers. One could foresee some framework that helps to guide researchers when encountering tough cases.”*

Health, Ethics and Law, University of Southampton (HEAL UoS)

*“It would be invaluable to have a critical review of ethical procedures and committees responsible for research among children in developing countries. Particularly valuable outcome could be the development of good practice guidelines. While there have been some recommendations produced (e.g. the Nuffield Report on Bioethics of Research in Developing Countries) for these, experience is that these recommendations have not been put into practice widely and there is urgent need to assist the improvement of ethical review and care of children in research in developing countries.”*

Professor Andrew Tomkins

### **The breadth of scope of ‘clinical research’**

*“Clinical trials and research covers many different types of illness. There is a big difference asking a young child to join an observational trial for a vaccination compared with a clinical trial for life threatening or life changing disease such as leukaemia. This means the patient information sheets need to be different and the whole issue of consent and assent has to be considered. At the moment there are blanket guidelines for all children entering any clinical trial. The current guidelines even talks about patient information sheets for under 5s. This is absolutely ridiculous regardless of the illness. A clear difference needs to be made between the types of illness.”*

Paediatric Oncology Reference Team (PORT)

### **Negative perceptions of clinical research**

*“If a patient (parent) trusts a doctor to prescribe a drug for which there is little evidence for benefit/superiority over another treatment (ie usual practice) that trust should extend to a fully peer- reviewed trial, that has considered the balance of risk over benefits of the proposed interventions.’ Often it does not. Clinical trials still have negative connotations (exploitation, commercial gain etc).”*

Professor Kathryn Maitland

### **Conclusion**

Both the responses to the call for evidence document, and the contents of this summary report will be considered by the Nuffield Council’s Working Party to support the recommendations and conclusions of its final report on *Children and clinical research: ethical issues*.

Annex A: Call for evidence

**NUFFIELD  
COUNCIL <sup>ON</sup>  
BIOETHICS**

**Children and clinical research:  
ethical issues**

**Call for evidence**

August 2013  
(closing date: 31 October 2013)

## Introduction

Clinical research involving children is essential if we are to improve our understanding of childhood diseases and conditions, and provide care for children based on the best possible evidence. Parents are often surprised and alarmed, for example, to find out that many medicines given to children have not been tested in children, and hence the evidence available as to how children may react to them is necessarily limited.<sup>1</sup> Clinical research involving children takes diverse forms: including clinical trials of new medicines or vaccines, research comparing existing standard treatments, research into psychological therapies, participation in longitudinal cohort studies or biobanks, and observational or interview-based research.

However, clinical research in children also raises ethical and practical difficulties: for children and parents; for research professionals and researchers; and for regulators and research funders. While adults may choose to undergo any inconvenience, discomfort and potential risks that may be involved in clinical research, it is much harder for parents to make such decisions on behalf of their children. Importantly, there is little consensus on what part children themselves should play either in decisions about their own research involvement, or in wider questions of how research is promoted and regulated.

This consultation seeks your views on these ethically challenging issues. Please follow the links below to comment on any, or all, of the highlighted areas of concern, explaining, where possible, *why* you hold a particular view. Your responses will help inform the deliberations of the Nuffield Council's Working Party on *Children and research: ethical issues*, whose aim is to publish a report with recommendations in early 2015.

<a href="#"><u>How should children be recruited to clinical research?</u></a>	<a href="#"><u>What research proposals should be regarded as ethically acceptable?</u></a>
<a href="#"><u>How should research in children be encouraged?</u></a>	<a href="#"><u>What should happen when the research is over?</u></a>
<a href="#"><u>Any other comments?</u></a>	
<a href="#"><u>How to submit your response</u></a>	

Note: throughout this consultation we have used the term 'children' as shorthand for children and young people up to the age of 18. Although the UK Clinical Trials Regulations define young people aged 16 and above as adults, we are interested in your comments regarding children and young people across the age-range, especially given the difficulties of matching chronological age with particular abilities or intellectual/emotional maturity.

Endnote references are available at page 88-90 of this summary document,

How should children be recruited to clinical research?

Background ([skip to questions 1-6](#))

Who decides if a child should take part in clinical research? This depends both on whether the research is categorised as a ‘clinical trial’ of a new medicine, and on the age of the child. Moreover, although the law is clear as to when children are entitled to make their own *treatment* decisions, it is much less clear about *research* decisions.

