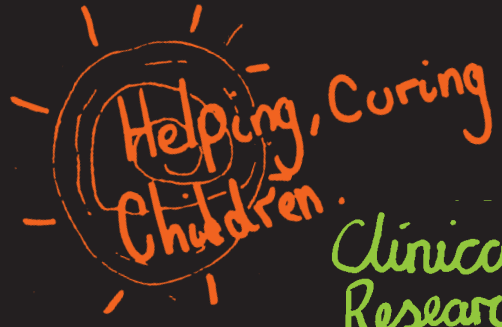




Well I want help children! (But could they make the table smaller)



I don't like injections!



Helping, Curing Children. Clinical Research

WHAT WE THINK!

I don't like the idea of getting pricked on the arm.



you will be OK

Me and MUM AND DAD Me and the doctor.



Having a lolly pop makes me feel better!



helping other people

It could hurt me and there might not be any cure.

People have check ups to see how they have progressed.

Doctors don't understand how children will get frustrated By changing their ROUTINES!

Children and clinical research: ethical issues

NUFFIELD COUNCIL ON BIOETHICS

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Children and clinical research: ethical issues

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The terms of reference of the Council are:

1. to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;
2. to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;
3. in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

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Many people have helped make this report possible. Over 500 children and young people, parents and professionals contributed in a plethora of ways: as members of our advisory 'stakeholder' group; by submitting evidence; by taking part in consultative events and surveys; by facilitating and participating in our school-based projects; by facilitating the wider involvement of children and young people; by critiquing an earlier draft of this report; and by advising on the content and format of the magazine and animation that aim to make our findings engaging and accessible for children and young people (see Appendices 2-5). We would like to thank them all for being so generous with their time and their knowledge. In addition to those named in the Appendices, we would like to thank Charmaine Chang, Phaik Yeong Cheah, Julia Dunne, Calvin Ho and Kevin Marsh for their informal advice on specific aspects of our work.

Most of all, we would like to thank members of the Working Party for the time, enthusiasm, and expertise they dedicated to this project.

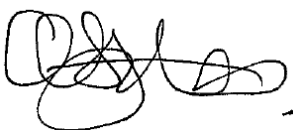
Foreword

It has been a huge pleasure and privilege to work with my fellow Working Party members, the Nuffield Council, and its secretariat to produce this report on the ethical issues surrounding children and young people's involvement in clinical research. We have benefitted greatly from the participation of many children and young people from the very beginning of the project. They have shared their experiences and expertise, taken part in a wide range of activities, critiqued our arguments and reviewed our published materials. At the same time, many experts in fields as diverse as philosophy, paediatric medicine and nursing, pharmaceutical regulation, child psychology, and law have given generously of their time, and helped us to ensure that our work is informed by their expertise. Many important stakeholder bodies and interested professionals have helped us to give due consideration to issues of relevance to clinicians, researchers, regulators and policy makers. A further and hugely important group to have helped us in our work are parents, the people charged with caring for and protecting their children, especially when they are unwell. They have encouraged us, whilst making us aware of the complex context within which we were working.

It has been particularly important to work with children, parents and experienced clinicians in order to challenge the idea that clinical research is something from which children need to be protected and essentially excluded. It is our belief that children will be best protected from ill health, disease and the impacts of disability through a greater commitment to evidence-based care. It is our further belief that, this being so, we need to find ethically and scientifically robust ways in which to conduct relevant clinical research. The time has come to protect children and young people *through* research not *from* research.

A modern health service needs to have research at its core, and children and young people deserve for their health needs to be addressed directly and effectively. We are not naïve to the challenges involved in balancing the requirements of science and the interests of those who will be invited to participate in research, especially at very difficult times of their lives. However, young people reassured us time and again that it was something they wanted to be part of, and our work has given us confidence that, with their support and involvement, great progress can be made.

I would like to close by giving special mention to Katharine Wright and Kate Harvey of the Council's Secretariat for their roles in this piece of work. Both approached the project with great commitment and imagination and they initiated, organised and saw through some of the most novel aspects of our work. From hosting stakeholder days run on popcorn and pizza, to supervising filming in schools and hospitals and sourcing teenage voiceover artists for animations, they did it all. At the same time, their hard work and support for the Working Party ensured that this report reflects the depth of investigation and scholarship for which the Nuffield Council on Bioethics is recognised and respected.



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Terms of reference

1. To consider whether the current systems for regulating clinical research strike the right balance with respect to:
 - promoting understanding of childhood conditions and the availability of evidence-based treatments for children;
 - the role children themselves should play in research decisions; and
 - the proper protection of child participants.

2. To consider, as may be necessary:
 - how it may be ensured that appropriate priority is given to research that is most likely to benefit children;
 - how the ethical acceptability of research projects should be determined, and the role of the various parties involved, including parents, in protecting children's welfare;
 - the relevance of a child's 'best interests' or capacity to 'benefit' in the context of consent to research, as opposed to treatment;
 - the importance of the international context;
 - any other aspects of the direct or indirect regulation of clinical research in children that may be relevant.

3. To draft a report and make recommendations as appropriate.

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Summary and conclusions

Introduction

1. In this report, we tackle an issue that has represented a major challenge for those concerned with the health and healthcare of children and young people: how can we ethically undertake the research needed to ensure their healthcare services are safe and effective, given that research often involves burdens and risks? Moreover, what role should children, young people and parents themselves play in influencing how research studies are carried out, and how can their voices help influence the wider research agenda?
2. The Nuffield Council on Bioethics has explored these issues through an expert Working Party, supported by a stakeholder group involving young people and parents. Throughout the project, input has been sought widely from young people, parents and professionals concerned with clinical research, in the UK and beyond. Views and experiences were sought through web-based surveys, an open ‘call for evidence’ and face-to-face meetings; through school projects in the UK and Kenya; and through networks of research professionals working in low and middle income countries from South East Asia to Latin America (see Introduction). While the focus of the report, and its concrete recommendations, are targeted primarily on the UK, we have thus sought to ensure that our ethical analysis and conceptual recommendations have as wide a resonance as possible.
3. In determining the scope of this report, we have interpreted what constitutes ‘clinical research’ broadly, as covering any form of research encounter with children and young people that holds out the prospect of improving healthcare, including preventative healthcare, in the future. While many of the ‘difficult cases’ cited to us during this project involve the administration of medicines or medical procedures, our approach is relevant to a wide range of research interventions.

Chapter 1: Context and ethos

The significance of context

4. In considering how clinical research involving children and young people may ethically take place, we start from a consideration of the *context* in which research takes place, and the many variables that may affect the ethical and social acceptability of proposed research studies. These variables include:
 - The nature and context of the research itself: ‘clinical research’ covers a wide range of potential research activity, with widely differing potential burdens and benefits for participants. The context in which it takes place creates different ethical challenges.
 - The context of particular children and their families: just as references to ‘children’ mask variations in age from newborn babies to young people on the verge of adulthood, different children within those age groups have different experiences and roles with respect to decision-making. These may be influenced by factors such as gender, family size and form, parenting style, health status, social and economic

situation, intellectual ability, and educational opportunity. Where children are ill, the nature and severity of that illness may be a particularly important contextual factor.

- The context of the wider social and political environment in which children and young people are being invited to take part in research, such as the domestic governance of research; access to healthcare; and dominant social attitudes to the notion of research, to parenting, to health professionals, and to risk.

The ethos of this report

5. Some fundamental attitudes, both to research, and to children and young people, have underpinned the Working Party's approach throughout its work:
 - **Scientifically valid and ethically robust research, that addresses questions of importance to the health of children and young people, should be seen as intrinsically good, and as a natural and necessary part of a healthcare system** (paragraph 1.19). It should not be perceived as a threat to children, as something to be apologised for, nor indeed as anything unusual. Without well-conducted research, there is no prospect of improving healthcare for children now or in the future, and there is a real risk that children will be harmed by procedures and medicines that are ill-adapted for their age-group or lacking an adequate evidence base. Such an approach is certainly not a blanket prescription of 'research at all costs' – but rather a challenge to the complacent notion that it is safe or ethical to continue promoting care to children without seeking to improve the evidence on which that care is based.
 - We base our work on **an understanding of children and young people as people who, in the context of their own family and social environment, have the potential from an early age to play an active role in determining their own lives and in engaging with others** (paragraph 1.25). Such an approach, which is commonplace in thinking about the role of children in many other areas of life, stands in stark contrast to many of the implicit assumptions of research governance, which tend to emphasise vulnerability and lack of competence.
6. Much has already been written as to what constitutes 'ethical practice' in clinical research – but generally from the starting point of research with competent adult participants. In this report, by contrast, we aim to start with a consideration of children and young people, and of their lived experiences of participation in research. We then use this understanding to reflect critically upon specifically child-related issues arising in clinical research, including assumptions of childhood vulnerabilities, the role of children themselves in decision-making, and the role of parents and others in promoting children's welfare.

Chapter 2: Being invited to take part in research – evidence and law

7. The first contact that most children and young people, and their families, will have with clinical research is when they are approached and invited to participate in a particular study. This chapter reviews first the empirical evidence of how, in practice, children and families make decisions about research participation, and then the role played by national law, international declarations, and good practice guidance.

Empirical evidence

8. The way in which children, young people and parents respond to the possibility of participating in clinical research is likely to depend on three broad factors:
 - The **nature of the research**: for example, whether it relates to a child's own condition, and the severity of that condition; whether the need for a decision arises at a particularly traumatic time, and how much time is available to think about it; the degree of risk or discomfort involved; and time and opportunity costs involved in taking part.
 - The **situation of children and their families**: their existing knowledge of research, and their attitudes towards both research and risk in general; their desire to help others through participation in research; and their perception of potential health or other benefit deriving from participation.
 - The **relationships between researchers and families**: the extent to which there are trusting relationships between children/young people, parents and researchers; and the quality of the communication between them.
9. Children and young people themselves are involved in participation decisions in very different ways: from no involvement at all, to joint decision-making with parents, to being the final decision-maker. These differences do not simply correlate with age, but appear to be influenced by many other factors including the severity of any illness, the suddenness of either the diagnosis or the opportunity to take part in research, children's and young people's prior experiences, and general family dynamics in decision-making.

Law and guidelines

10. In contrast with the context-specific nature of decision-making emerging from the empirical literature, regulatory approaches focus very much on the role and status of the decision-maker. In most cases, children or minors are, by default, assumed to be unable to make their own decisions, and authorisation is required instead from a parent or another legally-authorised proxy. International declarations, regulations and guidance take diverse approaches to the extent to which children or young people should, nonetheless, be *involved* in the decision. Most, but not all, make specifications relating to the (age-appropriate) information children and young people should receive, and the importance of involving them in the consent process in a manner appropriate to their maturity.
11. The term 'assent' is used widely within both international declarations on research ethics and in some national legislation to encompass this involvement, but with very different meanings and implications. These vary from "the emergent capacity to agree" of a three year old, to the "knowing agreement" of an adolescent who has not yet reached the legally established age of consent but who nevertheless has the capacity to make their own decisions. Unlike consent, assent has no legal force, but some guidelines require documentation that a child has assented to take part.
12. There is similar variation in how a child's dissent should be handled: in particular whether it should be 'considered', or by contrast, 'respected'.

Chapter 3: Developing research proposals – law and practice

13. This chapter provides an overview of the often extended process by which clinical research studies reach the point of recruitment described in the previous chapter. It addresses both the ‘drivers’ of research, and the mechanisms designed to ensure the quality of research studies.

What research takes place and why?

14. Clinical research studies may be funded by the commercial sector, charitable foundations, or public money. Some charitable and public sector funders set out high level priorities for the kind of research they wish to fund, but in practice most funding is allocated in response to the perceived quality of researchers’ proposals. Organisations such as the James Lind Alliance argue for a more targeted approach to research prioritisation, and involve both patients and professionals in their ‘priority setting partnerships’ (PSPs) which identify the most urgent research questions in particular areas of care.
15. Where research is funded by the commercial sector, governments may use regulatory requirements and incentives (‘sticks and carrots’) to influence their agenda. In the specific area of research on medicines, the EU Paediatric Regulation 2006 has increased the information available on medicines used for children and young people by requiring companies to develop paediatric investigation plans (PIPs) to include children and young people whenever they carry out trials of new medicines. New medicines are exempted from this requirement if they target conditions that do not arise in children, although the way these ‘class waivers’ operate in practice has been criticised. Incentives to encourage further research on off-patent medicines have not so far proved effective.
16. Action has also been taken at EU level to encourage collaboration, which is particularly important in research with children where conditions may be very rare and hence cohorts of potential research participants very small.

Scrutiny of research proposals

17. In order to protect potential research participants, international declarations and national guidance set a number of ‘threshold’ criteria that studies must meet, relating to the value of the research, the balance between benefits and burdens, and the management of risk. The design of research studies is subject to a detailed scrutiny process, involving both scientific (peer) and ethical review, to ensure that these requirements are met. The valuable contribution that children, young people and parents can make, both in commenting on study design, and ensuring information about the study is suitable for children and young people, is increasingly being recognised.
18. While many challenges arising in the peer and ethical review processes apply to all research scrutiny, regardless of the age of the potential participants, concerns specific to the ethical review of research involving children and young people were raised with the Working Party. These included anxieties that, the younger the potential participants, the more research ethics committees (RECs) tended to lean towards a protective or ‘parentalist’ approach. It was also argued that RECs must have access to specialist expertise in relation to relevant areas of children’s and young people’s healthcare in order to make a fair judgment about the risks and benefits of a proposed study.

Chapter 4: An ethical approach to children's involvement in research

19. This chapter draws on our underpinning ethos, on the available empirical evidence, and on our overview of existing regulatory approaches, to analyse the ethical issues at stake in seeking to involve children and young people in clinical research.

What is (ethically) different about children?

20. In order to consider what it is that is potentially different, ethically speaking, about children and young people in research, it is necessary to make some further distinctions within the very broad concept of 'childhood'. We identify three distinct paradigm cases: situations in which a child's or young person's potential for input into a decision about research raises distinct ethical questions:
- **Case One:** children who are not able at this time to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are so unwell or are unconscious.
 - **Case Two:** children who *are* able at this time to form views and express wishes, but who are clearly not yet able to make their own independent decisions about research involvement.
 - **Case Three:** children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be minors in their domestic legal system (paragraph 4.5).
21. All children, at the beginning of their lives, will fall into Case One, and most (although not all) will progress over time through Case Two to Case Three. This progression will not be straightforwardly linear, however. The nature of the particular research decision to be taken, and children's and young people's physical, emotional and mental condition at the time, will also determine which case is applicable for *this* child or young person for *this* decision. For example, a 12 year old might be in Case Two for some decisions, but in Case Three for others. A very ill 16 year old might be in Case Two, even if usually they would be in Case Three. Not all young people will reach Case Three – for example, if they have severe learning disabilities and need help with day-to-day decisions.
22. The **developmental aspect of childhood**, from the complete helplessness of a baby in Case One to the relative self-sufficiency of a young person in Case Three, also provides a helpful pointer in identifying what it is that is distinct or special about childhood. A factor that unites all three cases, correlating directly with this developmental nature of childhood, is that children have **parents** who play an important role, from both legal and ethical perspectives, with respect to making decisions on their behalf. Throughout this report we use the term 'parents' to refer to one or more adults taking on this role of parental responsibility whether or not they have a biological connection with the child (paragraph 4.8).

Responsibilities of parents

23. Ethical considerations that parents should take into account when making decisions with or on behalf of their children include (paragraph 4.10):
- Respect for children as **individuals**, regardless of their age or capacity. This may, for example, be expressed through consideration of children’s wishes, and respect for their bodily integrity, although children’s wishes may not always be determinative.
 - Recognition of children’s **developing capacity** for autonomous agency and the supportive or educational role of parents in helping their child develop and ‘practise’ decision-making skills and confidence.
 - Concern for children’s **immediate and longer-term welfare**. Immediate welfare interests at the time of the research may relate to factors such as any pain, anxiety, distress, or enjoyment associated with participation in research. Longer-term welfare interests relate to children’s and young people’s future ‘good’ including, but not limited to, questions of what is ‘best’ for them in terms of their physical health or personal interests. Parents also have a responsibility to seek to influence the values that their child acquires as they grow up, and to shape the kind of person their child becomes. This ‘shaping’ includes influencing how children understands their responsibilities to others, as social beings.

Understanding welfare

24. **We suggest that an understanding of children’s longer-term welfare should encompass the possibility of contributing to wider social goods. Such a contribution could take the form of participation in properly regulated clinical research in order to contribute to the knowledge base necessary to improve healthcare for all children in the future** (paragraph 4.28). This is not, of course, to say that anyone has a specific *duty* to take part in research; rather that, in determining what is ‘good’ for their children, parents should take into account the fact that their children are growing up in a social context. Participation in properly regulated research offers one possible opportunity for expressing social solidarity, and hence may be regarded as good for the child.
25. At the same time, in inviting children and parents to contribute to the ‘social goods’ of research, researchers should be confident that the study protocol does not pose unacceptable risks or burdens for children. Thus, alongside participation in research understood as an act of care for others, there must be concern for the physical and emotional well-being of every child participant.

Compatibility with children’s interests

26. The language of ‘best interests’ is often used to capture this general concern for children’s welfare, but is misleading in the context of clinical research, given that research-related procedures are not, primarily, carried out for the personal benefit of participants. **We therefore suggest that parental consent to research should be based on their confidence that participation in the proposed research is compatible with their child’s immediate and longer term interests** (paragraph 4.33).

Decision-making in the three paradigm cases

27. The way different families manage these ethical concerns will vary considerably. However, the *balance* is likely to shift in important ways as children progress through the three cases.
28. In **Case One**, where children cannot participate in decision-making, the sole focus is on the role of others (first and foremost children's parents) in making decisions on their behalf. While this report challenges the automatic assumption that all children are vulnerable in research in a way that adults are not (see paragraph 34), children in Case One are clearly vulnerable in a way that children in Cases Two and Three may not be, in that at this point they are entirely dependent on others to make decisions for them. Parents' primary concern in such circumstances will be for the welfare of their child.
29. In **Case Two**, children are able to contribute their view, but are not capable of making a participation decision independently. In addition to making judgments about their child's immediate and longer term welfare, parents will therefore need to determine how these factors should be balanced both against the respect due to their child's own views and feelings regarding research participation, and parents' general educational obligation to develop their child's decision-making capacity. Relevant considerations in any such decision include:
- the potential for their child to derive direct or indirect benefit from the proposed research, and the likelihood and severity of any associated risks;
 - the burden of research participation for their child – for example, whether they have particular anxieties about any of the procedures involved;
 - their child's own views and feelings about the proposed research;
 - the maturity and understanding of their child;
 - the value placed by the parents on the role of participation for their child's longer term welfare;
 - the relative strength of the parents' views with respect to the various welfare considerations listed above, and their child's feelings; and
 - the likely impact on their child's immediate and longer term welfare of overriding their preferences – for example, the degree of immediate distress and the risk of future lack of trust in clinicians or researchers if they are required to take part against their will (paragraph 4.39).
30. In **Case Three**, by contrast, the distinctive feature is children's or young people's potential capacity to make research participation decisions for themselves. Nevertheless, parents still retain important responsibilities with respect to promoting their children's welfare and seeking to influence the way they grow up. We suggest that, instead of seeking primarily to identify who (child or parent) is entitled to provide a legally effective consent or veto on research participation in this Case, the *ethical* focus should be on obtaining agreement within the family unit concerned. Thus, the starting assumption in any discussion as to whether a child or young person within Case Three should take part in a research study would be that this should normally be a **shared family decision**.
31. **In other words, we are making the claim that there is a morally significant difference between 'competent children' and 'adults', which may potentially justify differential treatment. Children, however intellectually capable, do not have full adult powers – and the corollary of that is that they also do not have full adult**

responsibilities. Parents are there, both ethically and legally, to share that responsibility until the agreed threshold of adulthood is reached (paragraph 4.47). In making this claim, it is crucial to acknowledge that ‘childhood’ is, at least in part, a social characterisation that will vary from society to society. The law in each society will set a norm judged appropriate for this parental power and responsibility to end: that is, the age of majority. It will vary around the world, and move over time; some jurisdictions may also choose to specify different ages for particular aspects of parental power to end. However, a line is always drawn *somewhere*.

32. Our threefold analysis of parental responsibilities is thus also applicable where children and young people fall into Case Three – but the *balance* of those responsibilities will be exercised differently from Case Two. The parental role in helping their child to *develop* capacity begins to fall away, but has not yet become redundant. Respect for their child as an individual who is able to make their own decisions will increasingly be the dominant feature of the parental role, but concerns about welfare will still be significant. In Case Three though, by contrast with Cases One and Two, such concerns will be expressed primarily in the form of *advice and support*, rather than through exercising the role of a substitute decision-maker.
33. An important aspect of this analysis of parental powers and responsibilities lies in their *discretionary* nature. A key aspect of parenting consists in the gradual yielding of responsibility, accompanied by appropriate levels of support, from parent to child.

Challenging vulnerability

34. The straightforward association often made between ‘childhood’ and ‘vulnerability’ was strongly challenged throughout the Working Party’s consultative activities. In many cases, the factors that may potentially make children feel, or be, vulnerable in the context of clinical research do not arise inevitably because of the nature of childhood; and nor are they necessary features of research. Rather, they arise in the *context* of the developmental nature of childhood – experienced, for example, in young children’s need for practical and emotional support in understanding what is proposed, or anxiety about the impact of research participation on their school life. Once the relevance of this context is recognised, there will often be scope to reduce vulnerability by modifying some aspects of the research.
35. The risk is that an unduly protective response to perceived or actual vulnerability may not only exclude children and young people from opportunities to participate in research activities, but also harm the interests of many children in the future by preventing potentially valuable research from taking place. However, an awareness that children *may* potentially be vulnerable in a research setting may nonetheless provide a useful alert to those professionally concerned with research: in brief, to ask themselves ‘does this research raise particular ethical challenges and what can I do about them?’ The real challenge for those professionals is thus the nature of the *response* they make to that alert. References to vulnerability in the context of children’s and young people’s involvement in research should never be treated as an automatic ‘brake’ on a research proposal.
36. We suggest that **an appropriate response by professionals to concerns about children’s potential vulnerability in research is to ensure that they work in partnership with children, young people and parents throughout the whole endeavour of research** (paragraph 4.59). Such a partnership approach will ensure that, whenever children and young people are invited to take part in clinical research, the procedures to which they are being invited to consent have been developed with the

input of others in a similar situation to themselves. Where it is not feasible to seek direct input from children in similar situations (that is, for some of the children in Case One), then this engagement will be carried out on their behalf by parents; but, as we discuss earlier in this chapter, parents will also continue to play a role as their children develop through Case Two to Case Three. Such an approach implies a fundamental shift from seeking to protect children 'from' research, to protecting them through their own active engagement with the way that research with children and young people is designed and carried out.

37. Finally, it is also important to be alert to the fact that **parents, too, may often need support in the context of their child's research involvement** (paragraph 4.61). Parents' day-to-day decision-making responsibilities are inevitably more challenging to exercise if the decision to be taken involves potential burden or risk for their child, or arises in highly emotional and difficult situations. This is an important recognition but, as with our analysis above with respect to children's potential vulnerabilities, should not be seen as placing an automatic brake on certain kinds of research being undertaken. Rather it acts as a prompt to consider how research studies may be developed and carried out, and how professionals can appropriately support parents, in a way that does not make unreasonable demands on either parents or children.

Chapter 5: Developing research proposals – the role of professionals

38. The question of whether or not research participation is compatible with children's or young people's interests depends not only on the view taken by individual children/young people and their parents as to the value of contributing to that research, but also crucially on the aim and design of the research itself. This chapter now considers the role of the many professionals involved in research, whose actions and attitudes have a powerful, if sometimes unseen, influence on the decisions that children and their parents are asked to make.

The role of professional virtues

39. Any system, however well-intentioned, devised to encourage and promote ethical research with children, may unwittingly lead either to unthinking adherence to a checklist of requirements, or may create such onerous hurdles that it acts, in practice, as a barrier to research. The question then is how to develop *reflexive* ethical practice that is not simply enforced top down by external requirements or organisations, but that becomes an inherent part of professionals' daily practice, and is sensitive to difference in national and social contexts. In the specific context of research with children and young people, we identify three particular virtues or values that have emerged repeatedly throughout the development of this report and that we suggest lie at the heart of professional ethical practice in this field:

- **Trustworthiness**, facilitating **trust**: children and parents will only feel able to take part in research if they can trust both the researchers with whom they are interacting, and the way the research is organised. Any functioning system of governance must also be able to trust the researchers who are subject to that governance.
- **Openness**: researchers need to share information clearly and honestly with children and parents – when inviting them to take part in research, during the research itself,

and afterwards. They also need to be willing to collaborate with, and learn from, other sectors of the research community, and across countries and continents.

- **Courage:** some research is difficult to do, and it may seem easier just not to do it. But if research is not carried out, then children will not have the best possible healthcare, and may even be given treatments that are harmful, because no one has done the research to find out. The proper involvement of children and young people in the research process, which involves at least some degree of transfer of power between adults and children, also involves courage (paragraph 5.8).

Professional responsibilities in developing research

40. In Chapter 4, we suggest that research professionals should respond to concerns about children's potential 'vulnerability' in research by asking themselves: 'does this research raise particular ethical challenges and what can I do about them?' We further argue that these challenges can best be explored in the light of children's and young people's *own* perceptions of the demands of the study. In the design and development of clinical research studies, researchers thus need to ensure that they have worked in partnership with children, young people and their parents from the beginning. Genuine partnership will help to ensure that important aspects of the research question have been considered from the perspective of those whom the research aims to benefit; that researchers are aware of and respond to those aspects of study design that might be of concern to prospective participants; and that information materials are clear and age-appropriate. There is a well-established network of young persons' advisory groups in the UK who are well-placed to take on aspects of this role, as are voluntary sector organisations that support children and families with particular conditions.
41. **We strongly welcome the approach taken in the UK by the Clinical Research Network: Children, and by the Scottish Children's Research Network, in establishing and supporting young persons' advisory groups. We note and welcome how similar groups are being developed in other countries, and in specific areas of healthcare, such as mental health. We also recognise that such groups are not cheap to run, and that at present their costs tend to be borne out of public funding allocations for research which are already under considerable pressure.** All stakeholders need to work together in order to ensure that these groups have a secure funding base for the future, and where necessary are able to expand in order to respond to increasing numbers of requests from researchers. In particular, it seems evident that the commercial research sector, which makes use of the groups' services, should contribute towards their costs. **Whatever the funding mechanism chosen, it is clearly critical that the independence of the groups should be maintained** (paragraph 5.15).

Recommendation 1

We recommend that the Clinical Research Network: Children and the Scottish Children's Research Network should initiate discussions with their industry partners on ways in which industry could contribute to the costs of young persons' groups in the UK, without compromising their independence.

Recommendation 2

We recommend that all sponsors of clinical research develop systems to guarantee that their quality control of research proposals involving children and young people exposes those proposals to expert advice on good practice, and to the views of young people and parents.

Recommendation 3

We recommend that INVOLVE should collaborate with the National Institute for Health Research's Research Design Service and relevant experts at the Medicines and Healthcare Products Regulatory Agency to explore how the design and regulatory scrutiny of clinical trials can take more account of the experience of young people who have previously taken part in trials, and of their families.

Professional responsibilities when reviewing research

42. When reviewing research protocols, research ethics committees (RECs) should have in view both their 'protective' and 'facilitative' roles. Consideration of the potential risks and burdens of the research *must* certainly play a central part in the ethical review of any research protocol, but at the same time the potential value of the research should not be overlooked.
43. Most jurisdictions require that research procedures should pose no more than minimal risk or burden to children and young people participating in the research, unless those risks and burdens are judged to be outweighed by the prospect of direct (health) benefits. Such an approach, however, stands in contrast to the risks that children and young people of a similar age are permitted, or even encouraged, to run in other areas of their daily life that may far exceed any definition of 'minimal', such as those involved in contact sports, or in learning to drive. While in some cases these risks may be recognised and explicitly justified by the (direct or indirect) benefits they are perceived to bring, this cannot always be assumed, particularly where participation is compulsory as in some school-based activities. How are members of RECs to respond to these conflicting societal messages as to what degree of risk is acceptable for what degree of (potential) gain? Rather than attempting to reproduce or revise any such lists of acceptable procedures, or comparator activities in daily life, we suggest that it is more appropriate to focus on the *expertise* that RECs, those tasked on a regular basis with making these judgments, are able to draw upon when approaching these questions.
44. **We conclude that, in order for RECs to be well placed to make these (sometimes very finely balanced) decisions as to whether, in a particular case, the burdens and risks presented by a study protocol can ethically be justified, it is essential for them to have access to appropriate expertise. We highlight two forms of such expertise: that of professionals with specialist knowledge of children's healthcare; and that of children and families (paragraph 5.23).**

Recommendation 4

We recommend that, whenever research ethics committees consider protocols relating to research with children, they should always ensure that they have timely access to expert advice from the relevant area of children's and young people's healthcare. Such

expertise may need to be obtained through an external adviser co-opted for the particular decision.

Recommendation 5

We recommend that the National Research Ethics Service, in cooperation with relevant Royal Colleges and other professional bodies, should establish a database of experts who are willing to act as REC advisors, from across the full range of potential clinical research areas involving children. The National Research Ethics Service might also consider ways in which researchers and research ethics committees might better communicate with each other with respect to any specialist areas of knowledge required to inform assessment of the protocol, for example through specific prompts in the online application form.

Recommendation 6

We further recommend that the National Research Ethics Service should keep under review the experiences of both research ethics committees and researchers with respect to the current system of ‘flagging’ committees as suitable for considering research with children and young people. If the evidence suggests any systematic difficulties with respect to the scrutiny of particularly complex or sensitive studies, the National Research Ethics Service should consider exploring alternative models, such as the creation of a limited number of expert research ethics committees, on the model, for example, of the Social Care Research Ethics Committee.

45. The Working Party was also struck by the difficulties that health professionals and others engaged in research sometimes appear to encounter in convincing their employers that the time required to serve as a REC member is time well-spent (paragraph 5.25).

Recommendation 7

We recommend that the UK Departments of Health, NHS Employers, Universities UK and the Health Research Authority should jointly consider what steps they can take to protect the professional time needed for research ethics committees to work effectively.

Recommendation 8

We further recommend that the Royal Colleges and professional bodies concerned with children’s and young people’s health should make their commitment to evidence-based care clear by reinforcing the professional responsibilities of their members to contribute to the ethical review of research over their professional lifetime. For example, involvement of some form in a research ethics committee (including in an *ad hoc* advisory role) could be encouraged as part of continuing professional development schemes. A number of rotational posts for trainees working in different areas of children’s and young people’s healthcare could be linked with their local research ethics committees.

46. The equally critical input that can be obtained from parents, children and young people as to the acceptability of particular risks and burdens in the context of research should be set alongside the importance of access to specialist professional expertise. RECs should routinely expect researchers to have involved children, young people and parents, as appropriate, in the design of their studies. RECs will then be able to draw on the reported opinions of children, young people and parents in order to assure themselves whether the study design is appropriate, whether any risks and burdens have been minimised and justified, and whether information materials are comprehensible to their target audience.

Recommendation 9

We recommend that research ethics committees should routinely require researchers to have involved children, young people and parents, as appropriate, in the design of their studies. Researchers who have not sought input in this way should be required to justify to the research ethics committee why this was not appropriate in their case, and be able to demonstrate an appropriate knowledge of relevant literature and guidance.

47. However, the responsibility of determining the ethical acceptability of a protocol, of making independent judgments about acceptable levels of risk and burden, and how these may be balanced against any possible benefits, remains with the REC. This assurance role of the REC is important not just with respect to the potential participants in the particular research study, but in order to promote wider public confidence and trust in the whole endeavour of research, especially where public knowledge of research and research procedures is lacking. **We take the view that the fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a ‘fair offer’ to children, young people and their parents, where the value of the research and its likely risks, burdens and benefits have been carefully weighed up** (paragraph 5.28).
48. In focusing on the role of the REC in ensuring that research involving children constitutes a fair offer to children and parents, it is also important to recognise the REC’s second and equally important function: its *facilitative* role, which arises in recognition of the essential social good of well-designed and well-conducted research. **It is not an ethically neutral act to say ‘no’ to a research proposal that might potentially lead to better outcomes for children’s and young people’s healthcare** (paragraph 5.34).

Drivers of research

Research prioritisation

49. There are major challenges inherent in determining what forms of research with children and young people should be prioritised. While the overall burden of any particular condition is clearly highly significant in considering priorities for research, this is not the only factor to be taken into account, as such an approach would necessarily overlook the impact of rare diseases on children and their families. Other considerations that must also be taken into account include the practical scientific question of which research directions are most promising at any particular time; and the unpredictable nature of research, with the prospect of findings in one field having unexpected influence in another.

50. **Given the complexity of these judgments on priorities, made more complex still by the myriad of potential funding sources, we conclude that our primary ethical concern with respect to prioritisation should relate to the process by which such decisions are reached. Drawing on our emphasis on the importance of partnerships between research professionals and potential research participants, we suggest that the key challenge for those responsible for making decisions about which studies to fund must be to ensure that key stakeholders, including children, young people, parents and professionals, are appropriately involved in those funding decisions** (paragraph 5.40). The model of the James Lind Alliance's 'priority setting partnerships' provides an excellent example of how this is already being achieved in some areas, such as in the care of preterm babies, and treatment of teenage cancer.
51. The European Medicines Agency's (EMA) Paediatric Committee (PDCO) also has an important part to play in this process of prioritisation, through its ongoing work developing inventories of 'paediatric needs' for medicines research across a range of therapeutic areas. **We note, and support, PDCO's general commitment to involving children and young people in its activities, and, in particular, proposals made in 2013 that such involvement should include input into the definition of significant therapeutic needs. We strongly encourage PDCO to continue to take these plans forward** (paragraph 5.42).
52. **We similarly endorse and encourage ongoing work by Enpr-EMA (the European 'network of research networks'), exploring how European children's research networks can contribute to the priority-setting debate, and how they can facilitate the involvement of children, young people and parents in those discussions. More, however, needs to be done to encourage debate at national and regional level about priorities across the range of childhood conditions. We encourage health departments (within the UK and beyond) to take the lead in initiating debate on the most pressing priorities in child health research in their own countries, and in ensuring that children, young people and parents, as well as relevant professional experts, are appropriately involved in those discussions** (paragraph 5.41).

Incentivising medicines research with children and young people

53. The 2006 Paediatric Regulation, combined with the incentives included within the Orphan Medicines Regulation, has started to make a real and welcome difference to the amount of information available to prescribers on the effect of medicines on children and young people. **We welcome the significant benefits that the 2006 Paediatric Regulation has brought about within Europe, in increasing the focus on medicines research with children. We recognise, in particular, the very positive and proactive approach EMA and PDCO have taken to their regulatory role, using it not only simply to police the system established by the Regulation, but also actively to promote effective, collaborative, research with children and young people through a variety of practical means. We strongly encourage the EMA and PDCO to build on these successes, using the opportunity of the forthcoming ten-year review of the Regulation with respect to any identified need for legislative change** (paragraph 5.44).
54. It is, however, clear to us that the class waiver system, whereby medicines targeting 'adult-only' conditions are exempted from the requirement to include children and young people in trials, is not working as originally intended. As a result, the opportunity for research that might in fact benefit children (for example, where the mechanism of action of the medicine is relevant to a different condition in children and young people) can be

lost. We note earlier in the report, in the context of ethical review, that it is not an ethically neutral act to say ‘no’ to a research proposal that might potentially lead to better outcomes for children’s and young people’s healthcare. Similarly, a loss of opportunity to promote research that is potentially important for children is a matter of ethical concern. We note that there is nothing to *prevent* sponsors of research from choosing to put forward a paediatric investigation plan (PIP), even where they would be entitled to receive a waiver, and indeed that some sponsors have done so. We urge sponsors to consider this option, and PDCO to raise awareness of it.

Recommendation 10

We recommend that the European Medicines Agency’s Paediatric Committee should complete its review of the class waiver system as a matter of urgency and ensure that where the mechanism of action of a medicine is potentially relevant for children and young people, research with children and young people goes ahead.

Recommendation 11

We recommend that where research sponsors are eligible for a waiver under the current class waiver system, they consider the evidence on the possible relevance of the mechanism of action of their product for *other* conditions occurring in children and young people. Wherever appropriate, they should undertake research with these age groups on a voluntary basis.

55. More needs to be done to incentivise or promote research with children on the use of off-patent medicines, including the development of age-appropriate formulations. A number of approaches were cited to us which we feel merit further consideration including those of transferable market exclusivity (allowing the value of an incentive to be transferred to a different product), or the use of imaginative tax breaks, if necessary on a country-by-country basis (paragraph 5.46).

Recommendation 12

We recommend that the European Medicines Agency should give serious consideration to innovative approaches to incentivisation for research with children on the use of off-patent medicines, as part of its preparation for the ten-year review of the 2006 Regulation.

Collaborative working

56. Industry is not, however, the only possible source of research activity with respect to off-patent medicines in children. Academic researchers and patient groups may also be well-placed to initiate work in this field, collaborating as appropriate with industry, or seeking additional support from the EMA, to ensure that regulatory requirements are met. The potential value of collaborative working as a response to the difficulties encountered with respect to off-patent medicines serves to highlight the much more general need for cooperation within children’s research. **While the realities of different academic, professional and commercial interests across the research sector cannot simply be ignored, we suggest that there is a strong ethical imperative for researchers working in the field of clinical research with children and young people to work collaboratively with each other, and with key stakeholders such as**

condition-specific family support groups, to the maximum extent possible (paragraph 5.47).

Chapter 6 – Taking part in research: professional responsibilities

57. We now turn to consider responsibilities in connection with professionals' *direct* interactions with children and their families: those that arise when children and young people are invited to take part in research, and indeed those that arise throughout and after the study itself.
58. While researchers do not take on a parental role, at particular points in time they occupy a professional role with respect to particular children or young people which, as an adult-child relationship, brings with it associated responsibilities. We suggest that these responsibilities might therefore be characterised as obligations to:
- treat children and young people as individuals of value in themselves;
 - support parents in their attempts to help their children develop their ability to make autonomous choices;
 - act in accordance with children's and young people's immediate and longer-term welfare (for example, minimising any distress arising in connection with research involvement, only proceeding if confident that participation in research is compatible with their interests, and being sensitive to the importance of maintaining family harmony with respect to research participation); and
 - act in accordance with the professional virtues outlined in Chapter 5: trustworthiness, openness and courage (paragraph 6.3).

Responsibilities to children and young people: consent and assent

Children and young people in Case Three

59. Children and young people fall within Case Three where they are capable of understanding what is involved in taking part in a particular piece of research and of deciding for themselves whether or not to take part, but are not as yet given full decision-making power under national legislation. **We take the view that, where children and young people have this level of understanding, professionals have an ethical obligation actively to seek their consent, not their 'assent', regardless of any additional requirements of national legislation** (paragraph 6.5). At the same time, we recognise that parents continue to have a legitimate interest in their children's decisions until their child is formally recognised as an adult within their national jurisdiction.

Recommendation 13

We recommend that, where children and young people have sufficient maturity and understanding, but are not yet treated as fully 'adult' by the law of their country, professionals should, wherever possible, seek consent from both the children or young people concerned, and from their parents.

60. The consent, once given, should be recorded in a way that is culturally appropriate and compatible with local socio-legal norms. In a UK context, this is likely to involve both the young person and parents signing the consent form; but other methods of documenting the consent process, such as audio or video recordings, or a note by the researcher,

may be equally acceptable, particularly where those methods are chosen as a result of local community engagement in the development of the study. A signature on a consent form is only a means of *recording* a decision; it is the decision itself, and the (ongoing) process that underpins that decision, that is the ethically significant part of the 'consent'.

61. There will, of course, always be cases where this shared decision-making model does not work: because of the nature of the research; or because of disagreement within the family; or in cases where children and young people do not have the kind of family support envisaged above. We return to the latter two cases below. **Where the nature of the research is such that parental involvement is believed to be inappropriate, or might undermine the research objective or even threaten a young person's well-being, we take the view that it may be ethically acceptable to approach children and young people in Case Three without parental knowledge or involvement. However, such approaches should be subject to specific review by a REC.** (paragraph 6.7). It would thus be open for a REC to approve a proposal that children and young people in Case Three be invited to participate in research, such as research exploring young people's drug use or sexual activity, where there was good reason to believe that parental involvement in the decision would prohibit the research, or compromise the accuracy of the information received.

Children and young people in Case Two

62. As soon as children are able, even at a basic level, to express views and wishes about the research, we argue that researchers have an obligation to *involve* them in a way that is appropriate to their understanding and development, and that respects the particular parenting approaches of their parents. The term 'assent' is often used to describe these interactions with children who do not, as yet, have the capacity to make independent decisions about research participation. However, there is little consensus on what, precisely, assent means, or how or when assent should be sought. A requirement for written assent further risks focusing attention primarily on the *act* of obtaining a signature, and away from the ethically-significant *process* of involving and engaging children appropriately.
63. We thus suggest that much greater clarity with respect to the assent of children to participation in research would be obtained by distinguishing clearly between the process of involving children in participation decisions, and the manner in which this involvement is subsequently recorded.

Recommendation 14

We recommend that requirements in guidance and regulation to 'seek' or 'obtain' assent from children who are being invited to take part in research should be understood as requirements to *involve* children, as much as they wish and are able, in the decision about participation. In devising assent processes, researchers should primarily be concerned with how best to develop trusting relationships with children and communicate information appropriately throughout the research.

64. The ways in which this involvement may be achieved will clearly vary significantly. Information materials appropriate to children's level of understanding and to the cultural environment in which the research is taking place are important, but even more important is the emphasis to be placed on sensitive and skilled communication. Researchers seeking ethical approval of their studies with children should be able to

demonstrate that all those who will be interacting directly with children and families as part of the proposed research have the necessary communication skills to do so effectively.

65. **The fact that children have been appropriately involved in the participation decision should be recorded for future reference. However, this record must not be perceived as the main point of the process** (paragraph 6.12). Assent forms constitute one possible form of documentation. They are not, however, the only (or necessarily the best) way of recording children's involvement. Alternative forms of documentation might include inviting children and young people to co-sign the consent form with their parents, or for parents to note on the consent form that their child has been involved in the decision. Increasingly, though, it may become more appropriate to use interactive online technologies, both as a means of sharing information about the research and recording children's involvement. The format of record chosen to document children's involvement must also, crucially, be culturally appropriate. In some contexts, signing a form may be perceived as threatening, rather than empowering. In such cases, alternative methods of documenting both assent and consent, such as voice or video records, drawing pictures, or making a note in children's health records, should be employed.
66. We recognise that the approach to consent and assent advocated in this chapter represents a significant shift in current practice, in emphasising how context-specific and child-specific these processes need to be. Such an approach imposes additional challenges both for researchers, and for those responsible for the scrutiny of research proposals. Practical guidance on realising these aims in practice will be needed.

Recommendation 15

We recommend that research funders encourage or commission good quality research proposals exploring how the approaches to consent and assent put forward in this report might best operate in practice. Such research would provide a secure foundation for future good practice guidelines, tools and resources that are sensitive to a range of contexts.

Responsibilities to children and parents together: challenges in shared decision-making

67. Parents take very different views on how their children should be involved in decision-making. We suggest that the starting point for professionals should always be one of *respect* for the parent's role in determining how, and at what speed, their child develops towards being an independent decision-maker. When approaching children and young people about the prospect of research participation, professionals must therefore be sensitive to the very variable forms of family dynamic that may be in play. However, this respect for individual parental approaches must run alongside and, where necessary, be constrained, by professionals' own direct responsibilities to children and young people: to respect them as individuals and to have regard for their welfare. **While professionals should respect parents' views with respect to their child's participation in decisions about research, parental preferences cannot act to cancel out professionals' own responsibilities. While parental consent renders their child's participation in research legally permissible, it does not make it mandatory, thus leaving an important area for professional discretion and judgment** (paragraph 6.19).

68. Where disagreement about research participation arises within families, it is the professional's responsibility to engage with both parents and children, with the aim of negotiating an acceptable solution that is respectful of all parties. Young children's wishes cannot always be determinative, particularly where researchers and parents reasonably believe that they might obtain significant benefit from participation, and it may well be appropriate to persuade or cajole them. However, professionals' own responsibilities towards children, and in particular the importance of creating a trusting relationship with them, place strict limitations on how far they should proceed in the absence of consensus.
69. **Where children (even young children with limited understanding of what is proposed) explicitly and consistently dissent, there will generally be both ethical and practical reasons why it would be right for professionals to accept that dissent, despite parental willingness to proceed. The more children are able to understand what is involved in a research proposal, the greater the justification needed to act against their clearly expressed wishes. The multiple factors in play in such cases, however, make simple 'yes' or 'no' answers as to how professionals should approach these difficult decisions impossible to offer** (paragraph 6.24). Rather, they reinforce the fundamental importance of reflexive professional practice, directed towards the creation and sustaining of open trusting relationships with children, young people, and their parents.
70. **Similar issues may arise where children or young people in Case Three wish to participate in a research study, but their parents do not agree. In such cases, professionals have an important role in seeking to inform and encourage parents. However, if these attempts prove unsuccessful, then in most cases participation in research should not go ahead** (paragraph 6.25). Even in countries where the law recognises coexisting powers of children/young people and their parents to consent (hence providing for a legally effective consent from a minor), professionals must take into account the position of children and young people within their families, and cannot simply ignore the realities of family hierarchies and the consequences for those involved of overriding them.
71. Questions of professional judgment may become particularly acute in circumstances where professionals have dual roles, both as researchers, and as clinicians providing care to children and young people who might potentially participate in their studies. In such cases, professionals must ensure that their own legitimate interests in the success of their research are not permitted to compromise the interests of children and young people under their care.

Recommendation 16

We recommend that, where a protocol indicates that children and young people may be recruited by a health professional responsible for their care, research ethics committees should explore with researchers the justification for this approach. Where such recruitment procedures are appropriate, research ethics committees may wish to assure themselves that there are support arrangements in place, such as access to another member of the research team to whom families can turn for additional information if they wish.

72. As we note in Chapter 1, innovative or experimental treatments may, occasionally, be provided outside the context of research (see paragraph ¶1.6). We take the view that,

wherever possible, novel therapies of any kind should be subject to properly evaluated research. Where, exceptionally, novel treatment outside the context of research is appropriate (for example, in some cases of ‘compassionate use’) it should be regarded as a professional obligation of the health professional concerned to ensure that information about the outcome of treatment and the clinical course of the patient’s condition is collected and made publicly available, for example through a registry or publication.

Recommendation 17

We recommend that the Royal College of Paediatrics and Child Health takes the lead with other Royal Colleges and relevant professional bodies in exploring how best to ensure that information as to the outcomes of ‘innovative’ or ‘experimental’ treatment given to children or young people outside the context of research is properly documented and made available to others concerned.

Responsibilities in the absence of parents

Temporary absence

73. Temporary absence of parents may arise either in the form of actual physical absence, or of ‘situational incapacity’ where parents are present but too shocked or distressed to make a decision. In such cases, professionals’ responsibilities towards children and young people take on an added importance, as they will be exercising these responsibilities alone rather than in support of parents’ decision-making role. If research decisions can reasonably be delayed until a parent is present and able to make a decision, clearly there is no justification for proceeding in their absence. However, there will always be some health-related situations linked, for example, with emergency care for children and young people, where the question of enrolling a child or young person in research without the support of their parent will arise. In such cases, the role of the REC in scrutinising the risks, burdens and benefits of the research will take on added importance.
74. Where a study involving emergency research in the absence of parental consent is approved by a REC, it will be critical to inform and involve parents as soon possible after the research begins. **This process should not be understood as ‘deferred’ or ‘retrospective’ consent, but rather, first, as the provision of information about what has happened, and then as an invitation to consent for future procedures (where appropriate) and for the use of any data gathered as a result of the earlier procedures** (paragraph 6.35). Similarly, where children and young people were in Case One at the time the research began because they were unconscious or in too much pain or distress, they should be invited to engage in discussion and participate in future decision-making as soon as they have recovered sufficiently to do so. Where children and young people were in Case Two at the time a decision to participate in emergency research was required, then all means (appropriate to the urgency of the situation) should be used to encourage them to participate in the decision. Unless there are very strong welfare reasons to the contrary, any hesitancy on the part of children or young people to participate should be respected. If young people are in Case Three, then their own decision to consent or refuse should similarly be respected.

Permanent absence

75. Some children may simply not have parents to support them at all. This may arise more often in low income countries, where a high number of children may be orphaned, living either in child-headed households or on the periphery of wider family groups without the regular support of a meaningful parent-child relationship. However, issues may also arise in high income countries in circumstances where teenagers live away from their immediate family as a result of relationship breakdowns, or where parental responsibility is exercised through institutional means: for example, where a local authority has parental responsibility for children and young people in care.
76. In the UK context, although the difficulties involved in seeking consent where parental responsibility is held at institutional level should not be underestimated, there will still always be *someone* who has the authority to give consent for looked-after children and young people (those in the care of the local authority) to take part in research. Work by the former Medicines for Children Research Network (MCRN) has demonstrated the crucial role played by individual research professionals in facilitating access to research for children in this situation; and also the importance of developing good working relationships with local social service departments, and raising their awareness of the potential value of such research participation.