For treatment, the law in the UK presumes that young people over 16 have the capacity to consent to treatment for themselves, although those with parental responsibility (usually their parents) retain the right to consent on their behalf up to the age of 18. Children under 16 who are considered ‘Gillick competent’ – that is, those who are judged to have “sufficient understanding and intelligence to enable them to understand fully what is involved in a proposed intervention” – are also deemed to have the capacity to consent to that particular treatment.<sup>ii</sup> However, there is no equivalent case law as yet on whether these rules should also apply to clinical research. Views differ on this point, and in particular as to whether it would be appropriate to use the ‘Gillick’ approach for under 16s in research decisions as well as in decisions about treatment.<sup>iii</sup> The only area of clinical research where the legal position on children’s consent is set out clearly is that of clinical trials of new medicines (“investigational medicinal products”), which are governed by their own regulations.<sup>iv</sup>

For clinical trials of new medicines, the Clinical Trials Regulations specifically define a ‘minor’ as being under the age of 16. Young people aged 16 and 17 in the UK are therefore regarded as adults, entitled to give, or withhold, consent for themselves if invited to participate in a clinical trial. (Most other European countries, by contrast, define ‘minors’ as those under the age of 18 in their legislation governing clinical trials.<sup>v</sup>) Where a child is under the age of 16, the UK regulations require the “informed consent” of a person with parental responsibility, and the child has no right of veto, although their explicit refusal should be considered by the researcher.

UK children under the age of 16 are not, therefore, legally entitled to make their own decisions about whether or not to participate in clinical trials of new medicines, and their legal position with respect to other forms of research is uncertain. This does not, of course, mean they will be excluded from all involvement in a decision about research involvement: the importance of obtaining the ‘assent’ or acquiescence of the child before proceeding with research is widely recognised.<sup>vi</sup> The concept of assent, however, is used in quite diverse ways: from compliance by a child as young as three,<sup>vii</sup> to the active agreement of a teenager who would be considered competent to consent to their own treatment;<sup>viii</sup> and there is ongoing disagreement about how useful it may be.<sup>ix</sup> An alternative approach to that of seeking separate parental consent and children’s assent is that of ‘collaborative’ or ‘shared’ decision-making, in which researchers and health professionals explicitly aim to negotiate a decision about research involvement with the family as a whole.<sup>x</sup>



Responsibilities of researchers and clinicians: Ethical dilemmas arise for researchers and clinicians when they consider whether or not to invite a child to participate in a particular research study. 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. The extent to which parents expect their children to participate in important decisions will also vary considerably, and researchers may be unsure whether it is their role, for example, to challenge parents who do not think it appropriate to involve a child in the decision-making process. Difficulties may, in particular, arise for researchers and clinicians where there is disagreement about a child's participation, whether between adults with differing views, or between parents and their child. Views also vary whether it is acceptable to offer children any form of reward as compensation or as a 'thank you' for taking part in research.

Certain kinds of research are the source of additional ethical challenges for researchers: for example research aiming to improve emergency care, or research relating to the treatment of injuries such as head injuries where non-accidental causes may sometimes be suspected.

#### Questions 1-6

*In responding to the questions below, you may find it helpful in some cases to distinguish between three broad groups of children:*

- *those incapable of any meaningful involvement in a decision (e.g. babies)*
- *those capable of expressing a view, whether verbally or through their behaviour (in varying degrees, from young children to teenagers)*
- *those who would be regarded as competent to consent for themselves if the intervention were for treatment, rather than research (those who are 16 or over, or under-16s meeting 'Gillick' requirements in connection with the particular intervention(s))*

- 1 What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?
- 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.)
- 3 How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?
- 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?

- 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?
- 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?

What research proposals should be regarded as ethically acceptable?

Background ([skip to questions 7-10](#))

International conventions such as the Declaration of Helsinki,<sup>xi</sup> CIOMS guidelines<sup>xii</sup> and the Council of Europe Oviedo Convention,<sup>xiii</sup> set down broad principles that should govern all research involving human participants, with the aim of ensuring that the well-being of individual participants should always take precedence over all other interests. Key requirements set out in the Declaration of Helsinki include that:

- participation should be fully voluntary;
- any risks have been adequately assessed and can be satisfactorily managed;
- the importance of the research must outweigh the inherent risks and burdens of the research; and
- the research proposal must be submitted to a research ethics committee for scrutiny and approval before the research may begin.

Additional protections are set out for research involving children: for example that consent has been given by an authorised representative, and that the research cannot be carried out in adults instead.

While there is general consensus on the importance of protecting children involved in clinical research, the various international conventions differ in some of their detailed requirements, and further differences emerge in the way these are then interpreted in national laws. In particular, approaches differ with regard to the central question of how to balance the risks and burdens faced by research participants against the potential benefits to future patients. This question is further complicated by the fact that in many cases a research study is closely connected with a child's treatment: for example in a clinical trial of a new medicine, or in a comparison of two or more standard forms of treatment. Sometimes the research procedure may be the treatment itself (such as the new medicine), while at others it will be separately identifiable (such as additional scans or blood tests to collect research data).