Recommendation 18

We recommend that the UK children's research networks (Clinical Research Network: Children and the Scottish Children's Research Network) work with the Children and Family Court Advisory and Support Service (Cafcass) to develop good practice guidance for social services departments and researchers to facilitate the opportunities for looked-after children and young people to participate in research.

77. While consent from a person (or organisation) with parental authority will always be necessary for children in Case one or Case Two, somewhat different issues arise in the context of children and young people in Case Three. Where researchers have reason to believe that those eligible for their study may include looked-after young people, and the burden and risk of the research is low, RECs could be asked to consider whether exceptions to the need for parental consent could be agreed.
78. In low income countries, however, it may often be the case that there is no one at all who is able to give or withhold consent on behalf of a child without parents. Where professionals have reason to believe that participation in research includes the prospect of direct benefit for children and young people, then there may be good welfare reasons why they should attempt to facilitate their access to research that has been judged to be both of value and a 'fair offer'. Judgments like these, however, require confidence and reflexivity on the part both of the researchers responsible for the study, and the REC members responsible for scrutinising it. Local stakeholder involvement will play an important role in helping RECs to determine whether research in these circumstances does indeed constitute a 'fair offer' for these children and young people. The challenges faced by professionals in these circumstances highlight the critical importance both of researchers' access to training in ethical considerations and of capacity building for RECs. Where it can be foreseen at the planning stage that children without parental support are likely to be eligible to participate, additional protections, such as an independent advocate able to witness the recruitment process, could be considered.

79. For young people in Case Three, in the absence of any adults who are able to give a legally effective consent, the young person's own consent, or decision not to participate, should be determinative. In making a judgment as to whether children or young people have this degree of maturity, researchers may legitimately take into account the degree of control and responsibility that children or young people are used to exercising in other areas of their life. However, in so doing it is critical to take into account whether children or young people really are able to take on this responsibility without finding it an undue burden. The role of professional discretion is crucial in ensuring that children and young people are not inappropriately excluded from worthwhile research, while avoiding burdening an already over-burdened child.

Points to consider when carrying out clinical research with children and young people

- Have you involved children, young people and parents in the development of your study?
 - In the design of the study itself? (e.g. the number of appointments or interventions required)
 - In the development of easy-to-understand information about the study?
- Does your study represent a fair offer to prospective participants? Are you confident that the value of the study, and its likely risks, burdens and benefits, have been carefully weighed up from the perspective of potential participants? Have children, young people and parents been involved in identifying possible benefits, risks and burdens?
- Is expertise in a particular area of children's healthcare important in order for the REC to understand the approach taken in this study? Has this been communicated to the REC, so that it is well placed to obtain advice if necessary?
- Are you able to demonstrate how you will communicate, and discuss, information about the study appropriately and sensitively with potential participants and their parents, so that they are able to make free and informed choices about whether to take part? Does everyone in your team who will be interacting with children, young people and parents have the necessary communication skills?
- Good assent practice is about the *process* of involving children and young people meaningfully in decisions about research. Are the particular methods you have chosen for involving children and young people in decisions about taking part the most appropriate ones?
- Children and young people who have the capacity and maturity to make their own decision about your study should be invited to give consent (not assent), even if the law additionally requires parental consent. Does your consent process and documentation allow for this?
- Decisions about research participation should, wherever possible, represent a shared decision between parents and children/young people. How will you encourage shared decision-making?
- Is the subject matter of your research such that it may be appropriate or necessary to recruit children and young people *without* the involvement of their parents? If so, can you justify the approach you have chosen?
- What arrangements have you made to support children and young people who do not have a parent, or another adult exercising a parental role, so that they are not excluded from your study?
- Will clinicians be responsible for recruiting children and young people, for whom they are providing care, to take part in research? If so, is this the most appropriate approach? Have you considered alternative approaches?
- Does the information provided for children, young people and parents explain how and when they can find out about the outcomes of the research? Will those outcomes also be explained in accessible language?

Chapter 7

80. In a brief concluding chapter, we return to the question at the heart of our terms of reference: that of determining how a proper balance is to be achieved between the benefits that clinical research may bring, the involvement of children and young people, and the protection of research participants. Drawing together the conceptual conclusions and recommendations that have emerged from our analysis, we argue that a critical feature of ethically robust research in which this balance is achieved lies in the recognition of children, young people and parents as genuine partners with professionals in the whole research endeavour. Clinical research must always be *with* children and young people, not 'on' them: they are not mere passive subjects but rather active participants in a joint enterprise of research. Such an approach casts a whole different light on how we understand the notion of the vulnerability of children and young people in research, and on how the potential for such vulnerability can be minimised through active participation of children, young people and parents in the prioritisation, design and scrutiny of studies.
81. Such partnerships complement, but do not replace, the responsibilities of professionals, whose practice should be guided by the professional virtues of trustworthiness, openness and courage, and who remain ultimately responsible for ensuring the proper protection of research participants. A third feature of ethically-robust research rests in its recognition of the diversity of both childhood experience, and the context in which research takes place, and the demands this diversity places on reflexive professional practice.
82. Finally, we note the commitment to evidence-based care that will be required in order to reach the point where clinical research is genuinely seen as a core 'everyday' part of health service provision. Substantial commitment will also be required on the part of policy-makers to increase knowledge of research among the general public.

Recommendation 19

We recommend that the All Party Parliamentary Group on Medical Research should take the lead in exploring ways of increasing general public awareness of clinical research in general, and of the benefits of such research for children's and young people's health and healthcare.

83. We thus conclude our report by highlighting the central importance of further work exploring the most effective methods of increasing knowledge and awareness of research, and the means of implementing them. For research to become part of the 'core business' of the NHS and other health services, it is important that we see an increasingly positive attitude towards research among potential participants and health professionals, together with confidence in the ethical robustness of that research.

Introduction

What is this report about?

In this report, we tackle an issue that has represented a major challenge for those concerned with the health and healthcare of children and young people: how can we ethically undertake the research needed to ensure their healthcare services are safe and effective, given that research often involves burdens and risks? On the one hand, everyone wants to be confident that health services provided to children and young people are soundly based on good evidence, while on the other, adults hesitate to ask too much of them, particularly when they are unwell. However, the evidence needed to make children's healthcare both safer and more effective depends critically on research involving children and young people themselves: children are not simply 'small adults'; and evidence obtained through clinical research with adults can never be enough on its own.

There are widely-shared anxieties about the ethical acceptability of involving children and young people in clinical research. Procedures undertaken for research purpose are, by definition, designed to produce information to benefit future patients or users of health services. They are not undertaken with the direct aim of benefitting the research participant, although in some forms of research, participants may additionally hope to benefit themselves. While it is widely accepted that adults may legitimately choose for themselves whether or not to take on the burdens, and sometimes risks, involved in clinical research studies, a more protective approach is taken towards children and young people. As a result, in an era where evidence-based care is held up as an ideal, the evidence base for care offered to children and young people falls well behind that for adults. Action is clearly needed to explore and elucidate these ethical questions.

The central ethical challenge in carrying out clinical research with children and young people might, at first sight, be presented as how best to balance two competing threats to their welfare: on the one hand from the risks and burdens of research, and on the other from the risks inherent in treatments or services for which there is an inadequate evidence base. However, there is a crucial third factor to add to this equation. **What role do children and young people have in all this? How should their voices, and the voices of their parents, be heard?** The question of how children, young people and their parents can influence and help shape the whole research agenda, from the initial choice of research topic and the design of a study, through to their own role in deciding whether or not to take part, is a central theme throughout this report. In brief, we argue that it is only *through* this involvement, through respecting children and young people as valued partners in a joint endeavour of research, that a proper balance between the risks and benefits of carrying out research can be found.

How did we go about it?

The Nuffield Council set up an expert Working Party in June 2013 to explore these issues, and at its first meeting the Working Party agreed to establish a stakeholder group of young people and parents to act as a sounding board throughout the project. The Working Party was also keen to build on the Council's usual consultative methods to ensure that as wide a range of voices as possible could be heard. The project began with a meeting at which young people, parents and professionals were invited to help frame the project by identifying the issues they saw as most ethically challenging within current governance arrangements for research with children and young people. These discussions then shaped a much wider

call for evidence, including online surveys for young people and parents, and a consultation targeted at professionals concerned with research. With the help of the stakeholder group and academic collaborators, we developed and filmed workshops with children and young people aged from ten to 18 in three Brighton schools, exploring the ethical implications of a mock asthma study, and the role of the research ethics committee. We also used a 'chocolate trial' to explain research methods to 60 primary school children, aged between eight and nine, in South West London, and explored their reactions to the idea of being invited to take part in a mock study on the common cold.

We then broadened out our geographical field of enquiry and with the assistance of members of the Working Party based in Kenya (see below) we were able to draw on the views of school children and community representatives in Kilifi, Kenya. A number of professionals working in low and middle income settings responded to the initial open call for evidence, and we were subsequently able to increase input from this important group through the help of the Global Health Reviewers Network and the Global Health Bioethics Network. In parallel to this series of consultative activities, the Working Party reviewed the published literature (primarily, but not exclusively, focused on the UK perspective), and held a number of 'factfinding' discussion meetings with academics and practitioners, based around themes such as the responsibilities of researchers, and the role of ethical review. Finally, the Working Party presented its emerging thinking to a 'stakeholder conference' of young people and parents in April 2014. Further details of all these activities are set out in the appendices to this report.

What the Working Party heard, read, and saw through these various engagement, consultative, and evidence-gathering activities has been critical to the project. We emphasise that we do not see the responses to our own consultative activities as equivalent to the data that might be obtained through carefully structured quantitative or qualitative research studies. In particular we are alert to the dangers of assuming that 'most' or 'many' young people, or researchers, or parents, hold particular views or behave in particular ways on the basis of those responses. Rather, like many other organisations involved in public engagement and public policy, we have tried to hear as many voices as possible, in order to be alert to the widest possible range of perspectives and insights. These are captured throughout our report in the quotations from our respondents, and have informed and challenged the Working Party's thinking. It is our hope that the range of methods that we have explored in this project will, in turn, be of use to those tasked daily with the practical challenges of involving children and young people in clinical research.¹

Defining our scope

When exploring a topic as potentially wide ranging as this, decisions have to be made about scope, and inevitably the lines drawn may at times seem somewhat arbitrary. In considering '**children and young people**', we have defined our focus as being on children from birth up to the age of 18, while recognising that both these boundary lines are porous. Babies may be recruited into research studies during their mothers' antenatal care, and young people's experiences in a research study do not change overnight on their 18th birthday. The law, on the other hand, makes very clear dividing lines between a foetus and a child once born, and a young person just before and just after the age of majority. In setting the scope of this report, we have taken these legal divisions as our starting point.

¹ For further discussion of methods of public involvement, see PiiAF Study Group (2014) *The public involvement impact assessment framework guidance*, available at: <http://www.piiaf.org.uk/documents/piiaf-guidance-jan14.pdf>, pp20-1; ScienceWise (2014) *The best of Sciencewise reflections on public dialogue*, available at: <http://www.sciencewise-erc.org.uk/cms/assets/Uploads/Best-ofFINAL.pdf>.

We have interpreted what constitutes ‘**clinical**’ **research** broadly, as covering any form of research encounter with children and young people that holds out the prospect of improving healthcare, including preventative healthcare, in the future. Thus, our scope includes, for example: vaccine research conducted in children’s own homes; interview-based research on risky healthy behaviours; qualitative research on children’s and young people’s experiences of using particular health services; research seeking to improve understanding of normal child development; and research exploring the safety and effectiveness of all forms of new interventions, such as medicines, surgical procedures or psychological therapies. The common threads in our broad interpretation of clinical research are the direct nature of the encounter between children, young people, parents and researchers (by contrast, for example, with routine notes-based research), and the link, or prospective link, with the clinical environment. We are, of course, aware of the many factors affecting children and young people’s physical and mental health and well-being that fall entirely outside that clinical environment, encompassing factors such as poverty, poor housing, poor diet, and dangerous physical environments. Such factors play a critical role in the life and health chances of many children, but they fall outside the scope of this particular inquiry. We have also touched only in passing on issues that specifically relate to the use of data or human tissue in research, which are substantial topics of inquiry in their own right.

When considering the project’s **geographical scope**, the Working Party was very keen to extend beyond a narrow focus on research in the UK. Research with children and young people relies even more heavily than other forms of research on international collaboration, because of the relative rarity of many childhood conditions. Moreover, UK-based funders, and researchers based in UK institutions, continue to play an important part in research in many low income countries, particularly with respect to diseases that are major contributors to childhood mortality. Yet we had to be realistic as to how widely we could extend our evidence-gathering. For practical reasons, our detailed analysis of both the law and the daily practice of research involving children and young people had to focus primarily around the position in the UK, albeit in the context of EU-wide regulation. At the same time, we were anxious not to fall into the trap of seeing the issues only from a western cultural perspective, in the context of a high income country with a well-established research infrastructure.

We were very fortunate in being able to include within our Working Party membership two researchers working in a major research site in Kenya, with an impressive track record in community engagement. These members enabled us to hear, in some depth, lay perspectives on research and research involvement from both children and young people, and parents living in very different circumstances, and with very different cultural traditions, from those from whom we heard in the UK. Through our online call for evidence, disseminated both through the Council’s own website and through international research networks, we were also able to hear from researchers working across Africa, in South East Asia, in Latin America, and in the United States.

Clearly, neither the engagement work in Kenya, nor the professional responses from researchers working in a number of low and middle income settings should be understood as providing a single or definitive ‘low income country’ or ‘non-UK’ perspective. However, just as the range of voices contributing within the UK alerted us to the widest possible range of attitudes and experiences, these inputs gave us additional insights into how the challenges involved in researching with children and young people might differ according to setting. They also indicated aspects of research with children and young people where there seemed to be substantial areas of consensus, regardless of geographical, economic, or cultural diversity.

Our aim in this report is to offer an *analysis* of the ethical issues arising in the context of clinical research with children and young people, culminating in a number of *conceptual recommendations* that will have resonance and value well beyond the UK. The specific *concrete recommendations* that follow, suggesting how our conceptual analysis might have practical consequences for professionals' practice are, by contrast, primarily focused at a UK audience. We hope that our analysis will, in due course, provide a useful starting point for others to debate and explore practical ramifications for clinical research with children and young people in their own settings.

Finally, in terms of scope, we have tried very hard to keep our focus on those ethical issues in clinical research that arise particularly in the context of research with children and young people, rather than straying into areas of 'general' research ethics. Our working approach has been to ground our analysis on what is special or distinctive about children and young people, and to build up from this an understanding of what forms of research governance are required in response. Such an approach contrasts with historical approaches to research governance, which have started from the paradigm case of 'competent' adults, and then added on further generic layers of protection for groups, such as children and young people, who are perceived as more vulnerable. Of course, in looking at what is distinctive about childhood, we also find what is shared between people of all ages: not least our common humanity, recognised and protected through the language of human rights and respect for individuals. It is therefore unsurprising that, at times, the issues that we identify as central in the ethical conduct of research with children and young people are common to all human participants.

A guide to this report

This report is aimed at many different audiences, and readers will of course approach it with diverse interests and expertise. The detailed Summary and Conclusions bring together the substantive arguments developed throughout the report, with cross-references to enable readers to jump to points of particular interest, while each chapter begins with a summary box highlighting the main points covered in that chapter and the analysis and conclusions it contains. The analysis and recommendations have also been produced in a range of different formats, including magazine-style and animated film versions for children and young people. The structure of this overarching document, which brings together all the Working Party's evidence-gathering and thinking in one place, is as follows:

- **Chapter 1** sets out the ethos of the report, providing an introduction to the main issues, as identified by the Working Party, and presenting the fundamental attitudes to research and to children and young people that have underpinned the Working Party's approach throughout its work.
- **Chapter 2** is a background chapter, giving an overview of the empirical evidence of children's, young people's, and parents' experiences of clinical research at the point of potential recruitment to a study (in practice, the first point at which most children, young people and parents will be confronted with research questions). This is followed by a summary of the regulatory approaches that govern this recruitment process.
- **Chapter 3** provides further background, stepping back chronologically from the moment of recruitment to research to consider all the factors that influence research up to that point: in the initial prioritisation of research topics; in the process of study design; and in the scientific and ethical review procedures that are designed to act as safeguards in the development of research protocols.

- **Chapter 4** provides the heart of the report, developing the Working Party's ethical analysis which is rooted in consideration of the position of children and young people within their families, and the responsibilities of their parents towards them in the context of decision-making about research. Its central concern is to articulate the circumstances in which children and young people may ethically participate in research, suggesting a new approach to concepts such as the 'best' interests of a child, and the presumed vulnerability of children and young people in research.
- **Chapter 5** draws on the analysis in Chapter 4 to explore the professional responsibilities of those engaged in shaping the research agenda: in determining the priority given (or not given) to particular research areas; in developing study design; and through the processes of scientific and ethical scrutiny. It should be read as a companion chapter to Chapter 3, applying the Working Party's ethical analysis to the background material presented earlier, in order to make recommendations within the UK/EU context.
- **Chapter 6** then returns to the professional encounter between researchers and children/young people and their families in a research study, exploring the implications of our ethical analysis in Chapter 4 for practitioners at the point of recruitment. It makes a number of practical recommendations, targeted primarily at a UK audience, but with potential resonance further afield.
- **Chapter 7** is a short concluding chapter, drawing together the main threads and conceptual recommendations of the report.

Chapter 1

Context and ethos

Chapter 1 – Context and ethos

Chapter 1: overview

The significance of context: in considering how clinical research involving children and young people may ethically take place, we start from a consideration of the *context* in which research takes place, and the many variables that may affect the ethical and social acceptability of proposed research studies. These variables include:

- The nature and context of the research itself: ‘clinical research’ covers a wide range of potential research activity, with widely differing potential burdens and benefits for participants. The context in which it takes place creates different ethical challenges.
- The context of particular children and their families: just as references to ‘children’ mask variations in age from newborn babies to young people on the verge of adulthood, different children within those age groups have different experiences and roles with respect to decision-making. These may be influenced by factors such as gender, family size and form, parenting style, health status, social and economic situation, intellectual ability, and educational opportunity. Where children are ill, the nature and severity of that illness may be a particularly important contextual factor.
- The context of the wider social and political environment in which children and young people are being invited to take part in research, such as the domestic governance of research, access to healthcare, and dominant social attitudes to the notion of research, to parenting, to health professionals, and to risk.

Ethos of this report: some fundamental attitudes, both to research, and to children, have underpinned the Working Party’s approach throughout its work:

- Scientifically valid and ethically robust research, that addresses questions of importance to the health of children and young people, should be seen as intrinsically good, and as a natural and necessary part of a healthcare system. It should not be perceived as a threat to children, as something to be apologised for, nor indeed as anything unusual. Without well-conducted research, there is no prospect of improving healthcare for children now or in the future, and there is a real risk that children will be harmed by procedures and medicines that are ill-adapted for their age group or lacking an adequate evidence base. Such an approach is certainly not a blanket prescription of ‘research at all costs’ – but rather a challenge to the complacent notion that it is safe or ethical to continue providing care to children without seeking to improve the evidence on which that care is based.
- We base our work on an understanding of children as people who, in the context of their own family and social environments, have the potential from an early age to play an active role in determining their own lives and in engaging with others. Such an approach, which is commonplace in thinking about the role of children in many other areas of life, stands in stark contrast to many of the implicit assumptions of research governance which tend to emphasise vulnerability and lack of competence.

Much has already been written as to what constitutes ‘ethical practice’ in clinical research – but generally from the starting point of research with competent adult participants. In this report, by contrast, we aim to start with a consideration of children and young people, and of their lived experiences of participation in research. We then use this understanding to reflect critically upon specifically child-related issues arising in clinical research, including assumptions of childhood vulnerabilities, the role of children themselves in decision-making, and the role of parents and others in promoting children’s welfare.

Introduction

- 1.1 Clinical research involving children and young people, from newborn babies to adolescents, has traditionally been seen as fraught with both ethical and practical challenges. Children are generally perceived as 'vulnerable', and hence in need of special protections to ensure that they are not exploited in research.² Both professionals involved in research and parents may feel uneasy about asking children and young people to accept the inconvenience, discomfort, burdens, and risks that may be associated with research procedures, especially where these are unfamiliar, not well adapted to children's needs, or invasive.³ Such anxieties may be particularly acute with respect to research involving babies.⁴ In the case of research relating to new medicines, additional concerns arise as to the potential effects of the medicine being tested on growing or developing organs.⁵ The pharmaceutical industry has, in the past, shown reluctance to study medicines in children, arguing that these ethical and practical challenges make it difficult to organise clinical trials involving children and that there are limited financial returns from what is often a comparatively small market.⁶
- 1.2 Yet clinical research involving children, from babies to adolescents, is essential if we are to improve our understanding of childhood diseases and conditions, and provide care for children and young people based on the best possible evidence (see Boxes 1.1–1.3). There is little public awareness that many medicines given to children have not in fact been tested in children, and hence the evidence available as to how children may respond to them, and the most appropriate dosage, is necessarily limited.⁷ 'Standard' care procedures may turn out, when compared with alternatives in a properly-conducted study, to be far from optimal, and even harmful.⁸ The lack of a good

² See, for example, The European Parliament and the Council of the European Union (2001) *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>; World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>.

³ Medical Research Council (2004) *MRC ethics guide: medical research involving children*, available at: <http://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/>, pp9-10.

⁴ Ward RM, and Kern SE (2009) Clinical trials in neonates: a therapeutic imperative *Clinical Pharmacology & Therapeutics* **86(6)**: 585-7.

⁵ Choonara I, and Sammons H (2014) Paediatric clinical pharmacology in the UK *Archives of Disease in Childhood*: Published online first (8 September 2014).

⁶ Choonara I (2000) Clinical trials of medicines in children *BMJ* **321(7269)**: 1093-4; Conroy S, McIntyre J, Choonara I, and Stephenson T (2000) Drug trials in children: problems and the way forward *British Journal of Clinical Pharmacology* **49(2)**: 93-7.

⁷ See, for example, Conroy S, McIntyre J, and Choonara I (1999) Unlicensed and off label drug use in neonates *Archives of Disease in Childhood-Fetal and Neonatal Edition* **80(2)**: F142-F5; Mukattash T, Millership J, Collier P, and McElnay J (2008) Public awareness and views on unlicensed use of medicines in children *British Journal of Clinical Pharmacology* **66(6)**: 838-45 (which found that 86 per cent of the 1,000 participants in the study had no knowledge of the use of unlicensed use of medicines in children; once informed, 62 per cent were concerned). Mukattash and colleagues also explored children's own perceptions of unlicensed use: Mukattash T, Trew K, Hawwa AF, and McElnay JC (2012) Children's views on unlicensed/off-label paediatric prescribing and paediatric clinical trials *European Journal of Clinical Pharmacology* **68(2)**: 141-8. A UK-based study on prescribing trends for children with acute lymphoblastic leukaemia (ALL) indicated that 55 per cent of prescriptions were licensed, 19 per cent were unlicensed, and 26 per cent were licensed drugs used off-label. See: Conroy S, Newman C, and Gudka S (2003) Unlicensed and off label drug use in acute lymphoblastic leukaemia and other malignancies in children *Annals of Oncology* **14(1)**: 42-7. More generally, see: Pandolfini C, and Bonati M (2005) A literature review on off-label drug use in children *European Journal of Pediatrics* **164(9)**: 552-8.

⁸ See, for example, the *Fluid expansion as supportive therapy* (FEAST) trial: Maitland K, Kiguli S, Opoka RO *et al.* (2011) Mortality after fluid bolus in African children with severe infection *New England Journal of Medicine* **364(26)**: 2483-95; Russell FM, Shann F, Curtis N, and Mulholland K (2003) Evidence on the use of paracetamol in febrile children *Bulletin of the World Health Organization* **81(5)**: 367-72; Watterberg KL (2010) Policy statement: postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia *Pediatrics* **126(4)**: 800-8. See also: Testing Treatments (13 May 2014) *Routine use of*

evidence base for much of the routine care provided for children highlights how there is no easy divide between 'standard' care, and care that is provided in the context of a research study. Indeed, it has been argued that, in practice, much routine care provided to children and young people is the equivalent of a research study with just one participant: the patient is exposed to all the risks of unproven care but with none of the protections offered through research governance.⁹ Moreover unproven care provided in such circumstances offers no contribution to evidence-based care in the future.