Approaches to balancing risk and benefit include:

- allowing only research that involves “minimal” risk or “minor increase over minimal risk” if there is no prospect of direct benefit to the child participant;<sup>xiv</sup>
- allowing risks that are “justified by the anticipated benefits to the subjects” if the research does offer the prospect of direct benefit to the child participant;<sup>xv</sup>
- allowing research where the risks are “minimized” and where the research offers a prospect of direct benefit to children participating in the study;<sup>xvi</sup>
- allowing research where the risks are “minimized” and where the research offers a prospect of direct benefit to children with the same condition (not necessarily those participating in the research).<sup>xvii</sup>

A further complication arises in connection with the general ethical and legal expectation that parents will act in their children’s ‘best interests’ (understood not simply in terms of medical interests but also taking into account wider welfare factors<sup>xviii</sup>) when making decisions about their medical care. In the UK, although there is no case law that specifically applies this approach to clinical research decisions, the Medical Research Council has suggested that it would be reasonable to do so.<sup>xix</sup> The question therefore arises as to whether it can ever be considered to be in a child’s best interests to experience discomfort, or be exposed to even minimal risk, where the primary aim is to obtain knowledge for future children, rather than to benefit that child’s health.

By contrast, it has also been argued that children should be seen as having a *right* to be involved in clinical research, especially where they are living with a serious condition for which there is currently no effective treatment. In such cases, it has sometimes been suggested that research ethics committees should be willing to approve research with higher levels of risk, if children and their parents are willing to accept these risks.

#### Questions 7-10

- 7 How helpful is the notion of the best interests of the child participant? How would you define ‘best interests’?
- 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)?
- 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.
- 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?

How should research in children be encouraged?

Background ([skip to questions 11-13](#))

Children, from newborn babies to teenagers, have long been seen as a ‘vulnerable’ group, in need of special protection to ensure that they are not exploited in research. However, these ethical concerns have not been the only factors inhibiting research in children: practical difficulties (for example the need to develop age-appropriate protocols) and commercial concerns (such as the limited financial returns from what is perceived to be a comparatively small market) have also played a part in limiting the amount of research taking place.<sup>xx</sup>

In recent years, widespread regulatory changes have aimed to encourage new research (specifically clinical trials) in children, and to increase the amount of information available about the effect of medicines in children. ‘Carrot and stick’ approaches have been introduced in both Europe<sup>xxi</sup> and the US.<sup>xxii</sup> these include financial incentives to pharmaceutical companies for providing more information for prescribers about the effect of medicines in children, and the requirement, where relevant, that data *must* be provided from studies in children before a new medicine can be licensed. By 2013, the US approaches had resulted in 481 changes in labelling on medicines used for children,<sup>xxiii</sup> while the more recent European regulations led to 77 such changes by 2011, along with the authorisation of 31 new medicines for paediatric use, and the approval of 72 new paediatric indications for medicines already authorised.<sup>xxiv</sup> Concerns have, however, been raised as to whether these incentives are sufficiently well targeted: in particular whether they encourage companies to carry out research that is high priority for children, rather than research into primarily adult conditions that may affect only a limited number of children.<sup>xxv</sup> A lack of coordination between research funders who are exploring similar childhood conditions can also lead to unnecessary duplication of research effort, with the resulting unnecessary burden on research participants (sometimes the same participants).<sup>xxvi</sup>

Awareness is also increasing about the potential for involving young people themselves to influence clinical research proposals as they affect children. The Paediatric Committee of the European Medicines Agency, which is responsible for reviewing companies’ paediatric investigation plans (proposals for carrying out studies in children) has recently published a ‘concept paper’ on the possible involvement of children and young people in their work.<sup>xxvii</sup>

#### Questions 11-13

- 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?
- 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?

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

What should happen when the research is over?

Background ([skip to question 14](#))

Ethical questions also arise as to what should happen when a clinical research project involving children is over. Such questions may arise both in terms of access to treatment in future (where the research is a clinical trial of a new medicine), and in terms of how children and their parents continue to be involved in the research at a policy level.

In clinical trials of new medicines, the decision may be taken not to proceed further with the research because of concerns about the safety or effectiveness of the medicine in the research group as a whole – but this may be a source of major anxiety for individual children and their families if they have seen considerable benefit from the medicine. There may also be practical or financial reasons why research funders decide not to pursue a particular research avenue. The question then arises as to whether there is any scope for children who have benefited from the new medicine to continue obtaining it.

In research more generally, there is a growing awareness that research participants value being treated as ‘partners’ in research (rather than simply as research ‘subjects’) and, for example, may be interested in finding out more about the results of research in which they have participated, even where this is unlikely to be relevant for their own health care.<sup>xxviii</sup> In the case of longitudinal research, it is possible for such ‘partnership’ to be more active: the Avon Longitudinal Study of Parents and Children, for example, which has collected information and biological samples from thousands of parents and children to form a substantial research resource, involves study participants in its governance arrangements – for example through membership of its Ethics and Law Committee.<sup>xxix</sup>

Question 14

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

Any other comments?

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.

## Annex B: Call for evidence GHRN network version



# Children and clinical research: consultation on the ethical issues

## Introduction

The UK-based Nuffield Council on Bioethics has set up a Working Party to develop a report on *Children and research: ethical issues*, to be published in early 2015. One remit of the Working Party is to consult as widely as possible with groups of people who may be affected by the report in future, including children and young people, parents, researchers, health professionals and a wider public. The Working Party is now seeking additional input to the report from stakeholders in low and middle income countries.

Clinical research involving children is essential if we are to improve our understanding of childhood diseases and conditions, and provide care for children based on the best possible evidence. Parents are often surprised, for example, to find out that many medicines given to children have not been tested in children, and so there is limited evidence about how children may react to them. Clinical research involving children takes many forms including: clinical trials of new medicines or vaccines, research comparing existing standard treatments, research into psychological therapies, participation in longitudinal cohort studies or biobanks, and observational or interview-based research.

However, clinical research in children also raises ethical and practical difficulties. While adults may choose to undergo any inconvenience, discomfort and potential risks that may be involved in clinical research, it may be harder for parents to make such decisions on behalf of their children. Importantly, there is little consensus on what part children themselves should play either in decisions about their own research involvement, or in wider questions of how research is promoted and regulated. This consultation seeks your views on these ethically challenging issues.

**Note:** throughout this consultation we have used the term 'children' as shorthand for children and young people up to the age of 18. We are interested in your comments regarding children and young people across the age-range, especially given the difficulties of matching chronological age with particular abilities or intellectual/emotional maturity.

## Section A: How should children be recruited to clinical research?

Guidelines on the ethical conduct of research generally take the view that children under the age of 18 years should not be allowed to decide for themselves whether to take part in clinical research, given their status as 'minors'. Consent must instead be sought from a parent, or from another adult with parental responsibility for the child. There are, however, exceptions to this approach. In the UK, but not the rest of Europe, for example, children over 16 years can give their own consent to participation in clinical trials but not necessarily for other forms of research. In Kenya, children under 18 years who are married, pregnant, a mother or a household head are considered 'mature' minors and are able to give consent for their own or their child's participation in research. Some argue that a child's age is not a very useful guide to a child's capacity to give or withhold consent, given how much children vary in ability and maturity.

Although in most cases children are not permitted to give their own legally-valid consent to research participation, the importance of *involving* them in the decision, through obtaining their 'assent' before proceeding with research, is widely recognised. The concept of assent, however, is used in quite different ways: from compliance by a child as young as three, to the active agreement of a teenager who might well be considered competent to consent to their own treatment. Attitudes also differ as to whether a child's *dissent* should be treated as a veto, meaning that they cannot be enrolled in research, or less strongly as just one factor to take into account in decision-making. An alternative approach to that of seeking separate parental consent and children's assent is that of 'collaborative' or 'shared' decision-making, where decision about research involvement is reached with the family as a whole.

Ethical dilemmas arise for researchers and clinicians when they consider whether or not to invite a child to participate in a particular research study. An invitation to participate, when given by a trusted professional, may be seen as support for the project, and may influence a parent's/child's decision. The extent to which parents expect their children to participate in important decisions will also vary considerably, and researchers may be unsure whether it is their role, for example, to challenge parents who do not wish to involve their child in the decision-making process. Difficulties may arise for researchers and clinicians where there is disagreement between adult family members or between parents and their child about research participation. Views also vary whether it is acceptable to offer children any form of reward as compensation or as a 'thank you' for taking part in research.

1. **What do you think are the main obstacles to recruiting children to research? How might these be overcome?**
2. **Who should make decisions about a child taking part in research? What part should the child play in the decision?**
3. **Concerns are sometimes expressed that families agree to take part in research for other reasons - e.g. because they think they will then get**

**access to better healthcare, or because rewards have been offered. What responsibilities do researchers have in this regard?**

## **Section B: What research proposals should be regarded as ethically acceptable?**

International conventions such as the Declaration of Helsinki<sup>5</sup> and CIOMS guidelines,<sup>6</sup> as well as national laws and guidelines, set down broad principles that should govern all research involving human participants. These guidelines aim to ensure that the well-being of individual participants should always take precedence over all other interests.

Additional protections are set out for research involving children: for example that consent has been given by an authorised representative, and that the research cannot be carried out in adults instead.

Despite these protections, there still remain significant ethical challenges for those undertaking research in children, because it is usually seen as the job of families and professionals to take decisions that are in the ‘best interests’ of the particular child. The primary aim of research, on the other hand, is to obtain knowledge to improve healthcare in the future, not to benefit the child taking part (although research may often go alongside treatment that *is* designed to benefit the child). Without such research, though, professionals cannot be confident that they are offering the best possible treatment to the children under their care.

4. **How can the interests of those children taking part in research be balanced against the interests of the future, unknown children who might benefit from the research?**
5. **Is it helpful to use the term ‘best interests’ in connection with children’s participation in research? Can you suggest any alternatives?**

### **How should research in children be encouraged?**

Children, from newborn babies to teenagers, have long been seen as a ‘vulnerable’ group, in need of special protection to ensure that they are not exploited in research. In addition, practical difficulties (for example the need to develop age-appropriate protocols) and commercial concerns (such as the limited financial returns from what is perceived to be a comparatively small market) have also played a part in limiting the amount of research taking place with children.