- 1.3 There is clearly a strong ethical imperative to ensure that the evidence base on which care for children and young people is based is as sound as possible. The aim of this report is to explore and elucidate the ethical concerns about the participation of children and young people in clinical research, to help obtain a clearer understanding of where these should, or should not, act as a barrier to research.

Box 1.1: Progress through research: the case of leukaemia¹⁰

The development of treatment for children who have leukaemia has been lauded as a particular success story for clinical research. The most recent statistics (2001-5) for the ten-year survival rates of children (0-14 years) in Great Britain who have leukaemia are at 81 per cent, compared with 27 per cent for 1971-5 (the oldest figures published by Cancer Research UK).

Early 'experimentation' in the US in the 1940s using folic acid antagonists resulted in improvement for some children with leukaemia, although at terrible cost in side effects which led to strong resistance from junior doctors caring for children on oncology wards. Significant progress was first made in the 1950s through the creation in the US of the first cooperative research group, bringing together patients from different hospitals in sufficient numbers for clinical trials. The 1960s brought about the use of chemotherapy using multiple elements, which improved survival rates significantly, and the 1970s and 80s brought further progress with the introduction of bone marrow transplants, and brain and spinal column radiation (craniospinal radiation). The 1970s also saw the establishment of the national trials for ALL (acute lymphoblastic leukaemia) in the UK (UKALL trials) which were open for every child diagnosed with ALL to participate in, and also increased sharing of expertise between US and UK researchers, for example through US training fellowships for paediatric oncology advertised in the UK press.

By the beginning of the 1980s, 80 per cent of all UK children with a diagnosis of ALL were being recruited into UKALL trials. The UK was, however, still seen as 'lagging behind' the progress achieved in the US: children were dying from infections such as pneumocystis during remission because the UK lacked the intensive support infrastructures available in US centres. By 1980, co-trimoxazole (an antibiotic) was administered as a way of preventing pneumocystis among children with ALL, and by the late 80s, five-year survival rates for children with leukaemia in the UK reached 68 per cent.

In the 1990s, studies examined environmental factors that may cause leukaemia in children. Researchers also identified the difference between ALL (a distinct disease in children) and acute myeloid leukaemia or AML (a very similar disease in adults and

unvalidated therapy is less defensible than careful research to assess the effects of those treatments, available at: <http://www.testingtreatments.org/2014/05/13/non-validated-therapy-often-dangerous-careful-research/>.

⁹ The equivalent of "conducting thousands of studies with an N=1": Ward RM, and Kern SE (2009) Clinical trials in neonates: a therapeutic imperative *Clinical Pharmacology & Therapeutics* **86(6)**: 585-7, at page 586.

¹⁰ See Appendix 1 for a detailed account of the history of leukaemia research, including the references from which this summary is drawn. See also: Wishart A (2006) *One in three: a son's journey into the history of science and cancer* (London: Profile Books).

children). Developments such as these are marked by a rise in the five-year survival rate to 75 per cent in the early 1990s, and 79 per cent in the late 1990s. Research continues into new chemotherapy drugs, resistance to chemotherapy, and stem cell transplants.

Box 1.2: Progress through research: family-based approaches to anorexia nervosa

Anorexia nervosa is a mental health disorder characterised by distorted body image and deliberately maintained low body weight. It is most commonly observed in adolescents.¹¹

Treatment for anorexia nervosa first emerged in the late 1960s, and took the form of inpatient treatment programmes with a focus predominantly on individual psychological therapy.¹² In the mid-1970s, however, this individual approach to therapy was questioned, and the prospect of introducing family-based treatment (FBT) as a means of treating anorexia nervosa was introduced. FBT attempts to change concessions that families may make when feeding their child, so that behaviours associated with eating are not sustained and do not become maladaptive.¹³

Research undertaken in the late 1980s at the Maudsley Hospital in London indicated that FBT had better outcomes than using an individual-based therapeutic approach, in which former inpatients attended therapy sessions on their own once they had been discharged.¹⁴ Since then, FBT has gradually been established as a valued therapeutic response to adolescents with anorexia nervosa. It is the treatment with the most evidence supporting its use,¹⁵ and is recommended by the National Institute for Health and Care Excellence (NICE).¹⁶

Box 1.3: Progress through research: malaria bed nets

Malaria has historically been one of the major global causes of death in young children, particularly in Africa. Towards the end of the last century it was estimated that between one and two million children under the age of five in Africa died each year as a result of malaria. In the mid-1980s, several small studies suggested that bed nets impregnated with insecticide might protect children from malaria. However, results varied from study to study and the true potential only became apparent following a series of large scale studies in The Gambia,¹⁷ Kenya,¹⁸ Burkina Faso,¹⁹ and Ghana.²⁰ These studies required

¹¹ Fisher C, Hetrick S, and Rushford N (2010) Family therapy for anorexia nervosa *Cochrane Database of Systematic Reviews* 4: CD004780; Micali N, Hagberg KW, Petersen I, and Treasure JL (2013) The incidence of eating disorders in the UK in 2000–2009: findings from the General Practice Research Database *BMJ Open* 3(5).

¹² See, for example, Warren W (1968) A study of anorexia nervosa in young girls *The Journal of Child Psychology and Psychiatry* 9(1): 27–40; Seinhausen H-C (2002) The outcome of anorexia nervosa in the 20th century *The American Journal of Psychiatry* 159(8): 1284–93.

¹³ Minuchin S, Baker L, Rosman BL *et al.* (1975) A conceptual model of psychosomatic illness in children: family organization and family therapy *Archives of General Psychiatry* 32(8): 1031–8; Lock J (2010) Treatment of adolescent eating disorders: progress and challenges *Minerva Psichiatrica* 51(3): 207–16, at page 209.

¹⁴ Russell GM, Szmulker GI, Dare C, and Eisler, II (1987) An evaluation of family therapy in anorexia nervosa and bulimia nervosa *Archives of General Psychiatry* 44(12): 1047–56.

¹⁵ Le Grange D (2005) The Maudsley family-based treatment for adolescent anorexia nervosa *World Psychiatry* 4(3): 142–6, at page 145; Lock (2010) Treatment of adolescent eating disorders: progress and challenges *Minerva Psichiatrica* 51(3): 201–16.

¹⁶ National Institute for Health and Care Excellence (2004) *Eating disorders: core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders*, available at: <http://www.nice.org.uk/guidance/cg9/chapter/guidance#anorexia-nervosa>, at 1.2.2.13.

¹⁷ D'Alessandro U, Olaleye B, Langerock P *et al.* (1995) Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme *The Lancet* 345(8948): 479–83.

¹⁸ Nevill CG, Some ES, Mung'ala VO *et al.* (1996) Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast *Tropical Medicine & International Health* 1(2): 139–46.

relatively intensive follow-up of tens of thousands of children in rural communities, including surveillance for disease and repeated blood sampling.

As a result of these studies, it became clear that impregnated bed nets could reduce the incidence of malaria by up to half and reduce all causes of childhood mortality by approximately 20 per cent. In 1998, the international *Roll back malaria* partnership adopted the use of impregnated bed nets as a major pillar of malaria prevention. From the early 2000s, international expenditure on malaria control has increased more than tenfold, and malaria deaths in Africa have reduced by 54 per cent.²¹ In the period 2012-4 alone, over 400 million impregnated bed nets were distributed in Africa. Although it is difficult to attribute effects to single interventions, there is no doubt that in the last ten years, many childhood deaths from malaria have been averted as a result of this intervention which depended on large scale research studies involving children across a number of African countries.²²

The context of clinical research with children and young people

- 1.4 We start this report by noting the significance of the *context* in which research involving children and young people takes place, and the many variables that will affect the ethical and social acceptability of proposed research studies. These variables include the nature and context of the research itself, the context of the particular child or young person and their family, and the context of the wider social and political environment in which children or young people are being invited to take part in research. This diversity is an important part of the backdrop to any research encounter between researchers and children/young people and their families: each set of circumstances and relationships will be unique, and it cannot be assumed that a single set of rules or principles can be uniformly applied.

The nature and context of research

“The term clinical research can be ambiguous and be interpreted as ‘clinical trials’. Health-related research involving infants, children and young people is, however, much broader, encapsulating any research intended to enhance knowledge and understanding of a health-related topic with the overall aim of enhancing the well-being and experiences of health service users.”²³

¹⁹ Habluetzel A, Diallo DA, Esposito F *et al.* (1997) Do insecticide-treated curtains reduce all-cause child mortality in Burkina Faso? *Tropical Medicine & International Health* **2**(9): 855-62.

²⁰ Binka FN, Kubaje A, Adjuk M *et al.* (1996) Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial *Tropical Medicine & International Health* **1**(2): 147-54.

²¹ World Health Organization (2014) *World malaria report*, available at: http://www.who.int/malaria/publications/world_malaria_report_2014/en/.

²² UNICEF estimates that, since 2000, over 1.1 million lives (both adults and children) have been saved worldwide due to increased investment and improved strategy with malaria control: UNICEF (2013) *Invest in the future: defeat malaria - World Malaria Day 2013*, available at: http://data.unicef.org/corecode/uploads/document6/uploaded_pdfs/corecode/Malaria_brochure_2May2013_177.pdf.

²³ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

“Distinguishing research on the basis of risk may help... Risks to do with taking a new medication, for example, are very different to those involved in cognitive or play assessment.”²⁴

“In harsh economic times other private philanthropy is needed to fund research alongside government funding.”²⁵

1.5 There are differing interpretations of what kinds of research activity come under the umbrella term ‘clinical research’.²⁶ As we explain in our Introduction, the Working Party has chosen a relatively broad approach, including within its remit any health-related research with children and young people that has two particular characteristics. First, the research should involve direct interaction between participants and researchers; we are not here concerned with purely observational or routine notes-based research where those taking part, or their parents, may not perceive themselves as ‘participants’. Second, it should have some present or prospective link with the clinical environment, in that the aim of the research is to contribute to the future improvement of healthcare services, including preventive healthcare services, available to children and young people. We thus include within our scope both traditional medical research exploring the origins and causes of childhood disease along with means of prevention, diagnosis and treatment; and also social science research exploring children’s and young people’s own perceptions of their health and experiences of health service use.²⁷ Excluded are the broader, systemic, and environmental influences on health that fall outside the remit of healthcare services. Examples of forms of research that fall within the remit of this report include:

- Studies to explore the **links between particular kinds of health-related behaviour** (such as levels of exercise, or eating patterns) **and particular illnesses**: for example, longitudinal studies that follow the health and development of a cohort of children as they grow up.²⁸
- Research to improve **understanding of normal childhood development**, such as the use of cognitive tests or brain scans to increase understanding of how the brain

²⁴ Academy of Medical Sciences, responding to the Working Party’s call for evidence.

²⁵ Together for Short Lives and Association for Paediatric Palliative Medicine Joint Research Group, responding to the Working Party’s call for evidence.

²⁶ See, for example, National Institute of Child Health and Human Development (2014) *Clinical trials and clinical research*, available at: <https://www.nichd.nih.gov/health/clinicalresearch/Pages/index.aspx>; NHS Choices (2014) *Clinical trials and medical research - types of research*, available at: <http://www.nhs.uk/Conditions/Clinical-trials/Pages/Healthresearch.aspx>, where the primary focus is on the involvement of *people* as research participants, by contrast with earlier animal studies; and Australian Government: National Health and Medical Research Council (2014) *National statement on ethical conduct in human research (2007): chapter 3.3 - interventions and therapies, including clinical and non-clinical trials, and innovations*, available at: <https://www.nhmrc.gov.au/book/chapter-3-3-interventions-and-therapies-including-clinical-and-non-clinical-trials-and>.

²⁷ For a useful overview of clinical research involving children, see: National Institute for Health Research (2014) *Children*, available at: <http://www.crn.nihr.ac.uk/children/>. This network was created in April 2014 from the former ‘Medicines for Children Research Network’ and the Paediatric (non-medicines) Specialty Group, bringing together both medicines and non-medicines research for children in the UK into a single network.

²⁸ See, for example, the Avon Longitudinal Study of Parents and Children (ALSPAC), which recruited 14,000 pregnant women and followed up the health and development of their children as they grew up. Studies like these may involve actively providing information (for example filling in questionnaires about eating patterns) or providing bodily tissue or samples (such as locks of hair, saliva, or blood), as well as letting researchers have access to routine health records: University of Bristol (2015) *Avon Longitudinal Study of Parents and Children*, available at: <http://www.bristol.ac.uk/alspac/>.

develops, which may then inform understanding of conditions such as dyslexia or epilepsy.²⁹

- Research to improve **understanding of patterns of disease in children**: for example, comparing cohorts of well and unwell children to investigate different causes of childhood pneumonia in a particular population.³⁰
- Studies exploring the **prevalence of particular conditions or health-related behaviours**, in order to target health promotion or treatment services appropriately: for example, in relation to young people's mental well-being; use of alcohol, tobacco or illegal drugs; or sexual activity.³¹
- Clinical trials that aim to obtain information about **how a new treatment or intervention works in children and young people**, and how this might compare with existing interventions where these exist.³² Sometimes trials will take the particular form of a 'randomised controlled trial' (RCT), where allocation to the new or standard intervention will be made on a random basis. Trials might compare different kinds of vaccines,³³ medicines,³⁴ behavioural interventions,³⁵ diagnostic techniques,³⁶ surgical methods,³⁷ ways of preventing disease,³⁸ devices (including those which facilitate independent living³⁹),⁴⁰ or ways of delivering a particular healthcare service.⁴¹ Clinical trials of new medicines or vaccines are known as 'clinical trials of investigational medicinal products' (CTIMPs) and are subject to special regulation (see Box 1.4 overleaf). Clinical trials may also be used to

²⁹ See, for example, UCL Institute of Child Health (2015) *Developmental neurosciences programme*, available at: <http://www.ucl.ac.uk/ich/research/developmental-neurosciences>.

³⁰ Berkley JA, Munywoki P, Ngama M *et al.* (2010) Viral etiology of severe pneumonia among Kenyan infants and children *JAMA* **303**(20): 2051-7.

³¹ See, for example, Pope HG, Hudson JI, Yurgelun-Todd D, and Hudson MS (1984) Prevalence of anorexia nervosa and bulimia in three student populations *International Journal of Eating Disorders* **3**(3): 45-51; Centers for Disease Control and Prevention (2014) *Youth Risk Behavior Surveillance System*, available at: <http://www.cdc.gov/HealthyYouth/yrbs/index.htm>.

³² Clinical trials might indicate that standard treatments are more effective than those being tested. See, for example, National Institutes of Health (23 December 2014) *Longer cooling, lower temperature no improvement for infant oxygen deprivation*, available at: <http://www.nih.gov/news/health/dec2014/nichd-23.htm>.

³³ See, for example, research undertaken by the Oxford Vaccine Group: Oxford Vaccine Group (2015) *Research*, available at: <http://www.ovg.ox.ac.uk/research>.

³⁴ See, for example, Graudins A, Meek R, Egerton-Warburton D, Oakley E, and Seith R (2014) The PICHFORK (pain in children fentanyl or ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries *Annals of Emergency Medicine* **65**(3): 248-54.

³⁵ See, for example, Magiati I, Charman T, and Howlin P (2007) A two-year prospective follow-up study of community-based early intensive behavioural intervention and specialist nursery provision for children with autism spectrum disorders *Journal of Child Psychology and Psychiatry* **48**(8): 803-12.

³⁶ For example, Huang H, Ideh RC, Gitau E *et al.* (2014) Discovery and validation of biomarkers to guide clinical management of pneumonia in African children *Clinical Infectious Diseases* **58**(12): 1707-15, which suggests that molecular markers could be developed into a point-of-care diagnostic tool to target cases of pneumonia that require antibiotic treatment.

³⁷ Such as the OXIC-2 study, aiming to find the best method of giving oxygen to a cyanotic child during surgery: ISRCTN Registry (2008) *A randomised controlled trial to compare normoxic versus standard cardiopulmonary bypass in cyanotic children undergoing cardiac surgery*, available at: <http://www.isrctn.com/ISRCTN81773762>.

³⁸ For example, research trials summarised in Mayo-Wilson E, Imdad A, Herzer K, Yakoob MY, and Bhutta ZA (2011) Vitamin A supplements for preventing mortality, illness, and blindness in children aged under 5: systematic review and meta-analysis *BMJ* **343**: d5094.

³⁹ Such as a computer game that could help to improve the functional vision of children who are visually impaired as a result of brain injury: Medical News Today (3 November 2014) *Computer game could help visually-impaired children live independently*, available at: <http://www.medicalnewstoday.com/releases/284764.php>.

⁴⁰ For example, MedicalPhysicsWeb.org (7 January 2015) *UCLA launches paediatric clinical trial of ADHD treatment with NeuroSigma's eTNS*, available at: <http://medicalphysicsweb.org/cws/article/newsfeed/59776>.

⁴¹ For example, through piloting different ways of making flu vaccines available to children to see which delivery method is the most effective and acceptable to children and parents: Wired-gov.net (29 July 2014) *Child flu vaccine pilots announced for second year*, available at: <http://www.wired-gov.net/wg/news.nsf/articles/Child+flu+vaccine+pilots+announced+for+second+year+29072014101500>.

compare a number of existing treatments or interventions, in order to inform evidence-based guidance.⁴²

- Research with children and young people with particular health conditions, to find out **how their condition affects their daily life**.⁴³
- Studies of **patient or service user experience**: for example, using questionnaires or interviews to find out about children's and young people's experiences of using particular health services, or of participating in clinical research.⁴⁴

1.6 Innovative or 'experimental' interventions are sometimes also provided in the treatment of an individual patient outside the context of a research study, and hence outside the formal safeguards established to protect research participants (see Chapter 3).⁴⁵ Use of such interventions is currently permitted within the professional discretion of clinicians, but is controversial precisely because it lies outside the safeguards required for research.⁴⁶ In some cases completely unproven 'therapies' may be offered fraudulently to desperate patients or parents.⁴⁷ Other issues arise where interventions that are the subject of research scrutiny are offered on the basis of 'compassionate use' to patients who are not themselves part of the study.⁴⁸ While such procedures fall outside the strict terms of reference of this report, we highlight later in this report where our analysis with respect to research also raises important questions with respect to innovative procedures or compassionate use (see paragraphs 6.29-6.30).

⁴² See, for example, National Institute for Health and Care Excellence (2006) *Methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents: NICE technology appraisal guidance 98*, available at: <http://www.nice.org.uk/guidance/ta98/resources/guidance-methylphenidate-atomoxetine-and-dexamfetamine-for-attention-deficit-hyperactivity-disorder-adhd-in-children-and-adolescents-pdf>.

⁴³ See, for example, Gabe J, Bury M, and Ramsay R (2002) Living with asthma: the experiences of young people at home and at school *Social Science & Medicine* **55(9)**: 1619-33.

⁴⁴ Gibson F, Aldiss S, Horstman M, Kumpunen S, and Richardson A (2010) Children and young people's experiences of cancer care: a qualitative research study using participatory methods *International Journal of Nursing Studies* **47(11)**: 1397-407.

⁴⁵ See, for example, the very well-publicised case of the child Ashya King, whose parents wanted to obtain 'experimental' treatment abroad: The Guardian (3 September 2014) *Ashya King's story shows the tensions between paediatricians and parents*, available at: <http://www.theguardian.com/commentisfree/2014/sep/03/ashya-king-tensions-paediatricians-parents-internet-empowerment1>.

⁴⁶ See, for example, the debate in 2014-5 in the UK on the Medical Innovation Bill (the 'Saatchi Bill') which sought to make it easier for doctors to offer such innovations, and the subsequent announcement of a review into medical innovation and technology: Department of Health (11 March 2015) *Review into medical innovation and technology: further details*, available at: <http://www.wired.gov.net/wg/news.nsf/articles/Review+into+medical+innovation+and+technology+further+details+11032015125656>.

⁴⁷ See the discussion of "hope versus hype" at: Treat-NMD (2014) *Hope versus hype: an online guide*, available at: <http://www.treat-nmd.eu/resources/ethics/stem-cell/hope-versus-hype/>.

⁴⁸ See, for example, Aartsma-Rus A, Furlong P, Vroom E *et al.* (2011) The risks of therapeutic misconception and individual patient (n= 1)"trials" in rare diseases such as Duchenne dystrophy *Neuromuscular Disorders* **21(1)**: 13-5.

Box 1.4: Different kinds of clinical trial

Clinical trials of new medicines or vaccines (investigational medicinal products) are categorised in different phases, sometimes grouped together under the headings of 'early' and 'late' development stages:

Early development stage

- **Phase 1:** initial first-in-human studies to establish safety, usually undertaken with a small number of healthy volunteers, although for some conditions (such as cancer) it may only be possible to undertake the research with people who have that condition. The goal is to find out the most frequent and serious adverse events associated with the new medicine or vaccine, and to find the safe range of doses.
- **Phase 2:** studies to find out how the medicine works in people with the particular condition, in order to find out how 'efficacious' it is (how effective in a carefully controlled environment), and the nature of any adverse effects. Usually phase 2 trials will involve no more than 100 people.

Late development stage

- **Phase 3:** studies undertaken with a much larger group of people with the condition (hundreds or thousands), in order to compare the new medicine with existing treatments or with a placebo if no standard treatment exists.
- **Phase 4:** studies occurring *after* the new medicine has been approved by the relevant licensing authorities, and hence can now be used in routine medical practice. These post-authorisation studies (which are not always required) collect further information on safety, effectiveness and side effects.⁴⁹

Wherever possible phase 1, and sometimes phase 2, trials will first be carried out in adults. However, where this is not possible (for example, in diseases only occurring in childhood), then first-in-human trials may exceptionally take place with children.⁵⁰ Phase 1 and phase 2 trials carried out with adults also often need to be repeated in children, in order to obtain pharmacokinetic information (information on what doses are required in children to give the same concentration of the medicine in the blood as seen in adults) to help find the right dose for children.

- 1.7 As the descriptions in paragraph 1.5 make clear, what is involved in taking part in clinical research varies enormously depending on the kind of research in question. At one end of the spectrum, participation may involve responding to a questionnaire on a one-off basis (for example, about a person's experience of using a particular health service). At the other end of the spectrum, research may involve taking a new medicine or other form of treatment, and at the same time taking part in additional procedures (such as extra scans and tests, or filling in questionnaires, in addition to any monitoring required for their own healthcare) required for research purposes.
- 1.8 Just as the time commitment, inconvenience, and potential for discomfort or distress will vary significantly between studies, so may the categories of possible risk arising out of research involvement. Some studies will involve little or no risk at all; some may

⁴⁹ See: NHS Choices (2013) *Clinical trials and medical research: phases of trials*, available at: <http://www.nhs.uk/Conditions/Clinical-trials/Pages/Phasesoftrials.aspx>; MRC Clinical Trial Unit (2014) *What is a clinical trial?*, available at: http://www.ctu.mrc.ac.uk/about_clinical_trials/what_is_a_clinical_trial/; See also: ClinicalTrials.gov (2014) *Glossary definition: phase*, available at: <http://clinicaltrials.gov/ct2/help/glossary/phase> for definitions of the four phases in a US context.

⁵⁰ See, for example, Deatrck JA, Angst DB, and Moore C (2002) Parents' views of their children's participation in phase I oncology clinical trials *Journal of Pediatric Oncology Nursing* **19(4)**: 114-21.

involve risks of psychological distress (for example, from discussing painful or embarrassing subjects, or from discomfort with being observed); and others may involve some degree of risk of physical harm. In some cases, risks may be related to procedures that are also part of standard care, such as an adverse reaction to a routine scan, side-effects from standard treatment, or inadvertent disclosure of confidential information. In other cases, risk may arise specifically in connection with the treatment being researched. One of the functions of research review is to ensure that any such research-specific risks are proportionate and properly managed (see paragraphs 3.48–3.56).