In recent years, widespread regulatory changes have aimed to encourage new research (specifically clinical trials) in children, and to increase the amount of information available

---

<sup>5</sup> World Medical Association (2013) *Declaration of Helsinki*, available at <http://www.wma.net/en/30publications/10policies/b3/>.

<sup>6</sup> CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf).



about the effect of medicines in children. ‘Carrot and stick’ approaches have been introduced in both Europe<sup>7</sup> and the US:<sup>8</sup> these include financial incentives to pharmaceutical companies for providing more information for prescribers about the effect of medicines in children, and the requirement, where relevant, that data *must* be provided from studies in children before a new medicine can be licensed.

Concerns have, however, been raised as to whether these incentives encourage companies to carry out research that is high priority for children, rather than research into primarily adult conditions that may affect only a limited number of children. A lack of coordination between research funders who are exploring similar childhood conditions can also lead to unnecessary duplication of research effort, with the resulting unnecessary burden on research participants (sometimes the same participants). Awareness is also increasing about the potential for involving young people themselves to influence what research should be prioritised, and how it should be carried out.

6. **With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions?**
7. **Do you have any views on whether 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?**

**Any other comments?**

---

<sup>7</sup> Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006.

<sup>8</sup> Since 1997 the US Government has provided financial incentives to the pharmaceutical industry to conduct paediatric clinical trials through legislation that offers an additional six-month market exclusivity to patents for all paediatric formulations of products that have been trialled in children. More recently, the Paediatric Research Equity Act (2003) gave the Food and Drug Administration (FDA) the authority to *require* paediatric studies of a new medicine if the FDA determines either that the medicine is likely to be used in a substantial number of children, or that it would provide a meaningful benefit for children over existing treatments.

## Annex C: Further responses to the GHRN blog and news posts

Global Health Reviewers published a blog post<sup>9</sup> and news story<sup>10</sup> to provide background on the call for evidence. These pieces themselves generated comments from GHRN contributors (see Box 1).

### Box 1

#### Responses to Global Health Reviewers' news article

"Hi, very interesting post there. I have one question which I feel is coming up in discussions frequently in global health research these days. Should there be consent for vaccinating children? If so who should give the consent? Should parents consent for their children to get vaccines?"

"I am Pediatric Infectious Diseases consultant and researcher who currently focuses on pediatric HIV and PMTCT in Nigeria. I am currently working on a large PMTCT study that has both mother (15+ years) and infant as participants, as well as two pediatric/adolescent HIV studies. My biggest challenges are lack of clear guidelines for consenting children under 18 years, and the clear definitions of emancipated minors. There are management guidelines that more strongly (but not fully) state what emancipated minors are, and how young a patient can be before testing or providing care without parental consent. However it is the law under which a researcher or clinician can get into trouble, However, the law is woefully inadequate in setting or explicitly discussing clear guidelines. 1. Pregnant teens under 18 years old, children living with HIV under 18 years, and the general population of children under 18 years who may want/need HIV testing become a huge problem if we are to test them or conduct research with them without parental consent. This has led to severely reduced access to HIV testing for young adolescents because they get turned away during outreach and clinic-based HIV testing. The only clear statement on age of consent is 16 years--for a child who has to undergo testing for establishment of paternity in a parental dispute. There is no clear legal statement on assent or emancipation, and part of that comes from the very authoritarian attitude towards children, even those who may have their own children. I think emancipated children (married-male or female; sexually active or seeking SRH care, head of household or independently self-supporting should be able to provide full consent. The issue is to establish that they fall into those categories. For HIV testing, a clear minimum age for consent for testing, regardless of whether they are emancipated or not, should be provided. However we should also consider if we ask the age of a child if they are independently coming in for a Haemoglobin vs HIV test."

"I wish to congratulate you on this research project and wish you a very successful completion in the midst of the challenges. It's usually difficult to provide access to quality care and treatment when laws are clearly not reflecting and addressing the true situation as it relates to minors and access to health care. Sad but true minors are sometimes the ones who suffer as a result of unclear legislation. However as health care providers we must protect and function in accordance with the laws, rules and regulations of the country in which we work and function."

<sup>9</sup> Global Health Reviewers (13 May 2014) *Blog: children and clinical research - consultation on the ethical issues*, available at: <https://globalhealthreviewers.tghn.org/community/blogs/post/383/2014/05/children-and-clinical-research-consultation-on/>.

<sup>10</sup> Global Health Reviewers (9 May 2014) *May issue of the month: children in research - ethical implications*, available at: <https://globalhealthtrials.tghn.org/community/groups/group/ethics/topics/501/>.

We however must continue to provide guidance in order to direct policy makers in the area of policy and legislation.”

“Vaccination is very important in the fight against vaccine preventable diseases. I think the government should provide legislation to protect populations against vaccine preventable diseases of which parent would have to comply, with exclusion for health and other reasons’. Also the reason for the government being responsible they will also be responsible for financing of the immunization thus freeing parents for that added burden of access because of inability to pay. On the other hand if it is for the purpose of vaccine trials a research ethics committee should examine the pros and cons and direct government of options in such case parents / communities should also be involved.”

### **Responses to Global Health Reviewers’ blog post**

“Having worked with kids for quite some time now, I can say that consenting the parents and the kids is a matter of putting the study into context. In my experience, a trained research nurse makes a whole new difference into consenting minors in studies which may appear to be “asking quite a lot”. Normally, the delivery of information, emphasis on equipoise, clear and simple explanation of randomisation, reassurances in terms of safety and monitoring are the information that when given in the right context can make the huge difference between a yes and a no.

“In my opinion, the Nuffield Council is doing a fantastic job by releasing an ethical guideline into this issue. Kids deserved to be in clinical trials and its down to us research nurses to innovate that perception that trials does not mean “using kids as guinea pigs”. On another note though, it is quite important to be culturally and ethically sensitive. My dilemma at work is when working with people with difficulty communicating in English. We use translators as is the norm here in the UK, but in my experience, there has been a high rate of rejection and I am worried that this is a case of “getting lost in translation”. I am quite interested if context in consent is being lost in translation when using this services.”

“The idea to develop a good guideline to protect the children is a welcome development and as researchers, it is our responsibility to use all means available to protect these vulnerable ones. Although I have not conducted any clinical research work using children, yet one of my major concerns in conducting clinical research among children has always been the subject of consent. Various versions of DoH have recommended that in situations where consent cannot be received from the under aged, such consent should be given by the child’s authorized representative. In the developing world, this can be very tight, legal and could have relative interpretations. Who is the child’s authorized representative? Should this have a legal definition? Is it right for another person to take consent for a child, while allowing the child to bear the pain and discomfort associated with the research? When the child grows and he gets to know about this how will he fill? Betrayed or protected? Another issue here is that of Justice or fair share from the study outcome. Will the parents of the child be able to afford the drug when finally approved? How about other children living in the LMIC?. We must do it right!!”

“The need to develop guidelines for children is important

First, I think it is essential to separate adolescents from children as this is important. The issues

that relate with adolescents do differ significantly than issues that relate with children. One of such is the need to engage adolescents in sexual and reproductive health research. The issue of autonomy is trickier with adolescents. I would want to argue that consenting for children (0-10years) is easier and the dilemma lies with adolescent - the very reason to differential between the two groups

I recently wrote a paper on this topic (accepted for publication with DWB and attached with this mail)<sup>11</sup> that argues for the feasibility of reducing the age of consent of adolescents to 14 from the current 16 highlighted in the Child Right Acts. However, there are provisos to this argument. As the document highlights, we do have a number of examples we can learn from in the field. There are lots of debates and discussions about engaging adolescents in research that can very well inform the Nuffield guideline. I also would advice that the Working Group wait for the outcome of the discussion on the same subject by the planned for Kenya on the 5th and 6th of June as well as one planned for Nigeria at the end of June. These discussions would be rich and can indeed influence the field. I look forward to reading more on this discussion.”

Just to further add to the discussion, I attach a draft paper we are working on publishing that also looks and discuss other ethical issues beyond the informed consent remits that are of important consideration in SRH research for adolescents.<sup>12</sup>

We argue that adolescents’ voluntary participation in research has been limited due to their perceived potential to be coerced into participation, and concerns that they may not fully comprehend the issues related to research risks. Many of the regulations for engaging research participants have been defined by age, rather than due consideration of psychological development.

Other ethical issues when considering engaging adolescents in research include minimizing therapeutic misconception, considerations in recruitment and retention, reimbursement types and amounts, and engagement of communities of adolescents on advisory boards of studies involving their population.

The attached manuscript discusses the potential challenges associated with recruitment of adolescents including those who are in early child marriages yet may be considered as autonomous to give informed consent by the Nigeria legislation. I do look forward to reading a lot more discussions on this forum.

Interesting perspectives from you Morenike. It does bring into light the variations of ethical issues surrounding paediatric consent with other external factors that contribute to the whole dynamics.

I can only speak to the practice in the UK. There is a Competency Framework Assessment that we can use when consenting adolescents when consenting/assenting adolescents or sometimes referred to as young persons. It is referred to as the Fraser Guidelines which includes the Gillick competency. See [link](#).

The proposition to eliminate the parents entirely in the consenting process of adolescents is a very delicate issue. Admittedly, there are certain situations when adolescents made contact with healthcare professionals and involving parents into the discussion can be an ethical minefield.

<sup>11</sup> Folayan MO, Haire B, Harrison A *et al.* (2014) Ethical issues in adolescents’ sexual and reproductive health research in Nigeria *Developing World Bioethics*: Published online first (9 June 2014).