- 1.9 A further important contextual aspect of research relates to whether the research procedures take place in a context quite separate from children's own day-to-day healthcare (for example, where children and young people participate in interview-based research at school on health-related behaviours), or is inextricably entwined with the treatment being provided for their particular medical condition (for example, in treatment of childhood cancers, where an element of randomisation of treatment will very commonly be part of treatment protocols). Where research relates to a child's own condition, the nature of that condition will clearly be highly significant: very different factors are likely to arise, for example, in research relating to sudden acute illness, research concerned with long-term conditions, and research with children with terminal illness (see paragraphs 2.6–2.10).
- 1.10 Until relatively recently, these two broad categories of research – research not connected with a person's care, and research undertaken as part of treatment for a particular condition – were widely described as 'non-therapeutic' and 'therapeutic' research respectively.⁵¹ However, this terminology has become less popular, not least because of fears that references to 'therapeutic research' could add to existing confusion between the primary aim of research (defined as an attempt to derive generalisable new knowledge) and the aims of any treatment which the child may be receiving within the research protocol for their own medical condition. The terms 'therapeutic' and 'non-therapeutic' research have therefore mainly been replaced in regulations and codes of practice with references to research that may, or may not, offer the possibility of benefit to a particular child. It has been suggested that it would add further clarity to distinguish, within any particular research protocol, those procedures that are potentially beneficial (such as the administration of a new medicine) and those procedures that are purely undertaken for research purposes (such as extra blood tests or other forms of monitoring).⁵²
- 1.11 Although the primary aim of research is the attempt to derive generalisable new knowledge, there is plenty of evidence that consent is often given for children's and young people's participation in research in the belief and hope that the procedures will

⁵¹ See, for example, the 1996 version of the Declaration of Helsinki which makes this distinction: World Medical Association (1996) *World Medical Association Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects* (Geneva: World Medical Association). 'Therapeutic' research was also sometimes, confusingly, known as 'clinical' research.

⁵² Miller PB, and Kenny NP (2002) Walking the moral tightrope: respecting and protecting children in health-related research *Cambridge Quarterly of Healthcare Ethics* 11(3): 217-29; Medical Research Council (2004) *MRC ethics guide: medical research involving children*, available at: <http://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/>, at paragraph 4.2. Vaccine trials, which are generally regarded as 'therapeutic' because the child may benefit by being protected from the condition in question, provide a useful illustration of this point: the administration of the vaccine is potentially therapeutic, while additional blood tests for research use only are not.

directly benefit them.⁵³ This may particularly arise in cases where parents of severely ill children see access to new, as-yet unlicensed medicines, innovative forms of surgery, or other forms of novel treatment as offering their child their ‘only hope’ of medical benefit.⁵⁴ Such examples illustrate the challenges, both practical and ethical, that researchers face as they try to communicate clearly the nature of any procedures proposed.

1.12 The context of the research endeavour may also differ depending on the sources of funding and support for the particular research study, and who is responsible for carrying it out.⁵⁵ Research may be funded by:

- public money, whether directly via government departments or through government-funded agencies;
- charitable sources, ranging from organisations with major endowments funding large-scale studies to small charities raising their funds from members and supporters; or
- the commercial sector, from large pharmaceutical companies to small biotechnology start-up businesses.

Researchers themselves may be health professionals (who may or may not be directly involved in caring for some of the participants in their studies); or may be academics or others working alongside health professionals. They may work in hospitals or university departments, or for charities or private sector companies. Depending on the source of funding (public, charitable or commercial), commercial implications of the proposed research will be of greater or lesser importance in determining the resources devoted to it.

1.13 Clinical research, by its nature, is an area of constant development, and any analysis of the context of research must be alert to the significant ways in which features of research may change. Recent developments in ‘stratified’ or ‘personalised’ medicine, for example, have led to increased understanding of how what is apparently the same medical condition may affect people in very different ways because of genetic or other factors. Such a recognition has major implications for research, for example in focusing attention on why a new medicine appears to work very well for some research participants, but has no beneficial effects for others. It may also add to the complexity of devising research protocols and recruiting participants: for example, where those eligible for the study are defined not only by the nature of their medical condition, but

⁵³ See, for example, Molyneux C, Peshu N, and Marsh K (2004) Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast *Social Science & Medicine* **59**(12) 2547-59; Shilling V, and Young B (2009) How do parents experience being asked to enter a child in a randomised controlled trial? *BMC Medical Ethics* **10**(1): 1-11; Miller VA, Baker JN, Leek AC *et al.* (2013) Adolescent perspectives on phase I cancer research *Pediatric Blood & Cancer* **60**(5): 873-8. See also: Appelbaum PS, Roth LH, Lidz CW, Benson P, and Winslade W (1987) False hopes and best data: consent to research and the therapeutic misconception *The Hastings Center Report* **17**(2): 20-4; Woods S, Hagger LE, and McCormack P (2014) Therapeutic misconception: hope, trust and misconception in paediatric research *Health Care Analysis* **22**(1): 3-21. A review of children’s oncology trials found that a new treatment is in fact just as likely to be inferior as superior to existing medicine: see Kumar A, Soares H, Wells R *et al.* (2005) Are experimental treatments for cancer in children superior to established treatments? Observational study of randomised controlled trials by the Children’s Oncology Group *British Medical Journal* **331**(7528): 1295.

⁵⁴ See, for example, the efforts to which parents of severely ill children may go to obtain a new (investigative) medicine outside a clinical trial if, for whatever reason, the child is not eligible to participate in the trial itself: Pinxten W, Nys H, and Dierickx K (2010) Access to investigational medicinal products for minors in Europe: ethical and regulatory issues in negotiating children’s access to investigational medicines *Journal of Medical Ethics* **36**(12): 791-4.

⁵⁵ As an indication of the division between commercial and non-commercial studies: 309 of the studies in the NIHR’s ‘Children’s portfolio’ to date have been funded commercially, while 584 were funded non-commercially (i.e. from public or charitable sources): NIHR, personal communication, 16 April 2015.

also by specific genetic or molecular markers.⁵⁶ The significance of these developments for research with children has recently been highlighted by The 100,000 Genomes Project, in which the genomes of 100,000 people will be sequenced and made anonymously available to researchers. The project website singles out the importance of research in this area for serious conditions affecting children, and identifies childhood cancers as one of its first priorities.⁵⁷

The context of the child and their family

“First is the need to define children. I advocate for a need to define the ethical considerations and needs of adolescents [as being] different from those of children. When these two are separated then the discussions can be shaped with more specificity.”⁵⁸

“A key question of integrity is important, particularly in those cultures where children’s rights are not emphasised and there may be undue and inappropriate pressure on a child from parent or community leader to become a participant in a study.”⁵⁹

1.14 Just as ‘clinical research’ covers an immensely wide range of activity, ‘children’ are, of course, an extremely heterogeneous group, from newborn babies to young people on the verge of adulthood. While the legal age of majority varies between countries (and may vary within countries for different purposes), the age of 18 is widely used as a marker for the end of childhood: the UN Convention on the Rights of the Child, for example, defines a child as “every human being below the age of 18 unless under the law applicable to the child, majority is attained earlier.”⁶⁰ However, while there is a need for clear rules on the age of majority for legal purposes, in practice children do not change overnight into adults. In healthcare services, a sudden move from paediatric to adult services can be very disruptive for young people with long-term care needs, and the need for transitional services is gradually being recognised.⁶¹ More generally, the UN reflects the gradual way in which children achieve the transition into adulthood

⁵⁶ For an overview of issues arising in the context of stratified medicine, see: Academy of Medical Sciences (2013) *Realising the potential of stratified medicine*, available at: <http://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf>.

⁵⁷ Genomics England (2014) *The 100,000 Genomes Project*, available at: <http://www.genomicsengland.co.uk/the-100000-genomes-project/>. See: Genomics England (2013) *Strategic Priorities Working Group report*, available at: http://www.genomicsengland.co.uk/wp-content/uploads/2013/06/GenomicsEngland_ScienceWorkingGroup.pdf, which identifies paediatric cancers as a priority area and states that: “systematic sequencing of the UK paediatric cancer population will likely identify many new targets as well as the potential to better understand the long-term serious treatment-induced complications that, as survival continues to improve, are becoming a significant health care issue.” See also: BBC News (1 August 2014) *DNA project ‘to make UK world genetic research leader’* available at: <http://www.bbc.co.uk/news/health-28488313> for a case study of a family’s experience of caring for a child with a genetic condition, and their hopes for progress in genetic research.

⁵⁸ Morenike O Folayan, Obafemi Awolowo University and the New HIV Vaccine and Microbicide Advocacy Society, responding to the Working Party’s call for evidence.

⁵⁹ Professor Andrew Tomkins, Institute for Global Health, UCL, London, responding to the Working Party’s call for evidence.

⁶⁰ United Nations: Office of the High Commissioner for Human Rights (1989) *Convention on the Rights of the Child*, available at: <http://www.ohchr.org/en/professionalinterest/pages/crc.aspx>, Article 1. See also: UNICEF (2005) *Convention on the Rights of the Child: frequently asked questions*, available at: http://www.unicef.org/crc/index_30229.html.

⁶¹ See: Wired-gov.net (9 June 2014) *NICE guidance to help tackle transition from children’s to adult services*, available at: <http://www.wired-gov.net/wg/news.nsf/articles/NICE+guidance+to+help+tackle+transition+from+childrens+to+adult+services+0906201415200> for information on NICE’s promise to develop guidance on transitions from children’s to adult services. See also: YoungMinds’ campaign “to improve transitions care from child and adolescent mental health services to adult mental health services”, which highlights the issue of young people “getting lost in the system when they reach 16”: YoungMinds (2015) *CAMHS transition*, available at: http://www.youngminds.org.uk/about/our_campaigns/transitions, and Murcott WJ (2014) *Transitions between child and adult mental health services: service design, philosophy and meaning at uncertain times* *Journal of Psychiatric and Mental Health Nursing* 21(7): 628-34.

through its definition of ‘youth’ which encompasses 15 to 24 year olds.⁶² Quite apart from these distinctions by age, references to ‘children’ as a group may also mask many other differences: relating, for example, to gender, family size and form (including absence of family where children live in institutional care), parenting style, health status, social and economic situation, intellectual ability, educational opportunity, and many others. Alongside this diversity of family situation, the clinical context in which the possibility of research involvement is raised will be particularly important: that is, whether or not research questions arise in the context of illness. When children are ill, the nature and severity of that illness will then be a further important contextual factor in the way that they and their families respond to the possibility of research involvement (see paragraph 2.30).

- 1.15 Moreover, there is significant cultural variation in how the whole notion of ‘childhood’ is perceived, both between regions of the world, and between sub-populations within one country. The extent to which children are protected in daily life, for example, may vary dramatically: a child who in one culture would be thought too young to walk to school on their own or be at home alone, might in another culture be expected to take primary responsibility for looking after younger siblings without supervision.⁶³ Such differences may be accompanied by significant differences in family hierarchies and the extent to which children and young people may normally expect to have their voices heard and their wishes considered. The perceived ending of childhood may also be affected by factors such as the usual age for marriage in a particular culture, or the absence or death of parents. Some jurisdictions include a concept of ‘mature minors’ where young people below the domestic age of legal majority are treated in law as no longer minors if they are married, have children themselves, or are household heads.⁶⁴ The extent to which children or young people in these situations have the freedom or authority to make their own decisions in practice will, of course, vary.

The context of the social, political and economic environment

“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.”⁶⁵

“... when in a study it is guaranteed that children will have specialised medical [treatment], it should not be seen as an [inducement] to participate...”⁶⁶

- 1.16 Clinical research, of whatever form, does not take place in a vacuum. As well as taking into account the particular circumstances of children or young people who are being invited to take part in research, it is also important to be alert to the wider social and political environment in which the research is taking place. Factors that may strongly

⁶² UNESCO (2014) *What do we mean by “youth”?*, available at: <http://www.unesco.org/new/en/social-and-human-sciences/themes/youth/youth-definition>.

⁶³ For a general introduction to diverse conceptions of childhood, see: Montgomery H (2009) *An introduction to childhood: anthropological perspectives on children’s lives* (Chichester: Wiley-Blackwell); James A, and James A (2012) *Key concepts in childhood studies*, Second Edition (London: Sage).

⁶⁴ Standard operating procedures for the Kenyan Ethics Review Committee, for example, specify that mature minors (understood as individuals under the age of 18 who are “married, pregnant, a mother or a household head”) may consent for themselves and for their children, but not for their siblings: KEMRI Wellcome Trust Research Programme (2009) *SOP 1: structure of the ERC*, available at: <http://www.kemri.org/dmdocuments/ERC%202014.pdf>, at paragraph 7.3.

⁶⁵ NIHR Clinical Research: Children, responding to the Working Party’s call for evidence.

⁶⁶ Eleonora Espinoza MD MSc, Denis Padgett MD MSc, Comité de Ética de Investigación Biomedica, Facultad de Ciencias Medicas, Universidad Nacional Autonoma de Honduras, Tegucigalpa Honduras, responding to the Working Party’s call for evidence.

affect the way proposed research studies are viewed by all concerned (including those involved in research governance, practitioners and researchers, and families and children/young people) include:

- public awareness and understanding of research in general: the extent to which research activity is seen as normal and valued, or, on the contrary, the extent to which it is seen as suspect and potentially exploitative;
- the domestic regulation of research, including the extent to which governments and other regulators see research as an activity to be promoted as a benefit or restrained as a threat;
- the extent to which research is seen as part of local health service provision, and responsive to local needs, or as an ‘outside’ activity, carried out primarily to benefit others or for suspicious motives;
- universality of access to healthcare and the extent to which research-related services may be perceived as an alternative route to care services;
- the local dominant culture in healthcare: for example, the extent to which a family-centred model is used in children’s services;
- local dominant social attitudes to the role of health professionals, and to researchers; for example, the extent to which it is seen as usual or permissible for lay people to challenge the views of professionals, or for health professionals to be open with patients about uncertainties and gaps in knowledge with respect to medical care;
- local dominant social attitudes to the role and rights of children/young people; to the roles and rights of women; and to the role of the wider (extended) family in making decisions about children and young people;
- general attitudes to risk and risk-taking, whether in connection with research or any other activity, and the extent to which wider socio-political attitudes are risk averse; and
- general access to the internet, social media and other communications, affecting, for example, the extent to which both children and parents have access to information and opinions about research other than those directly provided by researchers.

1.17 Finally, the complexity of the way in which these wider environmental factors may interact with contextual factors relating to the specific piece of research and particular children or young people should be noted. A generally ‘pro-science’ attitude in society, manifested as the belief that the biosciences can and will deliver solutions, may contribute to what has been termed a “collective therapeutic misconception”, strengthening beliefs as to the likelihood of direct benefit from participation in research.⁶⁷ Proactive support groups, which disseminate information about new research developments and research opportunities, may similarly inadvertently contribute to this collective misconception. We return to the ethical implications for researchers of such misunderstandings later in this report (see paragraph 6.18); alertness to the possibility of such environmental factors affecting participation decisions is clearly an important starting point.

⁶⁷ Woods S, Hagger LE, and McCormack P (2014) Therapeutic misconception: hope, trust and misconception in paediatric research *Health Care Analysis* **22(1)**: 3-21.

Ethos of the report

1.18 Later in this report, we will analyse in detail some of the specific ethical issues that arise when considering children’s and young people’s participation in clinical research (see Chapter 4). However, there are some fundamental attitudes, both to research, and to children, that have underpinned the Working Party’s approach throughout its work, and it is helpful to be explicit about these from the beginning. Below, we set out the ‘ethos’ that has underpinned our work throughout the project: first in relation to clinical research; and then in relation to children, both in general and in the specific context of clinical research.

Our ethos in relation to research

“[We should] instil a culture change amongst all professionals in contact with children – including in child health and mental health organisations and schools – so that research is accepted as an essential part of care.”⁶⁸

“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.”⁶⁹

“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.”⁷⁰

1.19 **The Working Party takes as its starting point the view that scientifically valid and ethically robust research, addressing questions of importance to the health of children and young people, should be seen as intrinsically good, and as a natural and necessary part of a healthcare system.**⁷¹ It should not be perceived as a ‘threat’ to children, as something to be apologised for, or indeed as anything unusual. Without well-conducted research, there is no prospect of improving healthcare for children now or in the future, and there is a real risk that children will be harmed by procedures and medicines that are ill-adapted for children or lacking an adequate evidence base (see Box 1.5). Such an approach is certainly not a blanket prescription of ‘research at all costs’ (see paragraph 1.27) – but rather a challenge to the complacent notion that it is safe or ethical to provide care to children without seeking to improve the evidence on which that care is based.

⁶⁸ Academy of Medical Sciences, responding to the Working Party’s call for evidence.

⁶⁹ Anonymous respondent to the Working Party’s call for evidence.

⁷⁰ Iain Chalmers, Coordinator, James Lind Initiative, responding to the Working Party’s call for evidence.

⁷¹ We endorse here the concept of research as integral to a ‘learning health care system’. See: The Hastings Center (2014) *Ethical oversight of learning health care systems*, available at: <http://www.thehastingscenter.org/LearningHealthCareSystems/>. See also: Faden RR, Kass NE, Goodman SN *et al.* (2013) An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics *Hastings Center Report* 43(s1): S16-S27, which proposes an ethics framework to support the transformation to a “learning health care system”.

Box 1.5: Risks of not carrying out research

- High doses of the antibiotic **chloramphenicol** have been associated with 'grey baby syndrome' in newborns and premature babies: symptoms include low blood pressure, and blue colouring of lips, nail beds and skin, and it may also lead to death. The cause was identified as impaired metabolism of chloramphenicol in young children.⁷² Current UK guidance limits its systemic use (that is, where it will affect the body as a whole) to treatment of life-threatening conditions, and warns of 'excessive' dosage and the need for plasma monitoring.⁷³
- **Sudden infant death syndrome (SIDS)**, also known as cot death, describes the sudden, unexpected, and unexplained death of a baby thought otherwise to be in good health.⁷⁴ Prior to the 1990s, parents were advised to place infants on their front (in the 'prone' position) when preparing them for sleep.⁷⁵ However, research in the early 1990s indicated that the rate of SIDS decreased dramatically (up to 50 per cent⁷⁶) when placed to sleep on their back or side.⁷⁷ This finding has led to a change in practice.⁷⁸
- **Cisapride** has been prescribed to over 36 million babies and young children worldwide to treat gastro-oesophageal reflux (movement of stomach contents back into the oesophagus). However, it was withdrawn from routine use in the UK and US in July 2000 because of concerns about rare, but very serious, adverse effects: sudden death, death from cardiac arrhythmia (abnormal heart rhythms) and serious non-fatal arrhythmia. A review of the available evidence by the UK Cochrane Collaboration to establish whether these risks of serious adverse events were outweighed by the benefits found no clear evidence that cisapride had significant benefits compared with placebo.⁷⁹

⁷² Mulhall A, de Louvois J, and Hurley R (1983) Chloramphenicol toxicity in neonates: its incidence and prevention *British Medical Journal (Clinical Research Edition)* **287(6403)**: 1424-7.

⁷³ British National Formulary for Children (2014) *Chloramphenicol*, available at: <http://www.evidence.nhs.uk/formulary/bnfc/current/5-infections/51-antibacterial-drugs/517-some-other-antibacterials/chloramphenicol>.

⁷⁴ NHS Choices (2013) *Sudden infant death syndrome (SIDS)*, available at: <http://www.nhs.uk/Conditions/Sudden-infant-death-syndrome/Pages/Introduction.aspx>. In 2012, the deaths of 158 babies were recorded as a sudden infant death. See: Office for National Statistics (2014) *Unexplained deaths in infancy: England and Wales - 2012*, available at: <http://www.ons.gov.uk/ons/rel/child-health/unexplained-deaths-in-infancy--england-and-wales/2012/rft-unexplained-infant-deaths.xls>.

⁷⁵ Gilbert R, Salanti G, Harden M, and See S (2005) Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002 *International Journal of Epidemiology* **34(4)**: 874-87.

⁷⁶ Willinger M, Hoffman HJ, and Hartford RB (1994) Infant sleep position and risk for sudden infant death syndrome: report of meeting held January 13 and 14, 1994, National Institutes of Health, Bethesda, MD *Pediatrics* **93(5)**: 814-9.

⁷⁷ Wigfield RE, Fleming PJ, Berry PJ, Rudd PT, and Golding J (1992) Can the fall in Avon's sudden infant death rate be explained by changes in sleeping position? *BMJ* **304(6822)**: 282-3.

⁷⁸ For an overview of the change in practice, and the impact of research in SIDS, see: Testing Treatments (2013) *Testing treatments: better research for better healthcare - second edition*, available at: http://www.testingtreatments.org/wp-content/uploads/2012/09/TT_2ndEd_English_17oct2011.pdf, pp13-4.

⁷⁹ The Cochrane Collaboration (2010) *Cisapride treatment for gastro-oesophageal reflux in children (review)* (London: Wiley).

Our ethos in relation to children

“... a child is already part of society, not simply a trainee adult.”⁸⁰

“... the child is the most important person in the clinical trial, so he / she must be informed in a comprehensive way and be able to decide and to express his / her opinion.”⁸¹

“They [children] are not subjects, they are actually living people.”⁸²

- 1.20 At different times and places, very different attitudes have been taken, whether implicitly or explicitly, to children as potential research participants. These include seeing children as ‘unknowing objects’ of the research, as ‘aware subjects’, or as ‘active participants’.⁸³ As ‘unknowing objects’, children are perceived as passive elements in research activity from whom no active engagement or input is expected. Such research might best be characterised as research ‘on’ children, rather than ‘with’ children. This approach to children explains the very high importance historically placed in research governance on the protection of children: where children taking part in research are seen solely in such passive terms, then there must be a particularly heavy burden on the researcher to demonstrate that they will not come to harm as a result of the research. Examples of deeply controversial research ‘on’ children carried out in the past (for example, the Willowbrook hepatitis research where children with learning disabilities were deliberately infected with hepatitis while living in a state institution⁸⁴) serve to demonstrate why the need for highly protective governance has since been given such emphasis.
- 1.21 Seeing children as ‘aware subjects’, on the other hand, recognises children’s potential for engagement with the research process, at least in terms of physical and emotional responses to the procedures involved in the research. However, such an approach still views their role within research as essentially a passive one. The Working Party takes the view that such an understanding of a child’s role in research is probably appropriate for newborn babies and very young children: those who are able to respond on an experiential basis to research-related procedures, but who do not as yet have any understanding as to what being involved in research might mean.⁸⁵ (We return below to the question of the role of their parents: see paragraphs 1.23, and 4.36–4.38.) However, as soon as children begin to develop the capacity to understand, even at a very basic level, that they are being asked to participate in order to help others, then something different is demanded of the researcher. Children from a very young age clearly express the desire, and an (evolving) ability, to take an active part in managing

⁸⁰ Richard Hain, responding to the Working Party’s call for evidence.

⁸¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁸² Participant in ‘Youth REC’ workshop. See: Spencer G, Boddy J, and Rees R (2014) *“What we think about what adults think”: children and young people’s perspectives on ethics review of clinical research with children* (London: Nuffield Council on Bioethics), at page 19.

⁸³ See the discussion of children as “unknowing objects”, “aware subjects” and “social actors” in Health Research Council of New Zealand (2013) *Ethics notes: children and research - ethical issues* (Auckland: Health Research Council of New Zealand), at page 1.

⁸⁴ Krugman S (1986) The Willowbrook hepatitis studies revisited: ethical aspects *Review of Infectious Diseases* **8(1)**: 157-62 (written by one of the doctors who carried out the research). For a summary of the studies, see: National Institute of Health Department of Bioethics (2009) *Willowbrook hepatitis experiments*, available at: http://science.education.nih.gov/supplements/nih9/bioethics/guide/pdf/Master_5-4.pdf.

⁸⁵ For a strong defence of the abilities of newborn babies to exercise agency, see: Alderson P, Hawthorne J, and Killen M (2005) The participation rights of premature babies *The International Journal of Children’s Rights* **13**: 31-50. We distinguish here between babies’ capacity for agency, as described by Alderson, and a capacity to understand that an intervention is being done to gain knowledge and help others, rather than directly in response to one’s own needs.

their own lives: toddlers, for example, make their preferences with respect to their own lives very clearly known, and at least some of the time will succeed in obtaining them. From a similarly young age, children are also routinely encouraged and expected to behave in ways that reflect the existence and needs of others: for example by sharing toys, taking turns, and saying 'please' and 'thank you'. There is widespread consensus that an important aspect of the care of children in the early years is to promote such 'pro-social' behaviour.⁸⁶

- 1.22 The Working Party therefore takes the very clear view that, **in the context of research, just as in other spheres of life, children from a young age should be understood not as 'subjects' of research but as 'active participants'**: as people who take a proactive role in determining the direction of their lives, in the context of a life shared with others.⁸⁷ Clearly the capacity of any individual child to act in this way at a particular time will vary, depending on any number of factors: their maturity, their state of health, and many other features of their family dynamics and upbringing (see paragraphs 1.14–1.15 and 2.16–2.22). We return later in this report to important distinctions within this catch-all category of 'childhood' (see paragraph 4.5). However, we make the general claim here that, as soon as any child begins to have this capacity for engagement, it is crucial for researchers to understand their role as one of carrying out research 'with' children, and not, as in the past, 'on' them.⁸⁸
- 1.23 The Working Party further takes the view that it is essential always to consider children in the context of their family. As we discuss in more depth later (see paragraphs 4.8–4.10), one of the ways in which children across the full age spectrum of childhood are different from adults, is the fact that they have **parents** (or others taking on the role of a parent⁸⁹) with well-defined social and legal duties to look after them during their legal minority. When considering the role of children, it is crucial to take into account the way they are situated within their families, the relationships they have with their parents and other family members, and the support (and sometimes conflict) that is found within families. A defining aspect of childhood, indeed one that underscores what is 'distinct' or 'special' about childhood, is the way in which children **develop**: in abilities, experience and maturity, from the complete dependency of a newborn baby to the

⁸⁶ See, for example, UK guidance on what is expected in early years care: Ofsted (2007) *Early years: getting on well - enjoying, achieving and contributing*, available at:

<http://webarchive.nationalarchives.gov.uk/20141124154759/http://www.ofsted.gov.uk/resources/early-years-getting-well>.

⁸⁷ For examples of how even very young children have demonstrated these abilities in very challenging situations, see: Panos London (2008) *Seen and heard: involving children in responses to HIV and AIDS*, available at: http://panos.org.uk/wp-content/files/2011/03/seen_and_heardwbAZlg.pdf. For a wider discussion of the importance of seeing children as 'human beings' rather than 'human becomings', see: Balen R, Blyth E, Calabretto H *et al.* (2006) Involving children in health and social research: 'human becomings' or 'active beings'? *Childhood* **13**(1): 29-48 and James A, and Prout A (1997) *Constructing and reconstructing childhood: contemporary issues in the sociological study of childhood*, Second Edition (Abingdon: Routledge). See also: Lee N (2001) *Childhood and society: growing up in an age of uncertainty* (Buckingham: Open University Press), Part One.

⁸⁸ We note that a similar shift in characterising the relationship between researcher and research participant has taken place in very recent years with respect to adults. See, for example, an illuminating account from a longstanding member of staff at the UK's Medical Research Council: Cope J (25 February 2014) *From guinea pigs to partners: a changing relationship with research participants*, available at: <http://www.insight.mrc.ac.uk/2014/02/25/from-guinea-pigs-to-partners-a-changing-relationship-with-research-participants/>; and Johansson V (2014) From subjects to experts - on the current transition of patient participation in research *The American Journal of Bioethics* **14**(6): 29-31. The UN Convention on the Rights of the Child requires, at Article 12(1), that "States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child."

⁸⁹ Throughout this report, we use the term 'parent' to include anyone exercising 'parental' responsibilities towards a child or young person: this therefore includes legal guardians and others authorised to take on a parental role. We return in Chapter 6 to the situation of children who have no adult at all to provide this kind of parental support (see paragraphs 6.37–6.41).

(relative) self-sufficiency of a young adult.⁹⁰ Parents and wider family both have a critical role to play in nurturing, sustaining, and also shaping that development.⁹¹

- 1.24 The way in which this family responsibility is exercised – including the extent to which it is shared by others outside the immediate nuclear family – varies significantly, both between families and between cultures, and it is essential for researchers to be sensitive to the realities of any particular child’s family life. We note how in the UK, along with many other countries, a ‘family-centred’ approach is explicitly taken by children’s healthcare services, and suggest that such an approach is a necessary part of research relationships, whether or not that research is directly bound up with children’s own treatment.⁹² There will, of course, also be people *outside* children’s families (however defined) with whom children have significant relationships, whether through personal connection such as being close family friends, or as a result of professional responsibility such as children’s teachers or support workers. Moreover, as children get older, the influence both of their wider peer group and their particular circle of friends will increase significantly, affecting their attitudes, values and behaviour.
- 1.25 **The Working Party has based its work on an understanding of children as people who, in the context of their own family and social environment, have the potential from an early age to play an active role in determining their own lives and in engaging with others.** Such an approach, which is very much in line with thinking about the role of children in other areas of life (see paragraphs 1.21–1.22), stands in stark contrast to many of the implicit assumptions of research governance, in particular in relation to children’s perceived vulnerability and passivity.
- 1.26 The regulation of clinical research with children and young people, as we note above (see paragraph 1.1), has been based on the assumption that, by their nature, they constitute a ‘vulnerable group’, and that such vulnerability automatically demands a protective response.⁹³ Yet it is far from clear that a child or young person, if well-supported by their parents and others, is *necessarily* any more vulnerable in the context of research than any other potential research participant. Clearly any child or young person *may* be vulnerable – as may any adult – but the automatic assignation to *all* children and young people of the label of ‘vulnerability’ seems highly dubious in the context of an approach to childhood that emphasises both children’s developing abilities to influence their own lives, and the support potentially to be found within families. We return to this question in Chapter 4, in light of our analysis of the evidence regarding the way that children, young people and their families engage with the prospect of participating in clinical research. In particular, we suggest that an important

⁹⁰ The Working Party is, of course, aware that there will be children who, for a number of reasons, do not reach this point of self-sufficiency. We discuss this point further in Chapter 4.

⁹¹ See, for example, Eekelaar J (1994) The interests of the child and the child’s wishes: the role of dynamic self-determinism *International Journal of Law, Policy and the Family* **8**(1): 42-61, at page 52, who argues that a primary role of parents is to “mediate between the developing personality of the child and the social world.”

⁹² Inwald D (2008) The best interests test at the end of life on PICU: a plea for a family centred approach *Archives of Disease in Childhood* **93**(3): 248-50. See also: Verkerk MA, Lindemann H, McLaughlin J *et al.* (2014) Where families and healthcare meet *Journal of Medical Ethics* **41**: 183-5 and Lindemann Nelson H, and Lindemann Nelson J (1995) *The patient in the family: an ethics of medicine and families* (Oxford: Routledge). Developing this approach, it has been argued that the “approach of family-centred care needs to be redirected towards a *child-centred care approach* which incorporates the rights of the child to participate in all aspects of health care delivery in conjunction with the need of their family.” See: Söderbäck M, Coyne I, and Harder M (2011) The importance of including both a child perspective and the child’s perspective within health care settings to provide truly child-centred care *Journal of Child Health Care* **15**(2): 99-106, at page 104.

⁹³ Exploration of how children are routinely perceived as ‘innocent’ or ‘vulnerable’, except for when their behaviour is condemned as ‘delinquent’ is an important theme in childhood studies literature. See, for example, the discussion of representation (pp98-9), innocence (pp68-70), vulnerability (pp132-4), and delinquency (pp37-9) in James A, and James A (2012) *Key concepts in childhood studies*, Second Edition (London: Sage).

element of research governance should be concerned with the way in which the potential for research to *create* vulnerability may be minimised.

Our ethos in relation to the ethics of research with children

- 1.27 As Boxes 1.1–1.3 demonstrate, clinical research with children offers the prospect of significant, potentially life-changing, developments in clinicians' understanding of children's conditions, and in their ability to provide better, more effective treatments for children and young people. However, as we note in paragraph 1.19, the wider benefits that research may potentially bring cannot be our only consideration. Implicit in our endorsement of 'ethically robust' research is the requirement that research must be carried out with due regard to the interests and welfare of all who are potentially affected. It is important to acknowledge that this requirement has not always been followed, and that there have been circumstances where unethical research practice has led to children being exploited and harmed.⁹⁴
- 1.28 Agreed requirements as to what constitutes 'ethical practice' in clinical research are spelled out in a number of international declarations such as the Declaration of Helsinki, and incorporated in various forms into national regulations and professional guidance. It is, however, almost invariably the case that such regulation (whether ethical or legal) starts from the paradigm example of the competent adult research participant, and then adapts that approach to other situations. Much has also been written as to how to ensure that these requirements (once identified) might be embedded in professional practice. In the UK context, for example, professional guidance for those involved in research is found in good practice guidance for doctors⁹⁵ and other health professionals,⁹⁶ in academic requirements for research integrity,⁹⁷ and in specifications for the good governance of ethical review committees.⁹⁸ In its 2013 report on novel neurotechnologies, the Nuffield Council analysed the important role of professional virtues in encouraging and promoting reflexive ethical practice: in that particular context through a proper balancing of the virtues of inventiveness, humility and responsibility.⁹⁹ Much can be learned from all these approaches which on the one hand emphasise the role of rules and procedures, and on the other professionals' personal integrity and responsibilities.
- 1.29 However, as our discussion of our ethos with relation to children makes clear, there are many ways in which children differ from adults – and we cannot assume that an ethical framework for research with children is simply an ethical framework for research with adults with additional protections. Specific child-related issues, including assumptions of childhood vulnerabilities, the role of children themselves in decision-making, and the

⁹⁴ See, for example, Brierley J, and Larcher V (2010) Lest we forget... research ethics in children: perhaps onerous, yet absolutely necessary *Archives of Disease in Childhood* **95**(11): 863-6.

⁹⁵ See, for example, General Medical Council (2010) *Good practice in research and consent to research*, available at: http://www.gmc-uk.org/Research_guidance_FINAL.pdf_31379258.pdf.

⁹⁶ See, for example, Royal College of Nursing (2009) *Research ethics: RCN guidance for nurses*, available at: http://www.rcn.org.uk/_data/assets/pdf_file/0007/388591/003138.pdf; The British Psychological Society (2010) *Code of human research ethics*, available at: http://www.bps.org.uk/sites/default/files/documents/code_of_human_research_ethics.pdf.

⁹⁷ See, for example, Universities UK (2012) *The concordat to support research integrity*, available at: <http://www.universitiesuk.ac.uk/highereducation/Documents/2012/TheConcordatToSupportResearchIntegrity.pdf>.

⁹⁸ Department of Health (2011) *Governance arrangements for research ethics committees: a harmonised edition*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213753/dh_133993.pdf.

⁹⁹ Nuffield Council on Bioethics (2013) *Novel neurotechnologies: intervening in the brain*, available at: <http://nuffieldbioethics.org/project/neurotechnology/>.

role of parents and others in promoting children's welfare (to take only a few examples) constantly arise in research with children, and need close consideration.

- 1.30 We thus see the primary task of this report as one of critical reflection on these and other ethical concepts that inform the way in which we think about ethical behaviour with respect to research with children. In so doing, we aim to promote much greater clarity in their use, and thereby to remove any unnecessary barriers to the participation of children and young people in research arising from anxieties that prove unfounded or misplaced. We begin our exploration with an attempt to understand the realities of children's lived experiences of research, and how these intersect with current legal and ethical requirements (Chapters 2 and 3). In light of the understanding we obtain, and of our subsequent reflection on the ethical concepts specifically arising in research with children (Chapter 4), we then consider the professional responsibilities of the wide range of professionals engaged in research with children, and how these might best be characterised (Chapters 5 and 6). Our central conceptual conclusions and recommendations are drawn together in a final chapter.

Chapter 2

Being invited to take part
in research: evidence and
law

Chapter 2 – Being invited to take part in research: evidence and law

Chapter 2: overview

The first contact that most children and young people, and their families, will have with clinical research is when they are approached and invited to participate in a particular study. This chapter reviews first the empirical evidence of how, in practice, children and families make decisions about research participation, and then the role played by national law, international declarations, and good practice guidance.

Empirical evidence: the way in which children, young people and parents respond to the possibility of participating in research often depends on three broad factors:

- **The nature of the research:** for example, whether it relates to a child's own condition, and the severity of that condition; whether the need for a decision arises at a particularly traumatic time, and how much time is available to think about it; the degree of risk or discomfort involved; and time and opportunity costs in taking part.
- **The situation of children and their families:** their existing knowledge of research, and their attitudes towards both research and risk in general; their desire to help others through participation in research; and their perception of potential health or other benefit deriving from participation.
- **The relationships between researchers and families:** the extent to which there are trusting relationships between children / young people, parents and researchers; and the quality of the communication between them.

Children and young people themselves are involved in participation decisions in very different ways: from no involvement at all, to joint decision-making with parents, to being 'final' decision-makers. These differences do not simply correlate with age, but appear to be influenced by many other factors including the severity of any illness, the suddenness of either the diagnosis or the opportunity to take part in research, children's and young people's prior experiences, and general family dynamics in decision-making.

Law and guidelines: in contrast with the context-specific nature of decision-making emerging from the empirical literature, regulatory approaches focus very much on the role and status of the decision-maker. In most cases, 'children' or 'minors' are, by default, assumed to be unable to make their own decisions, and authorisation is required instead from a parent or another legally-authorized proxy. International declarations, regulations and guidance take diverse approaches to the extent to which children or young people should, nonetheless, be *involved* in the decision. Most, but not all, make specifications relating to the information that children and young people should receive, and the importance of involving them in the consent process in a manner appropriate to their maturity.

The term '**assent**' is used widely within both international declarations on research ethics and in some national legislation to encompass this involvement, but with very different meanings and implications. These vary from "the emergent capacity to agree" of a three year old, to the "knowing agreement" of an adolescent who has not yet reached the legally established age of consent but who nevertheless has the capacity to make their own decisions. Unlike consent, assent has no legal force, but some guidelines require documentation that a child has assented to take part. There is similar variation in how a child's '**dissent**' should be handled: in particular whether it should be 'considered', or 'respected'.

Introduction

- 2.1 The first contact that most children and young people and their families will have with clinical research is when they are approached and invited to participate in a particular study. We therefore begin our review of the empirical evidence relating to the experiences of children, young people and their parents in clinical research at this point of recruitment. We go on to consider the role of domestic law, international declarations, and good practice guidance, in shaping families' experiences of being recruited to take part in clinical research, before turning in Chapter 3 to look at the many requirements that researchers must meet before they are able to reach this point of recruitment. As we note in paragraph 2.62, there are a number of inconsistencies and uncertainties at present with respect to the role of children and young people in making decisions about research involvement, and having outlined these in this chapter, we set out our own approach in Chapter 6.

How children, young people and families make decisions in practice

- 2.2 Our exploration of children's and young people's lived experiences of taking part in research draws both on the published literature (primarily, but not exclusively concerned with practice in the UK), and on the additional insights we gained from the many people who contributed directly to this project: respondents to our call for evidence, members of our stakeholder group, and participants at our factfinding meetings, and school and community projects (see Appendix 2). These direct contributions illuminate and bring to life the general themes arising in the published literature, and examples (chosen to illustrate the range of views expressed) are quoted at the beginning of each section, and in Box 2.1 below.
- 2.3 The issues that emerge as important to children and families in deciding whether or not to take part in research fall into three broad categories, and we have followed these in our summary below. We look first at influences relating to the nature of the research itself; second, at influences relating to the situation of children and their families; and third, at the relevance of the relationships between researchers, children and young people, and their families. We conclude with a review of the (limited) evidence relating to the respective roles of children and their parents in making the final decision to participate or not.
- 2.4 It is important to note at the outset that, inevitably, the evidence referred to in the following section paints only a partial picture. Much of the literature about how families make decisions in practice draws on the use of hypothetical questions: asking families who may have no first-hand experience of participation in clinical research what they think they would do in a given scenario. Many more research studies have been carried out with parents than with children and young people themselves; and research seeking parents' opinions features less input from fathers than from mothers.

Box 2.1: Examples of research involvement from our stakeholder group

The Working Party's initial meeting with its stakeholder group of parents and young people provided a vivid snapshot of the various ways in which decisions about research involvement may be made, and the factors that may influence these decisions:

- One young person started making their own decision about research involvement from the age of 13: this was the point at which the balance of decision-making shifted from the parent (with their child's involvement/agreement), to the young person (with the involvement of their parent).
- Another child had been involved in a trial at age four. It would have been good if they had been given simple, jargon-free information – after all it was *their* bone marrow being taken. They were subsequently withdrawn from the study because of deterioration in their condition.
- One parent refused consent for their child to take part in a trial because the protocol included too many blood tests, to be taken by a non-specialist nurse rather than a phlebotomist.
- Consent was refused to another trial because it involved a blood test, and the child had needle phobia.
- Very positive experiences of being involved in a trial were reported in a case where the researcher / clinician involved knew the patient well, and made them feel their opinions counted. Knowing that involvement in research has helped to make a new treatment available for people worldwide is a “proud moment”.
- Participation in a trial was refused because of a failure to provide adequate information for parents. This arose in a context where a parent was invited to sign a form that said that they *had* been given the opportunity to discuss concerns with a named individual – whom they had never met.
- It was reported that, at one clinical trials unit, parental consent forms that were unaccompanied by any documentation about children's assent would be queried in order to explore with researchers why this had arisen.

Participation decisions: the relevance of the nature of research

2.5 The decision whether or not to take part in research may first of all be influenced by the *nature* of the particular clinical research study, and the demands it may place on children and their families. In some cases, these demands may be inherent in the nature of the research; in others, however, they may be amenable to change. We note examples, both in the literature and in our own evidence gathering, of where suggestions for such changes have been made.

Severity of health condition being researched

“You know... a child can be involved in research when he is sick... Now there as the parent, you accept immediately because you want... your child to get well.”¹⁰⁰

¹⁰⁰ Community representative, contributing to Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

“My child has a chronic condition and I would happily allow her to participate in a research study that might improve the treatment options for other children (even her own in the future).”¹⁰¹

- 2.6 We noted earlier that an important aspect of the context in which children are invited to take part in clinical research relates to the extent to which the research is associated with, or divorced from, care for children’s own health conditions (see paragraph 1.9). In the case where research relates to a child’s existing health condition, considerable diversity exists with respect to the seriousness of that condition, the availability of acceptable treatment options, and the extent to which it is sudden and acute, or chronic and long-standing.
- 2.7 Where research relates to treatment for a severe condition with no ‘standard care’ treatment options, parents have indicated that they feel they have little, if any, choice in making decisions about their child’s participation in a clinical trial.¹⁰² The experience of parents whose children have untreatable life-threatening conditions is captured vividly by the comment that “there was not a decision to make really – save my daughter. You save my daughter and I will do anything it takes.”¹⁰³ Such an experience forms a stark contrast not only with the situation in which parents of healthy children find themselves, but also those of children who have a chronic, but stable, condition.¹⁰⁴ Mothers of children with diabetes, for example, who had lived with the diagnosis and reality of their child’s illness for some time, described themselves as being confident about making their own choices as to what would be right for their child, and would make the decision based on their perceptions of the risks, benefits and opportunities presented by the proposed study.¹⁰⁵ These distinctions may, however, be less important in connection with survey-based research, where parents may feel more unconstrained in their choices, irrespective of the severity and acuteness of their child’s condition.¹⁰⁶
- 2.8 Two particular areas of research with children appear to have particularly high participation rates: those of cancer and neonatology.¹⁰⁷ Indeed, as many as 70 per cent

¹⁰¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁰² Deatrick JA, Angst DB, and Moore C (2002) Parents’ views of their children’s participation in phase I oncology clinical trials *Journal of Pediatric Oncology Nursing* **19(4)**: 114-21; Caldwell PHY, Butow PN, and Craig JC (2003) Parents’ attitudes to children’s participation in randomized controlled trials *The Journal of Pediatrics* **142(5)**: 554-9.

¹⁰³ Stevens PE, and Pletsch PK (2002) Ethical issues of informed consent: mothers’ experiences enrolling their children in bone marrow transplantation research *Cancer Nursing* **25(2)**: 81-7, at page 84. See also: Caldwell PHY, Butow PN, and Craig JC (2003) Parents’ attitudes to children’s participation in randomized controlled trials *The Journal of Pediatrics* **142(5)**: 554-9; Fisher HR, McKeivitt C, and Boaz A (2011) Why do parents enrol their children in research: a narrative synthesis *Journal of Medical Ethics* **37(9)**: 544-51. Attendees at Nuffield Council on Bioethics (2013) *Factfinding meeting: making research decisions: who decides and how?* (London, 9 September: Nuffield Council on Bioethics) reiterated the message that parents may be willing to do anything to get a particular new treatment for their child where serious illnesses have been diagnosed.

¹⁰⁴ Fisher HR, McKeivitt C, and Boaz A (2011) Why do parents enrol their children in research: a narrative synthesis *Journal of Medical Ethics* **37(9)**: 544-51, which compared the perception of ‘choice’ between parents with terminally ill children will do ‘anything that might help’, and parents of healthy or stable children.

¹⁰⁵ Pletsch PK, and Stevens PE (2001) Children in research: informed consent and critical factors affecting mothers *Journal of Family Nursing* **7(1)**: 50-70, at page 61.

¹⁰⁶ See, for example, Liaschenko J, and Underwood SM (2001) Children in research: fathers in cancer research - meanings and reasons for participation *Journal of Family Nursing* **7(1)**: 71-91. Fathers of children engaged in cancer research were found to focus on possible benefit for their child when considering ‘experimental’ studies, but cited altruism as a reason for participation in survey research.

¹⁰⁷ Snowdon C, Brocklehurst P, Tasker R *et al.* (2014) Death, bereavement and randomised controlled trials (BRACELET): a methodological study of policy and practice in neonatal and paediatric intensive care trials *Health Technology Assessment* **18(42)**: 1-410 identified 50 RCTs as having enrolled babies or children from 2002-6; approximately 50 per cent of UK NICUs and PICUs participated in at least one of these trials. Collectively, they enrolled over 3,000 children.

of children and young people diagnosed with cancer may be included within trials.¹⁰⁸ It has been suggested that these high participation rates may be influenced by the value placed by both professionals and parents on research in connection with these serious health conditions, but may also reflect possible parental reluctance to say 'no' to the clinical team on whom their child's care depends (see also paragraph 2.27).¹⁰⁹ However, severity of condition does not guarantee the existence of a professional culture conducive to research: there are many other serious health conditions affecting children where the need for research into more effective treatments may be as acute as in cancer but where a strong research culture, in which most clinicians are also involved in carrying out research, has not yet emerged.¹¹⁰

Research proposed in traumatic, highly emotional, or sensitive situations

*"There are particular difficulties in carrying out research in neonatal palliative care, largely because parents of newborns may not have had time come to terms with their baby's poor prognosis and the introduction of a palliative care approach, let alone considering participation in research studies."*¹¹¹

*"... research into the use of drugs or sexual relationships, where involvement of the parents or other family members may be problematic".*¹¹²

2.9 Associated closely with research that addresses severe conditions are circumstances where participation decisions about clinical research are made in traumatic or highly emotional situations. In the context of neonatal clinical research, for example, 'fear' has been identified as the dominant parental emotion, underscoring almost all elements of decision-making.¹¹³ Attendees of a factfinding meeting with the Working Party highlighted a set of circumstances where a baby could be born, enrolled into a research study, and die, within 24 hours. Since a baby who is thought to be highly unlikely to live will not usually be recruited into research, the invitation to consider research may be a source of (false) hope for parents.¹¹⁴ At the same meeting, it was suggested that finding out that a child or young person has a long-term or serious

¹⁰⁸ Ablett S, and Pinkerton C (2003) Recruiting children into cancer trials - role of the United Kingdom Children's Cancer Study Group (UKCCSG) *British Journal of Cancer* **88(11)**: 1661-5; Byrne-Davis LMT, Salmon P, Gravenhorst K, and Eden TOB (2010) Balancing high accrual and ethical recruitment in paediatric oncology: a qualitative study of the 'look and feel' of clinical trial discussions *BMC Medical Research Methodology* **10**: 101.

¹⁰⁹ Shilling V, and Young B (2009) How do parents experience being asked to enter a child in a randomised controlled trial? *BMC Medical Ethics* **10(1)**: 1-11, at page 4.

¹¹⁰ See, for example, the argument put forward in Davies JC (2013) Cystic fibrosis: bridging the treatment gap in early childhood *The Lancet* **1(6)**: 433-4 that cystic fibrosis research in very young children should become the norm, not the exception, as in oncology – there are almost no evidence-based treatments for this age group.

¹¹¹ Together for Short lives and Association for Paediatric Palliative Medicine Joint Research Group, responding to the Working Party's call for evidence.

¹¹² Health, Ethics and Law, University of Southampton (HEAL UoS), responding to the Working Party's call for evidence.

¹¹³ Snowdon C, Elbourne D, and Garcia J (2006) "It was a snap decision": parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials *Social Science & Medicine* **62(9)**: 2279-90.