<sup>12</sup> Folayan MO (2014) Beyond informed consent: ethical considerations in the design and implementation of sexual and reproductive health research among adolescents *African Journal of Reproductive Health* **18(3)**: 118-26.

However, in our practice, we are guided by the said guidelines which is also applied into consenting for other purposes not just research. Admittedly, I have not had the opportunity to do this yet in practice but in my opinion the guideline is an invaluable resource when making decisions as a clinician. Also, our practice culture involves accessing support from other colleagues in discussing similar “ethically dubious” issues, where perspectives from other clinicians can help make a consensual decision with the aim of fulfilling “best interest of the patient” principle while keeping in balance with other pertinent principles such as rights of patient to self-determination and nonmaleficence.

Again, thank you for your insight and it brings light to a different perspective in another part of the globe.

## **Annex D: Call for evidence – KEMRI version**

*In responding to the questions below, you may find it helpful in some cases to distinguish between three broad groups of children:*

- *those incapable of any meaningful involvement in a decision (e.g. babies)*
- *those capable of expressing a view, whether verbally or through their behaviour (in varying degrees, from young children to teenagers)*
- *those who would be regarded as competent to consent for themselves if the intervention were for treatment, rather than research (In the UK, this would correspond to children aged 16 years or over, or under-16s meeting ‘Gillick’ requirements in connection with the particular intervention)*

- 1. What do you consider to be the main obstacles to recruiting children to research? How might these be overcome?**
- 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.). As part of your answer to this question, please consider the following:**
  - i) How useful is the concept of assent? Is it helpful to distinguish between consent and assent for young people?**
  - ii) 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?**
  - iii) Parents’ views on whether (and how) children should be involved in decisions may be very different. How should the law and professionals take account of such different parenting approaches?**
- 3. Concerns are sometimes expressed that families agree to take part in research for other reasons e.g. because they think they will then get access to better healthcare, or because rewards have been offered. What responsibilities do researchers have in this regard?**
- 4. In relation to question 3, 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?**

- 5. How helpful is the notion of the best interests of the child participant? How would you define 'best interests'?**
- 6. 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)?**
- 7. 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.**
- 8. 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?**
- 9. 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?**
- 10. With limited resources, how would you decide which childhood conditions should be the priorities for research? Who should be involved in making these decisions?**
- 11. What responsibilities do funders, researchers and stakeholder groups have to encourage the coordination of children's clinical research?**

## Endnotes

---

- <sup>i</sup> See, for example, Conroy S, McIntyre J, Choonara I *et al.* (1999) Unlicensed and off label drug use in neonates *Archives of Disease in Childhood Fetal Neonatal Edition* **80(2)**: F142–5; Conroy S, Choonara I, Impicciatore P *et al.* (2000) Survey of unlicensed and off-label drug use in paediatric wards in European countries *BMJ* **320(7227)**: 79–82; Mukattash TL, Millership JS, Collier PS and McElnay JC (2008) Public awareness and views on unlicensed use of medicines in children *British Journal of Clinical Pharmacology* **66(6)**: 838–45; and Ward RM and Kern SE (2009) Clinical trials in neonates: a therapeutic imperative *Clinical Pharmacology & Therapeutics* **86(6)**: 585–7.
- <sup>ii</sup> *Gillick v West Norfolk and Wisbech AHA* [1986] AC 112; for more detail on the law in England and Wales with regard to consent to treatment, see: Department of Health (2009) *Reference guide to consent for examination or treatment: second edition*, available at: <https://www.gov.uk/government/publications/reference-guide-to-consent-for-examination-or-treatment-second-edition>.
- <sup>iii</sup> See, for example, Medical Research Council (2004) *MRC ethics guide: medical research involving children*, at page 24, and Hunter D and Pierscionek BK (2007) Children, Gillick competency and consent for involvement in research *Journal of Medical Ethics* **33(11)**: 659–62.
- <sup>iv</sup> The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended, generally referred to as the ‘Clinical Trials Regulations’.
- <sup>v</sup> The UK Clinical Trials Regulations transpose the EU Clinical Trials Directive into UK law. The Directive itself is silent on the age at which ‘minors’ become adults, and member states of the EU therefore have discretion in how this is determined in national law. However, EU Regulation 1901/2006 defines the ‘paediatric population’ as encompassing those aged under 18, and the recommendations of an EU *ad hoc* group on the implementation of the Directive states that ‘minors’ should ordinarily be understood as those under 18, with the exception of where national legislation specifies an earlier age of majority: see European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraphs 5.2 and 5.4.
- <sup>vi</sup> See, for example, Royal College of Paediatrics and Child Health: Ethics Advisory Committee (2000) Guidelines for the ethical conduct of medical research involving children *Archives of Disease in Childhood* **82(2)**: 177–82.
- <sup>vii</sup> European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraph 7.
- <sup>viii</sup> See, for example, the discussion in Baylis B and Downie J (2006) The limits of altruism and arbitrary age limits *American Journal of Bioethics* **3(4)**: 19–21.
- <sup>ix</sup> See, for example, Baines P (2011) Assent for children’s participation in research is incoherent and wrong *Archives of Disease in Childhood* **96(10)**: 960–2; and Sibley A, Sheehan M and Pollard AJ (2012) Assent is not consent *Journal of Medical Ethics* **38(1)**: 1–3.
- <sup>x</sup> Coyne I and Harder M (2011) Children’s participation in decision-making: balancing protection with shared decision-making using a situational perspective *Journal of Child Health Care* **15(4)**: 312–9.
- <sup>xi</sup> World Medical Association (2008) *Declaration of Helsinki*, available at <http://www.wma.net/en/30publications/10policies/b3/>. The 1996 version, while superseded by later revisions, is cited in the EU Directive and UK Clinical Trial Regulations.
- <sup>xii</sup> CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: [http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf).