¹¹⁴ Nuffield Council on Bioethics (2013) *Factfinding meeting: making research decisions: who decides and how?* (London, 9 September: Nuffield Council on Bioethics). See also: Snowdon C, Brocklehurst P, Tasker R *et al.* (2014) Death, bereavement and randomised controlled trials (BRACELET): a methodological study of policy and practice in neonatal and paediatric intensive care trials *Health Technology Assessment* **18(42)**: 1-410, where parents had to make a rapid decision about taking part in a RCT which sought to assess the effect of whole-body cooling for babies who had suffered perinatal asphyxia following complicated deliveries. Whole body cooling was only available to babies of parents who agreed to take part in the RCT; but only 50 per cent would be allocated to the intervention arm of the trial; the remaining 50 per cent in the control arm did not receive whole body cooling. The authors of this study note, at 62, that "where babies are critically ill and the trial intervention may offer some hope, allocation to the control arm can be a very disappointing experience for parents." See also: Embleton ND, and Rankin J (2014) The BRACELET study: implications for the design of randomised controlled trials in neonatal and paediatric intensive care *Archives of Disease in Childhood - Fetal and Neonatal Edition* **100(2)**: F97-8.

illness has the potential to change fundamentally the nature of family relationships, and what it is to be a parent.¹¹⁵ It is therefore very important for researchers to have a real understanding of how decisions about research are made in this ‘new world’ of parenting a seriously-ill child, and this can only be obtained through research with those parents, even at this very difficult time.¹¹⁶

- 2.10 Participation decisions may also be influenced by the sensitivity of the proposed research question,¹¹⁷ such as research that addresses young people’s sexual behaviour or use of drugs. The challenging question of parental involvement in decisions about young people’s participation in such research was highlighted by respondents to the Working Party’s consultation both in the UK and in Africa.¹¹⁸ In some cultural contexts, it might also be the case that parents prefer to consult respected members of their community before making a decision about providing consent for adolescents to take part in sexual and reproductive health research.¹¹⁹ There is considerable diversity in what may be considered a ‘sensitive’ research topic: other sensitive areas of research, for example, may include questions surrounding a child’s weight,¹²⁰ or appearance.¹²¹

Time pressures at point of recruitment

“Children in particular need time, they need to know that we value their opinion...”¹²²

- 2.11 A significant factor affecting how both children and parents approach the possibility of participation in research is that of the time pressure under which they are asked to make the decision. In cases where research protocols are closely intertwined with treatment options, decisions about participation might have to be made almost immediately after a diagnosis has been made: the experience of young people with cancer and their families has been described as a “whirlwind of consent activities immediately after diagnosis”.¹²³ The importance of parents having time to think about

¹¹⁵ See, for example, Bluebond-Langner M, Belasco JB, Goldman A, and Belasco C (2007) Understanding parents’ approaches to care and treatment of children with cancer when standard therapy has failed *Journal of Clinical Oncology* **25(17)**: 2414-9.

¹¹⁶ Nuffield Council on Bioethics (2013) *Factfinding meeting: making research decisions: who decides and how?* (London, 9 September: Nuffield Council on Bioethics).

¹¹⁷ See, for example, Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99(10)**: 887-91, which observes that “in most instances, the child’s assent or consent should be underpinned by parent consent, but this can be problematic where sensitive subjects, such as sexual health, contraception, and adolescent behavioural studies are involved, and there is a duty to preserve confidentiality.”

¹¹⁸ For example, Morenike O Folayan, Obafemi Awolowo University and the New HIV Vaccine and Microbicide Advocacy Society, and Health, Ethics and Law, University of Southampton (HEAL UoS), both responding to the Working Party’s call for evidence.

¹¹⁹ 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).

¹²⁰ Barratt R, Levickis P, Naughton G, Gerner B, and Gibbons K (2013) Why families choose not to participate in research: feedback from non-responders *Journal of Paediatrics and Child Health* **49(1)**: 57-62 notes, at page 61, that “a primary objective of any study is to do no harm. Overweight and obesity in childhood are sensitive issues and some parents were particularly conscious of the impact of the study on their child.” See also: Warren JM, Golley RK, Collins CE *et al.* (2007) Randomised controlled trials in overweight children: practicalities and realities *International Journal of Pediatric Obesity* **2(2)**: 73-85.

¹²¹ See, for example, Williams LBDSM, Dures EP, Waylen AP *et al.* (2012) Approaching parents to take part in a cleft gene bank: a qualitative pilot study *The Cleft Palate - Craniofacial Journal* **49(4)**: 425-36.

¹²² Professor Faith Gibson, responding to the Working Party’s call for evidence.

¹²³ Stevens PE, and Pletsch PK (2002) Ethical issues of informed consent: mothers’ experiences enrolling their children in bone marrow transplantation research *Cancer Nursing* **25(2)**: 81-7, at page 84. See also: Deatrick JA, Angst DB, and Moore C (2002) Parents’ views of their children’s participation in phase I oncology clinical trials *Journal of Pediatric Oncology Nursing* **19(4)**: 114-21.

participation decisions, and also having time to discuss it with their partner,¹²⁴ and the researchers,¹²⁵ has been noted by several commentators. Children and young people have also commented on tight timelines within which participation decisions need to be made, and have highlighted the importance of having someone to explain to them *why* research (in a general sense) is undertaken, *before* being asked to enrol into a study (see also paragraphs 2.17–2.18).¹²⁶ Clearly, this urgency for decisions to be made does not apply for all forms of research, and other studies have indicated that parents and children have been given plenty of time to consider participation decisions.¹²⁷

Discomfort and risk

“Operationally, one of the main obstacles for recruiting young children is the thought of blood sampling.”¹²⁸

“Concern over painful or uncomfortable procedures, many of which are technically more challenging in children such as venepuncture...”¹²⁹

“I would be very worried if any new drug is to be administered. Any drug that has been approved and has been used for other conditions would make me feel more relaxed.”¹³⁰

2.12 Participation decisions may also be affected by perceptions of discomfort, pain or risk. As the quotations above indicate, the use of needles in blood sampling is often raised as a particular concern.¹³¹ Discomfort from blood sampling can be alleviated, for example, through the use of anaesthetic creams,¹³² or by taking blood at the point at which children visit clinics for a ‘standard’ blood test, so that there are “no extra pokes, no extra pain”.¹³³ However, anxieties about these procedures may still persist.

¹²⁴ Cartwright K, Mahoney L, Ayers S, and Rabe H (2011) Parents’ perceptions of their infants’ participation in randomized controlled trials *Journal of Obstetric, Gynecologic & Neonatal Nursing* **40(5)**: 555-65.

¹²⁵ See: Vanhelst J, Hardy L, Bert D *et al.* (2013) Effect of child health status on parents’ allowing children to participate in pediatric research *BMC Medical Ethics* **14(1)**: 7, where 13 per cent, 29 per cent, and 40 per cent of parents of healthy, ambulatory, and non-ambulatory sick children, respectively, would have like to spend more time with investigators discussing the trial.

¹²⁶ See: Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125(4)**: e876-e883, at e880. 87 per cent (n=32) of children who participated in this study indicated that this approach would be helpful. See also paragraph 2.30 where we note how children and young people may be removed from participation discussions and decisions in cases where their participation is deemed to be necessary immediately and urgently.

¹²⁷ See, for example, Burgess E, Singhal N, Amin H, McMillan D, and Devrome H (2003) Consent for clinical research in the neonatal intensive care unit: a retrospective survey and a prospective study *Archives of Disease in Childhood-Fetal and Neonatal Edition* **88(4)**: F280-6, where 62 per cent of parents of neonates reported that they had enough time to make a decision about their baby’s participation in research. See also: Sammons HM, Atkinson M, Choonara I, and Stephenson T (2007) What motivates British parents to consent for research? A questionnaire study *BMC Pediatrics* **7(1)**: 12, where 95 per cent of parents indicated that they were given enough time to make a decision.

¹²⁸ EMIG, responding to the Working Party’s call for evidence.

¹²⁹ Professor Jane C. Davies, responding to the Working Party’s call for evidence.

¹³⁰ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹³¹ See: Wolthers OD (2006) A questionnaire on factors influencing children’s assent and dissent to non-therapeutic research *Journal of Medical Ethics* **32(5)**: 292-7, where 46 per cent of dissenting children made their decision because of worries about having a blood sample taken.

¹³² Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99(10)**: 887-91.

¹³³ Thomas M, and Menon K (2012) Consenting to pediatric critical care research: understanding the perspective of parents *Dynamics* **24(3)**: 18-24.

2.13 Parents and children will, of course, be concerned about the possible risks associated with research compared to the known outcomes of previous treatment,¹³⁴ and be put off by possible side effects.¹³⁵ Parents may also have particular concerns about the ‘unknown’ risks of participation.¹³⁶ Research proposals that are perceived to be low risk, or involve painless procedures, by contrast, have been shown to make it easier for parents to agree to participate.¹³⁷ Approaches to risk when making participation decisions may differ according to whether a protocol is considered by a parent or a young person: young people have been observed to agree to higher risk research more willingly than their parents.¹³⁸ However, this willingness to take risks in the context of research needs to be considered alongside the well-established evidence that risk-taking behaviour peaks in adolescence.¹³⁹ In particular, adolescents are more likely than children and adults to make risky decisions in situations of high emotion and in the presence of peers. The peak in risk-taking during adolescence is believed to be due, at least in part, to asymmetrical development of the brain’s reward system, which temporarily becomes more responsive during adolescence, while brain systems involved in impulse and inhibitory control seem to develop more gradually over childhood and adolescence.¹⁴⁰

Time and opportunity costs

“Participation must coincide with treatment schedules and not be in addition. The treatment schedule / office visits, hospital stays for a cancer patient is already extensive, so combining visits should be reasonably easy for the researchers.”¹⁴¹

2.14 Parents have commented that hassle and inconvenience play significant roles in their decision to *refuse* to allow their child to take part.¹⁴² Conversely, parents’ willingness to

¹³⁴ See: Eiser C, Davies H, Jenney M, and Glaser A (2005) Mothers’ attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children *Child: Care, Health and Development* **31(5)**: 517-23, where three mothers stated that they withheld consent for their child to take part in a clinical trial because of concerns about the possible risks associated with a new treatment compared with the success of previous treatment.

¹³⁵ See, for example, Harth S, and Thong Y (1990) Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study *BMJ: British Medical Journal* **300(6736)**: 1372-5; Fisher HR, McKeivitt C, and Boaz A (2011) Why do parents enrol their children in research: a narrative synthesis *Journal of Medical Ethics* **37(9)**: 544-51.

¹³⁶ See, for example, Fisher HR, McKeivitt C, and Boaz A (2011) Why do parents enrol their children in research: a narrative synthesis *Journal of Medical Ethics* **37(9)**: 544-51, where reasons for parental refusal tended to cite the unknown risks of the therapies being tested.

¹³⁷ Vanhelst J, Hardy L, Bert D *et al.* (2013) Effect of child health status on parents’ allowing children to participate in pediatric research *BMC Medical Ethics* **14(1)**: 7. See also: Perez ME, Langseder A, Lazar E, and Youssef NN (2010) Parental perceptions of research after completion of placebo-controlled trials in pediatric gastroenterology *Journal of Pediatric Gastroenterology and Nutrition* **51(3)**: 309-13, where 91 per cent of parents’ decision to participate may have been made because of the perception that risk was minimal.

¹³⁸ For example, Brody JL, Annett RD, Scherer DG, Perryman ML, and Cofrin KM (2005) Comparisons of adolescent and parent willingness to participate in minimal and above-minimal risk pediatric asthma research protocols *Journal of Adolescent Health* **37(3)**: 229-35 observed that young people were more willing to take part in above-minimal risk asthma research, compared to parents who were asked to assess the same protocol.

¹³⁹ Spear LP (2013) Adolescent neurodevelopment *Journal of Adolescent Health* **52(2)**: S7-S13.

¹⁴⁰ Van Leijenhorst L, Moor BG, Op de Macks ZA *et al.* (2010) Adolescent risky decision-making: neurocognitive development of reward and control regions *NeuroImage* **51(1)**: 345-55.

¹⁴¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁴² See, for example, Harth S, and Thong Y (1990) Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study *BMJ: British Medical Journal* **300(6736)**: 1372-5; van Stuijvenberg M, Suur MH, de Vos S *et al.* (1998) Informed consent, parental awareness, and reasons for participating in a randomised controlled study *Archives of Disease in Childhood* **79(2)**: 120-5; Hayman R, Taylor B, Peart N, Galland B, and Sayers R (2001) Participation in research: informed consent, motivation and influence *Journal of Paediatrics and Child Health* **37(1)**: 51-4.

participate in clinical research may increase if inconveniences decrease.¹⁴³ Young people have also suggested that hassle plays a key role in participation decisions,¹⁴⁴ a point emphasised by those who took part in the Working Party's stakeholder event.¹⁴⁵ Practical suggestions put forward in response to these obstacles to participation include the advantage of researchers offering flexible start times, and making time commitments more transparent from the start of the process.¹⁴⁶

- 2.15 Time spent participating in clinical research may also lead to commensurate opportunity costs for families, such as less time to play or socialise; such factors may have a direct effect on participation decisions.¹⁴⁷ Suggestions for how such issues may be addressed include providing services such as child-friendly play areas, but also reducing waiting times,¹⁴⁸ and exploring the possibility of undertaking research procedures at home, rather than in clinics.¹⁴⁹

Participation decisions: the situation of children and their families

- 2.16 While the factors outlined above focus on features of the research itself or the clinical circumstances in which the need for research arises, these will be experienced in diverse ways by children and their families, depending on their own situation. This section focuses on those factors shown to affect participation decisions that stem from the particular situation, knowledge or attitudes of children and young people, and their families. As such, these are not generally factors that can be changed by researchers although, as indicated below, some may potentially be influenced by higher levels of awareness about clinical research in the population as a whole, and by good communication (see also paragraphs 2.28–2.29).

Knowledge and attitudes with respect to research and risk

“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

¹⁴³ Caldwell PHY, Butow PN, and Craig JC (2003) Parents' attitudes to children's participation in randomized controlled trials *The Journal of Pediatrics* **142**(5): 554-9.

¹⁴⁴ For example, Brody JL, Annett RD, Scherer DG, Perryman ML, and Cofrin KM (2005) Comparisons of adolescent and parent willingness to participate in minimal and above-minimal risk pediatric asthma research protocols *Journal of Adolescent Health* **37**(3): 229-35 found that just under 35 per cent of adolescents indicated that hassle played a role in participation decisions.

¹⁴⁵ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>. Factors identified by participants as likely to put them off research participation included: “things that affect your daily life or things you like doing, like sport”; “if it goes on too long or gets boring”, and “inconvenience for parents”.

¹⁴⁶ Barratt R, Levickis P, Naughton G, Gerner B, and Gibbons K (2013) Why families choose not to participate in research: feedback from non-responders *Journal of Paediatrics and Child Health* **49**(1): 57-62. This suggestion was echoed by a response to our call for evidence from the University of Cambridge Department of Paediatrics which noted that this obstacle might be overcome by “making [it] more convenient for busy parents and children to participate in research studies.” See: Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>, at page 9.

¹⁴⁷ See, for example, Barratt R, Levickis P, Naughton G, Gerner B, and Gibbons K (2013) Why families choose not to participate in research: feedback from non-responders *Journal of Paediatrics and Child Health* **49**(1): 57-62, which observed that families are less likely to take part in research if time commitments are too onerous. Hein IM, Troost PW, de Vries MC *et al.* (2015) Why do children decide not to participate in clinical research: a quantitative and qualitative study *Pediatric Research*: (Accepted article preview published online 9 April) similarly found that “many children mentioned that participating would impact on their time-schedule, and children of all ages mentioned they did not want to miss school.” See also: Caldwell PHY, Butow PN, and Craig JC (2003) Parents' attitudes to children's participation in randomized controlled trials *The Journal of Pediatrics* **142**(5): 554-9.

¹⁴⁸ Caldwell PHY, Butow PN, and Craig JC (2003) Parents' attitudes to children's participation in randomized controlled trials *The Journal of Pediatrics* **142**(5): 554-9, at page 558.

¹⁴⁹ Chantler TE, Lees A, Moxon ER *et al.* (2007) The role familiarity with science and medicine plays in parents' decision making about enrolling a child in vaccine research *Qualitative Health Research* **17**(3): 311-22.

*be used as a 'guinea pig'[...] Addressing misconceptions regarding the purposes of clinical research more generally may be helped by publishing good practice or positive case examples.*¹⁵⁰

*"I would not want to subject my child to something that would potentially harm them and I would not want their privacy to be at risk."*¹⁵¹

*"I would have no concern. Research can only be a good thing."*¹⁵²

- 2.17 Participation decisions can be influenced by families' attitudes to and understanding of research, and the threat it may pose to their children. As the last two quotes above illustrate, these anxieties differ substantially from family to family. Parents may find participation decisions less stressful where they themselves have medical backgrounds, or are more familiar with the language of science and medicine (either professionally or as healthcare consumers);¹⁵³ if they have higher levels of understanding of standard research procedures or the right to withdraw from clinical research; or if they are more confident in their abilities to evaluate the research being proposed.¹⁵⁴ Conversely, the way families make participation decisions in clinical research may be affected by conceptual and communication ambiguities, or lack of knowledge. Many families may be unfamiliar with the concepts of 'randomisation' and 'control arms',¹⁵⁵ or even the term 'research' itself.¹⁵⁶
- 2.18 The NIHR Clinical Research Network: Children, responding to our call for evidence, suggested that "publicity and training to highlight the benefits of and opportunities to undertake paediatric research" could be beneficial in supporting recruitment of children into research. The Oxford Vaccine Group noted that the same problem of a lack of knowledge can arise in clinicians too, observing that if clinicians are "better informed, they may be willing to partake or encourage families to become involved in research." Members of the Working Party's stakeholder group similarly placed particular emphasis

¹⁵⁰ British Medical Association, responding to the Working Party's call for evidence.

¹⁵¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁵² Ibid.

¹⁵³ Chantler TE, Lees A, Moxon ER *et al.* (2007) The role familiarity with science and medicine plays in parents' decision making about enrolling a child in vaccine research *Qualitative Health Research* **17(3)**: 311-22; Cartwright K, Mahoney L, Ayers S, and Rabe H (2011) Parents' perceptions of their infants' participation in randomized controlled trials *Journal of Obstetric, Gynecologic & Neonatal Nursing* **40(5)**: 555-65.

¹⁵⁴ Hoberman A, Shaikh N, Bhatnagar S, and *et al.* (2013) Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters *JAMA Pediatrics* **167(6)**: 561-6.

¹⁵⁵ For example, Woolfall K, Shilling V, Hickey H *et al.* (2013) Parents' agendas in paediatric clinical trial recruitment are different from researchers' and often remain unvoiced: a qualitative study *PLoS ONE* **8(7)**: e67352 found that despite practitioners explaining how the randomisation process worked, some parents were confused. For example, some mistakenly believed that researchers made the decision about which arm of the trial their child was allocated to, rather than allocation being conducted by computer randomisation. However, Kupst MJ, Patenaude AF, Walco GA, and Sterling C (2003) Clinical trials in pediatric cancer: parental perspectives on informed consent *Journal of Pediatric Hematology/Oncology* **25(10)**: 787-90, at page 789, highlight that one of the reasons for parents' distress during the consent process was due to "the computer choosing – randomization."

¹⁵⁶ Molyneux C, Peshu N, and Marsh K (2004) Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast *Social Science & Medicine* **59(12)**: 2547-59; Participants in the Community Engagement Consent Workshop: Kilifi; Kenya (2013) Consent and community engagement in diverse research contexts *Journal of Empirical Research on Human Research Ethics: An International Journal* **8(4)**: 1-18.

on the importance of action to address poor levels of knowledge about research in society as a whole.¹⁵⁷

2.19 As we noted above (see paragraphs 2.12–2.13), concerns about possible pain or discomfort, and any risks involved in the research, are an important factor in decision-making about research. Parents will come to different conclusions about what is acceptable to ask their child to do, with some perhaps understandably adopting an approach that researchers should “do it on someone else”.¹⁵⁸ Children and young people similarly take diverse approaches to risk. While young people have been observed to agree to higher risk research more willingly than their parents (see paragraph 2.13), this approach to research is naturally not adopted by every child or young person. One young person who responded to our Survey Monkey question about what should happen if they *didn't* want to take part in research, but their parents thought that they *should*, highlighted the role of fear in decision-making: “you shouldn't have to [take part] because you could be scared, and you're the one who is taking part, not your parents.”

Desire to help others

*“... it will have the possibility of helping children and may even save lives/change for the better.”*¹⁵⁹

*“... the research would still be done with other children, and I wouldn't be at risk. Selfish, but that would be what I would do.”*¹⁶⁰

*“It depends how it would help them, because if they had cancer, I would. If they had chicken pox I wouldn't.”*¹⁶¹

2.20 The desire to help others is cited as a factor influencing the participation decisions of some children and young people.¹⁶² This emerged as a strong theme in the direct engagement the Working Party had with children and young people through its stakeholder group, school workshops and online survey. However, as indicated in the quotations above, concerns about risk, or doubts about the likely value of the research, may also play an important role.

2.21 A desire to help others may also play a part in *parents'* deliberations about research participation. A high percentage of parents participating in neonatal research, for example, believe that their baby's participation in research will improve the care of

¹⁵⁷ Nuffield Council on Bioethics (2013) *Stakeholder meeting* (London, 17 July: Nuffield Council on Bioethics). See also: Participants in the Community Engagement Consent Workshop: Kilifi; Kenya (2013) Consent and community engagement in diverse research contexts *Journal of Empirical Research on Human Research Ethics: An International Journal* **8**(4): 1-18.

¹⁵⁸ Caldwell PHY, Butow PN, and Craig JC (2003) Parents' attitudes to children's participation in randomized controlled trials *The Journal of Pediatrics* **142**(5): 554-9, at page 557.

¹⁵⁹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people's responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁶⁰ Ibid.

¹⁶¹ Ibid.

¹⁶² See, for example, Broome ME, Richards DJ, and Hall JM (2001) Children in research: the experience of ill children and adolescents *Journal of Family Nursing* **7**(1): 32-49; Wolthers OD (2006) A questionnaire on factors influencing children's assent and dissent to non-therapeutic research *Journal of Medical Ethics* **32**(5): 292-7; Wendler DJ (2008) Children's and their parents' views on facing research risks for the benefit of others *Archives of Pediatrics & Adolescent Medicine* **162**(1): 9-4; Cherrill J, Hudson H, Cocking C *et al.* (2010) Clinical trials: the viewpoint of children with a chronic illness compared with healthy children *Archives of Disease in Childhood* **95**(3): 229-32; Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125**(4): e876-e883.

future babies,¹⁶³ while a parent whose child was taking part in a phase 1 oncology trial similarly comments: “if nothing else, it will help somebody else down the road.”¹⁶⁴ These altruistic instincts might be directed towards other families in similar situations,¹⁶⁵ or more generally be understood as part of “being a good citizen” and associated actions of social responsibility.¹⁶⁶ Parents might also recognise that their child benefits from the participatory altruism of other children in the past.¹⁶⁷ For bereaved parents – for example, those whose baby took part in neonatal research – participation may also be a source of satisfaction, or even pride; that their baby, however short his or her life, made a contribution to the world.¹⁶⁸

Perceived health or other benefit to participants

“I have a child with congenital heart defect and I happily enrol him in studies which could be beneficial for him and cast more light on his condition.”¹⁶⁹

“I was glad that they had asked because I knew it was probably his only chance of survival because of the level of intensive care that he was being given once he got there... just having the chance of him surviving, I was grateful.”¹⁷⁰

“Ok with me you see I will enjoy because I will be able to interact with the different people from different back grounds also... you will enjoy that.”¹⁷¹

2.22 Participation decisions are also affected by the perception (from both parents and young people) that a young person’s condition will improve if they take part in a study.¹⁷² The prospect of ‘direct benefit’ for their child is a major factor influencing parents’ decisions to enrol their children in research, particularly where their child is seriously ill.¹⁷³ There may be additional expectations that children will receive

¹⁶³ See, for example, Morley C, Lau R, Davis P, and Morse C (2005) What do parents think about enrolling their premature babies in several research studies? *Archives of Disease in Childhood-Fetal and Neonatal Edition* **90**(3): F225-8, where 94 per cent of parents whose premature babies had been invited to join several studies believed that their baby’s participation would improve future neonatal care.

¹⁶⁴ Deatrick JA, Angst DB, and Moore C (2002) Parents’ views of their children’s participation in phase I oncology clinical trials *Journal of Pediatric Oncology Nursing* **19**(4): 114-21, at page 118.

¹⁶⁵ See: Byrne-Davis LMT, Salmon P, Gravenhorst K, and Eden TOB (2010) Balancing high accrual and ethical recruitment in paediatric oncology: a qualitative study of the ‘look and feel’ of clinical trial discussions *BMC Medical Research Methodology* **10**: 101, where four out of five parents who commented on the scientific imperative of a clinical research trial expressed positive views about helping families in other situations.

¹⁶⁶ Fisher HR, McKeivitt C, and Boaz A (2011) Why do parents enrol their children in research: a narrative synthesis *Journal of Medical Ethics* **37**(9): 544-51.

¹⁶⁷ Ibid.

¹⁶⁸ Nuffield Council on Bioethics (2013) *Factfinding meeting: making research decisions: who decides and how?* (London, 9 September: Nuffield Council on Bioethics).