- 
- <sup>xiii</sup> Council of Europe (1997) *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (Convention on human rights and biomedicine)*, and its *Additional protocol* concerning biomedical research (2005), available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>.
- <sup>xiv</sup> US Department of Health and Human Services, Code of Federal Regulations, 45 CFR 46.404 & 46.406, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.406>.
- <sup>xv</sup> US Department of Health and Human Services, Code of Federal Regulations, 45 CFR 46.405, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.405>.
- <sup>xvi</sup> Interpretation of the Clinical Trials Directive in Clinical Trials Regulations: The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031 as amended, Schedule 1, Part 4, paragraph 10.
- <sup>xvii</sup> Interpretation of the Clinical Trials Directive by EU *ad hoc* group: European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, at paragraph 12.
- <sup>xviii</sup> See, for example, *Re T (a minor) (wardship: medical treatment)* (1996) 35 BMLR 63 (Court of Appeal).
- <sup>xix</sup> Medical Research Council (2004/2007) *MRC ethics guide: medical research involving children*, at page 29.
- <sup>xx</sup> Gennery B (2000) Clinical research in children: a pharmaceutical industry view *Paediatric and Perinatal Drug Therapy* **4(2)**: 67–70.
- <sup>xxi</sup> Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006. These requirements may be waived where appropriate: for example where the disease or condition for which the medicine is being developed only arises in adults, or where use of the medicine is likely to be ineffective or unsafe in children. Where information from the ‘paediatric investigation plan’ is included in a new medicine’s ‘summary of product characteristics’, then the developer of the drug is granted a six-month extension of the supplementary protection certificate (effectively extending the benefit of the patent by six months). For ‘orphan’ medicinal products, this incentive takes the form of an extra two years’ market exclusivity in addition to the ten years’ market exclusivity that is already granted on authorisation of an orphan medicine.
- <sup>xxii</sup> Since 1997 the US Government has provided financial incentives to the pharmaceutical industry to conduct paediatric clinical trials through legislation that offers an additional six-month market exclusivity to patents for all paediatric formulations of products that have been trialled in children. More recently, the Paediatric Research Equity Act (2003) gave the Food and Drug Administration (FDA) the authority to require paediatric studies of a new medicine if the FDA determines either that the medicine is likely to be used in a substantial number of children, or that it would provide a meaningful benefit for children over existing treatments.
- <sup>xxiii</sup> FDA (2013) New paediatric labeling information database, available at: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.
- <sup>xxiv</sup> European Commission (2013) *Better medicines for children – from concept to reality: general report on experience acquired as a result of the application of Regulation EC No 1901/2006 on medicine products for paediatric use*, at paragraph 4.3 (summaries of product characteristics changed in 65 products authorised at national level and 12 authorised centrally) and 4.2.
- <sup>xxv</sup> Choonara I (2000) Clinical trials of medicines in children *BMJ* **321(7269)**: 1093–4 (with reference to the US regulations).

---

<sup>xxvi</sup> European Commission (2013) *Better medicines for children – from concept to reality: general report on experience acquired as a result of the application of Regulation EC No 1901/2006 on medicine products for paediatric use*, at paragraph 5.5; see also: Wall Street Journal (18 February 2013) Families push for new ways to research rare diseases, available at: <http://online.wsj.com/article/SB10001424127887324432004578306364187833702.html>.

<sup>xxvii</sup> European Medicines Agency (2012) Concept paper on the involvement of children and young people at the Paediatric Committee (PDCO), available at [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2012/09/WC500132555.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/09/WC500132555.pdf).

<sup>xxviii</sup> See, for example, the discussion in Nuffield Council on Bioethics (2011) *Human bodies: donation for medicine and research*, available at: <http://nuffieldbioethics.org/donation>, at paragraphs 7.70–1.

<sup>xxix</sup> Avon Longitudinal Study of Parents and Children (2013) *Ethics*, available at: <http://www.bristol.ac.uk/alspac/participants/ethics/>.