¹⁶⁹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁷⁰ Cartwright K, Mahoney L, Ayers S, and Rabe H (2011) Parents’ perceptions of their infants’ participation in randomized controlled trials *Journal of Obstetric, Gynecologic & Neonatal Nursing* **40**(5): 555-65.

¹⁷¹ Secondary school student, contributing to Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

¹⁷² Wagner KD, Martinez M, and Joiner T (2006) Youths’ and their parents’ attitudes and experiences about participation in psychopharmacology treatment research *Journal of Child & Adolescent Psychopharmacology* **16**(3): 298-307.

¹⁷³ Vanhelst J, Hardy L, Bert D et al. (2013) Effect of child health status on parents’ allowing children to participate in pediatric research *BMC Medical Ethics* **14**(1): 7.

enhanced medical care¹⁷⁴ or improved access to medicines¹⁷⁵ if they participate. These expectations of wider health benefits may arise particularly in social contexts where families do not otherwise have routine access to healthcare, or where healthcare associated with research centres is perceived as being of higher quality.¹⁷⁶ There may, however, be significant disparity between professionals' expectations of likely benefit and parental hopes: in the context of cancer treatment, for example, it has been observed that "having explained to parents that there is nothing to offer to combat the disease, the physician cannot expect that parents will stop looking".¹⁷⁷ A parent who responded to our Survey Monkey questionnaire similarly illustrated the role of hope, commenting: "if very lucky, he might happen to be an early beneficiary of a wonder drug."¹⁷⁸ As we note at paragraph 2.17, parents' perceptions of the likelihood of benefit in the context of research may be affected by their work or educational backgrounds, and the insights they have as a result into research practice.¹⁷⁹

- 2.23 Participation decisions may also be affected by *non*-health-related motivations, such as an interest in science generally,¹⁸⁰ the chance to learn something new,¹⁸¹ or because some research processes can be fun.¹⁸²

¹⁷⁴ Morley C, Lau R, Davis P, and Morse C (2005) What do parents think about enrolling their premature babies in several research studies? *Archives of Disease in Childhood-Fetal and Neonatal Edition* **90**(3): F225-8; Chappuy H, Doz F, Blanche S *et al.* (2006) Parental consent in paediatric clinical research *Archives of Disease in Childhood* **91**(2): 112-6; Chantler TE, Lees A, Moxon ER *et al.* (2007) The role familiarity with science and medicine plays in parents' decision making about enrolling a child in vaccine research *Qualitative Health Research* **17**(3): 311-22. The question of a 'trial effect' is debated: see: Brauholtz DA, Edwards SJL, and Lilford RJ (2001) Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect" *Journal of Clinical Epidemiology* **54**(3): 217-24 and Koschmann C, Thomson B, and Hawkins DS (2010) No evidence of a trial effect in newly diagnosed pediatric acute lymphoblastic leukemia *Archives of Pediatrics & Adolescent Medicine* **164**(3): 214-7, which disputes the argument that there is benefit *per se* of being in a trial (such as better monitoring leading to better outcomes).

¹⁷⁵ Woolfall K, Shilling V, Hickey H *et al.* (2013) Parents' agendas in paediatric clinical trial recruitment are different from researchers' and often remain unvoiced: a qualitative study *PLoS ONE* **8**(7): e67352.

¹⁷⁶ This emerged very clearly in the Kilifi consultation: Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme). It is also well-evidenced in the published literature: see, for example, Masiye F, Kass N, Hyder A, Ndebele P, and Mfutso-Bengo J (2008) Why mothers choose to enrol their children in malaria clinical studies and the involvement of relatives in decision making: evidence from Malawi *Malawi Medical Journal* **20**(2): 50-6; Molyneux S, Mulupi S, Mbaabu L, and Marsh V (2012) Benefits and payments for research participants: experiences and views from a research centre on the Kenyan coast *BMC Medical Ethics* **13**(1): 13. The challenge for researchers (not necessarily even health researchers) is captured by Nyambedha EO (2008) Ethical dilemmas of social science research on AIDS and orphanhood in Western Kenya *Social Science & Medicine* **67**(5): 771-9 who reports how, in response to his long-term study on the effect of AIDs on orphans in western Kenya, he is regularly asked "What are you going to do to the orphans after you have studied them?"

¹⁷⁷ Bluebond-Langner M, Belasco JB, Goldman A, and Belasco C (2007) Understanding parents' approaches to care and treatment of children with cancer when standard therapy has failed *Journal of Clinical Oncology* **25**(17): 2414-9, at page 2418.

¹⁷⁸ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁷⁹ See, for example, Cartwright K, Mahoney L, Ayers S, and Rabe H (2011) Parents' perceptions of their infants' participation in randomized controlled trials *Journal of Obstetric, Gynecologic & Neonatal Nursing* **40**(5): 555-65, at page 558, where it was observed that parents with a medical background felt that participation in a RCT was of little significance.

¹⁸⁰ See: Bernhardt BA, Tambor ES, Fraser G, Wissow LS, and Geller G (2003) Parents' and children's attitudes toward the enrollment of minors in genetic susceptibility research: implications for informed consent *American Journal of Medical Genetics Part A* **116A**(4): 315-23, at page 318, where a 12-year-old participant states: "I just like to participate in anything that can help people because I want to be a doctor when I grow up".

¹⁸¹ Ondrusek N, Abramovitch R, Pencharz P, and Koren G (1998) Empirical examination of the ability of children to consent to clinical research *Journal of Medical Ethics* **24**(3): 158-65, at page 161, where participants indicated that among "good things [that] might happen to you because you are in this study" was the chance that they might have to know "about calories and/or how much muscle they have".

¹⁸² *Ibid.*, where participants indicated that they could benefit by 'having fun'.

Participation decisions: the relationship between children, families and researchers

2.24 Finally, participation decisions may also be influenced by the nature of the relationship between children, young people, families, and researchers, and in particular the quality of the communication between them. Such relationship factors may be able to be addressed by researchers by changing the way they interact with children and their families.

Good relationship between families and researchers

“I think it is really important that the study is as personal as it can be – a personal connection between the researcher and the participants.”¹⁸³

“To get people on board they need to feel special and not a sheep and a big herd. It is the little touches for example good manners, nothing is too much trouble, refreshments on arrival, individual care, someone to have done their homework about your child even if it just checking when their birthday is as I say it is the little touches. Researchers also need a good bedside manner :)”¹⁸⁴

“Like Tambo [community facilitator]... now perhaps, maybe my child has been given those drugs and she took it, knowing Tambo will come, ‘How is she doing, no problem?’ ‘No problem. She is doing well’ and he passes by. Then we know we have someone in our midst who cares [other participants: Yes] for us.”¹⁸⁵

2.25 The ability to feel comfortable with researchers is an important aspect of participation decisions. One study exploring young people’s experiences included the suggestion “try and not scare anyone” from one participant,¹⁸⁶ a comment echoed in the Working Party’s own online questionnaire for young people where responses included noting that “doctors and nurses being friendly” would put them at ease.¹⁸⁷ Parents may be similarly affected by the friendliness and familiarity of the research team.¹⁸⁸ Confidence in the wider research team has also been shown to be important for parents who are

¹⁸³ Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>.

¹⁸⁴ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

¹⁸⁵ Community representative contributing to Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

¹⁸⁶ Shilling V, Williamson PR, Hickey H *et al.* (2011) Processes in recruitment to randomised controlled trials (RCTs) of medicines for children (RECRUIT): a qualitative study *Health Technology Assessment* **15(15)**: 1-116, at page 48.

¹⁸⁷ The role of ‘bedside nurses’ has also been highlighted in good practice guidance on seeking parental permission: for example, Lebet R, Fineman LD, Faustino EVS, and Curley MAQ (2013) Asking for parents’ permission to enroll their child into a clinical trial: best practices *American Journal of Critical Care* **22(4)**: 351-6 suggests that nurses are trusted more than other healthcare professionals. In addition, the role of the wider team in research participation, for example statisticians and data managers, has also been acknowledged in the context of leukaemia trials: Moscucci O, Herring R and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20(1)**: 23-52.

¹⁸⁸ See: Hoberman A, Shaikh N, Bhatnagar S, and *et al.* (2013) Factors that influence parental decisions to participate in clinical research: consenters vs nonconsenters *JAMA Pediatrics* **167(6)**: 561-6, which observed that parents were significantly more likely to consent if they thought that the researcher was friendly and professional.

involved with making decisions about their child's participation,¹⁸⁹ as has the reputation of the research institute.¹⁹⁰

- 2.26 Conversely, concerns are sometimes expressed by researchers that good relationships with participants might serve unduly to increase their hopes in the possible outcome of the research. Moreover, researchers might find themselves emotionally invested in the outcome, raising concerns that effective professional engagement with participants could potentially lead to “inappropriately high trial expectations” on both sides.¹⁹¹ Researchers may try to avoid giving advice to children and their parents about participating because of these fears of undue influence; however, this might lead to parents feeling abandoned by the very professionals they expect to advise and support them.¹⁹²
- 2.27 Professionals may also feel discomfort in the fact that their trusted status can make it hard for families to say *no* to participating in a study;¹⁹³ similarly, parents may feel conflicted if they refuse to take part in a study that is being run by their child's doctor.¹⁹⁴ The same issues of discomfort may arise in connection with children and young people's own sense of freedom to refuse to participate.¹⁹⁵

Quality of communication

- 2.28 As we note above (paragraphs 2.17–2.18), children and families vary significantly in their background knowledge about clinical research and research procedures at the point when they are first approached and invited to consider research participation. The way such an invitation is communicated by researchers is clearly critical, but the language and terminology used to convey information about research proposals may,

¹⁸⁹ Chappuy H, Doz F, Blanche S, Gentet JC, and Tréluyer JM (2008) Children's views on their involvement in clinical research *Pediatric Blood & Cancer* **50(5)**: 1043-6: 41 per cent of parents (n=12) highlighted the importance of having confidence in the investigator. See also: Hoffman T, Taaed R, Niles J *et al.* (2007) Parental factors impacting the enrollment of children in cardiac critical care clinical trials *Pediatric Cardiology* **28(3)**: 167-71, at page 171, which concluded that “the majority of parents believed that being approached about a clinical trial by the patient's primary pediatric cardiologist or cardiothoracic surgeon was most desirable as opposed to being approached by the principal investigator or the research coordinator. Comfort likely plays a significant role in this process.”

¹⁹⁰ Nabulsi M, Khalil Y, and Makhoul J (2011) Parental attitudes towards and perceptions of their children's participation in clinical research: a developing-country perspective *Journal of Medical Ethics* **37(7)**: 420-3, which observed that “trust in the doctor and in the institution where the study is conducted was mentioned by 14 parents and seemed to play a main role in facilitating or hindering participation.”

¹⁹¹ Peay HL, Tibben A, Fisher T, Brenna E, and Biesecker BB (2014) Expectations and experiences of investigators and parents involved in a clinical trial for Duchenne/Becker muscular dystrophy *Clinical Trials* **11**: 77-85. Three researchers who took part in this study voiced retrospective concerns about having been too positive with the families who participated.

¹⁹² Coyne I (2010) Research with children and young people: the issue of parental (proxy) consent *Children & Society* **24(3)**: 227-37; Gillies K, and Entwistle VA (2012) Supporting positive experiences and sustained participation in clinical trials: looking beyond information provision *Journal of Medical Ethics* **38(12)**: 751-6. See also: Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme), where the dangers of either too much or too little trust by families in researchers are discussed.

¹⁹³ Shilling V, Williamson PR, Hickey H *et al.* (2011) Processes in recruitment to randomised controlled trials (RCTs) of medicines for children (RECRUIT): a qualitative study *Health Technology Assessment* **15(15)**: 1-116, at page 57.

¹⁹⁴ See, for example, Shilling V, Williamson PR, Hickey H *et al.* (2011) Processes in recruitment to randomised controlled trials (RCTs) of medicines for children (RECRUIT): a qualitative study *Health Technology Assessment* **15(15)**: 1-116, at page 79, which highlighted that parents experienced difficulties in refusing to take part because of obligations to the hospital and its practitioners, personal commitment, and anticipated regret.

¹⁹⁵ Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125(4)**: e876-e83 asked children if they felt free to dissent to study participation, and 14 out of 37 (38 per cent) said they did not. Eight of these children decided to enrol; out of those, three gave the reason that this was due to pressure from parents; one child indicated pressure from doctors; and four as combined pressure from parents and doctors. Shilling V, Williamson PR, Hickey H *et al.* (2011) Processes in recruitment to randomised controlled trials (RCTs) of medicines for children (RECRUIT): a qualitative study *Health Technology Assessment* **15(15)**: 1-116, at page 46, note the response of one young person who had not met the practitioner before the trial began, who stated, “[maybe] it was better, maybe someone separate [...] in case they might object to us not, um, taking part in the study”.

in some cases, be inaccessible both to parents¹⁹⁶ and to children and young people.¹⁹⁷ It was suggested to the Working Party that much better use of information technology could help reduce communication difficulties, and could also reduce the burden of research participation, for example through the use of appropriate apps to gather information without interfering with children's everyday lives.¹⁹⁸ It was noted, however, that while children and young people may, in general, be very comfortable with using these technologies, professionals and parents might not have the same expertise.

2.29 Children with severe communication difficulties can be particularly overlooked: they may be excluded by doctors from discussions about research because of assumptions that they are unable to understand the protocol (even when they are fully able to do so), or excluded altogether from the pool of potential participants.¹⁹⁹ Language barriers and the associated potential for misunderstandings could also make participation decisions difficult for potential participants and their family members.²⁰⁰ In response to these difficulties, our stakeholder group argued that parents who do not speak English with confidence need appropriate support to make the right decisions for their child, and that even if an interpreter is available, the process may still feel very intimidating. Instead, the group suggested that participation decisions should be staged over several discussions, including the opportunity for private discussions between parents and the interpreter, and using the interpreter as a mediator between parents and clinicians, as necessary.²⁰¹ Techniques such as the use of art and craft, photography, and cartoons have also been used to facilitate the involvement of children with speech or communication difficulties, or those whose first language is not English.²⁰²

The involvement of children and young people in decision-making

“Personally if my parents told me I wasn’t allowed to take part in the trial, I think that I would listen to them cos I would kind of trust their judgment on whether they think it is safe or not.”²⁰³

¹⁹⁶ See, for example, Zupancic JAF, Gillie P, Streiner DL, Watts JL, and Schmidt B (1997) Determinants of parental authorization for involvement of newborn infants in clinical trials *Pediatrics* **99**(1): e6; Chantler TE, Lees A, Moxon ER *et al.* (2007) The role familiarity with science and medicine plays in parents’ decision making about enrolling a child in vaccine research *Qualitative Health Research* **17**(3): 311-22; Shilling V, Williamson PR, Hickey H *et al.* (2011) Communication about children’s clinical trials as observed and experienced: qualitative study of parents and practitioners *PLoS ONE* **6**(7): e21604.

¹⁹⁷ See, for example, van der Pal S, Sozanska B, Madden D *et al.* (2011) Opinions of children about participation in medical genetic research *Public Health Genomics* **14**(4-5): 271-8, at page 275, where 42 per cent of participation children, in particular younger children (aged 6-8) said that they would like to receive a special letter with tailored information written specially for them.

¹⁹⁸ Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics). One example of this kind of innovation (in the context of care rather than research) is a breathing exercise app for people with cystic fibrosis. See: PC Advisor (2 September 2014) *Cystic fibrosis app takes out top prize at 2014 iAwards*, available at: <http://www.pcadvisor.co.uk/news/network-wifi/3542652/cystic-fibrosis-app-takes-out-top-prize-at-2014-iawards/>. See also: NHS (2012) *Shared decision making*, available at: <http://sdm.rightcare.nhs.uk/>.

¹⁹⁹ Nuffield Council on Bioethics (2013) *Stakeholder meeting* (London, 17 July: Nuffield Council on Bioethics). See also: Morris J (2003) Including all children: finding out about the experiences of children with communication and/or cognitive impairments *Children & Society* **17**(5): 337-48 and Garth B, and Aroni R (2003) ‘I value what you have to say’. Seeking the perspective of children with a disability, not just their parents *Disability & Society* **18**(5): 561-76.

²⁰⁰ For example, Nabulsi M, Khail Y, and Makhoul J (2011) Parental attitudes towards and perceptions of their children’s participation in clinical research: a developing-country perspective *Journal of Medical Ethics* **37**(7): 420-3 noted that the Arabic translation for the word ‘randomisation’ is ‘ashwa’l’ meaning happening in a haphazard way. There is no other Arabic equivalent.

²⁰¹ Nuffield Council on Bioethics (2013) *Stakeholder meeting* (London, 17 July: Nuffield Council on Bioethics).

²⁰² See: Alderson P, and Morrow V (2011) *The ethics of research with children and young people: a practical handbook* (London: SAGE Publications), at pages 53 and 113.

²⁰³ Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>.

“I believe that my child has a right to be part of any decisions regarding his treatment and the risks they may be exposing themselves to.”²⁰⁴

“I think... for example, my parents maybe are not that educated so maybe they won't understand what the research is about while I will have understood but now if you go tell them they'll tell you 'Oh, don't go to do that!' But I'll know the importance of the research. For me, I'll participate. I might not tell them and secretly do it but I know it has importance. If they won't understand, I will have to hide it from them. I won't tell them!”²⁰⁵

“The parent has seen the sun earlier so she has... I mean she knows a lot... she has experienced a lot and she has seen a lot... whatever she tells you, you can also think well about it, that parents love you unconditionally, she can never have bad intentions for you.”²⁰⁶

- 2.30 The published literature suggests that children and young people are involved in participation decisions in very different ways.²⁰⁷ Some have indicated that they did not take part in the decision at all,²⁰⁸ whereas others indicated that the decision had been taken jointly,²⁰⁹ or, in some cases, that they were the ‘final’ decision-maker.²¹⁰ Contrary to expectation, these differences do not appear simply to correlate with age.²¹¹ The severity of a child’s illness, and the suddenness of either the diagnosis or the opportunity to take part in research, may both be important factors with respect to a child’s possible involvement in the decision. Examples have been cited of young people with cancer being excluded from discussions about taking part in research and enrolled in studies with immediate effect; this contrasts with the more active role of young people with diabetes in making decisions about research participation, where

²⁰⁴ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

²⁰⁵ 17 year old student, contributing to Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

²⁰⁶ *Ibid.*, contribution of an 18 year old student.

²⁰⁷ See, for example, 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; Coyne I, and Gallagher P (2011) Participation in communication and decision-making: children and young people’s experiences in a hospital setting *Journal of Clinical Nursing* **20**(15-6): 2334-43; Coyne I, Amory A, Kiernan G, and Gibson F (2014) Children’s participation in shared decision-making: children, adolescents, parents and healthcare professionals’ perspectives and experiences *European Journal of Oncology Nursing* **18**(3): 273-80.

²⁰⁸ See: Chappuy H, Doz F, Blanche S, Gentet JC, and Tréluyer JM (2008) Children’s views on their involvement in clinical research *Pediatric Blood & Cancer* **50**(5): 1043-6, where 41 per cent of children said that they had not contributed to the participation decision, for reasons including confidence in their parents, having no choice about taking part, or that the decision was too difficult.

²⁰⁹ Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125**(4): e876-e83.

²¹⁰ For example, 85 per cent of adolescents who participated in Miller VA, Baker JN, Leek AC *et al.* (2013) Adolescent perspectives on phase I cancer research *Pediatric Blood & Cancer* **60**(5): 873-8 indicated that they were the final decision-maker. Fifty per cent of participants also stated that the most important individual to influence their decisions was themselves.

²¹¹ Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125**(4): e876-e83: the children who said they wanted “total involvement” in making decisions ranged between nine and 19, while those who wanted “a little involvement” ranged from seven to 16. Almost none, however, wanted to make decisions solely on their own: 97 per cent wanted to involve parents and 94 per cent physicians. See also: Chappuy H, Doz F, Blanche S, Gentet JC, and Tréluyer JM (2008) Children’s views on their involvement in clinical research *Pediatric Blood & Cancer* **50**(5): 1043-6: only two of the 29 young people (aged 16 and 18) taking part in the study said they made the research decision for themselves.

there is no pressure or urgency about taking part.²¹² While one study found that children would have liked to be more involved in the decision than they were, few actually appeared to raise this with their parents or doctors.²¹³ However, research with children who have long-term conditions suggests that they are able to make informed and “wise” decisions in their own best interests and should be treated as “informed partners”.²¹⁴ Similarly, children with chronic illnesses may be more knowledgeable about research concepts such as placebos than their healthy counterparts.²¹⁵ In contrast, children who suddenly become acutely ill or have just received a frightening diagnosis may, temporarily, be much less capable of taking part in decision-making than they are in their ordinary lives.²¹⁶

2.31 These variations with respect to children’s roles in decision-making were also expressed by children and young people who contributed to our evidence-gathering activities, when invited to consider what role in a (hypothetical) research decision they should have. They approached their involvement in participation decisions from three distinct perspectives:

“I think I should decide because it’s my own risk.”²¹⁷

“You should talk about it at home as they [parents] might have a good reason why you shouldn’t take part in the research.”²¹⁸

“If mummy and daddy say no I shouldn’t do it.”²¹⁹

Again, these differences in children’s assumptions about their (hypothetical) decision-making role did not correlate directly with age: while some nine year olds felt strongly that they should decide alone, some sixth formers participating in our Youth REC film made clear they would be guided by their parents,²²⁰ as did 17 and 18 year old students taking part in our school-based consultation in Kilifi, Kenya.²²¹

2.32 In many cases, parents and children will both contribute in some way to a participation decision, with family dynamics and relationships determining how the final decision is

²¹² Broome ME, Richards DJ, and Hall JM (2001) Children in research: the experience of ill children and adolescents *Journal of Family Nursing* 7(1): 32-49.

²¹³ Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* 125(4): e876-e883. All of the 37 children interviewed would have liked to have been involved in the decision about taking part in oncology research but 18 had no memory of being involved. Only four participants discussed increased decision-making roles with parents.

²¹⁴ See: Alderson P, Sutcliffe K, and Curtis K (2006) Children as partners with adults in their medical care *Archives of Disease in Childhood* 91(4): 300-3, which observed that children who have type 1 diabetes can, from around four years of age, begin to understand the principles of controlling diabetes, and can therefore make informed decisions.

²¹⁵ Cherrill J, Hudson H, Cocking C et al. (2010) Clinical trials: the viewpoint of children with a chronic illness compared with healthy children *Archives of Disease in Childhood* 95(3): 229-32.

²¹⁶ Nuffield Council on Bioethics (2014) *Factfinding meeting with members of PORT* (London, 18 December: Nuffield Council on Bioethics).

²¹⁷ Nuffield Council on Bioethics (25 November 2013) *Blog: what do you mean - ask children?!*, available at: <http://blog.nuffieldbioethics.org/?p=907>.

²¹⁸ Nuffield Council on Bioethics (2013) *Survey Monkey questionnaire: analysis of young people’s responses* (London: Nuffield Council on Bioethics).

²¹⁹ Ibid.

²²⁰ Nuffield Council on Bioethics (25 November 2013) *Blog: what do you mean - ask children?!*, available at: <http://blog.nuffieldbioethics.org/?p=907>; Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>.

²²¹ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

reached.²²² Practical challenges may arise, however, as to how initial information about the proposed study can best be shared between researchers, parents and children, in order to facilitate this approach. While the obvious approach may be to provide information to parents and children together in joint meetings with the researcher, this may sometimes cause difficulties for parents because they are unprepared for what will be said, and hence may be less able to support their child in absorbing the information. Thus, a *shared* approach to participation decisions might, in practice, actually undermine parents' ability to give emotional care to their children.²²³ An alternative approach preferred by some parents is therefore for researchers to give them information about the study first, so that they can share it with their child in a way they feel most appropriate.²²⁴ Some children and young people, on the other hand, have resisted this approach, saying they would prefer researchers to talk to them directly, rather than solely to their parents.²²⁵ Moreover, as well as supporting how participation decisions are made, family relationships can also put pressure for decisions to be made in favour of a particular course of action. For example, for terminally ill children, an agreement to participate in research may stem from a desire to do as their family wishes.²²⁶

- 2.33 Even where children are not able to take an active part in the decision at all (for example, for research involving babies, or children who are too ill to communicate), the issue of shared decision-making may still arise with discussions both between parents, and with wider family and friends.²²⁷ Some studies have found that, despite the consultative role of family and friends, final decisions about participation tend to be made by mothers,²²⁸ although this can present particular challenges in more patrilineal societies where decision-making is traditionally seen as the father's role.²²⁹ Some

²²² See, for example, Olechnowicz JQ, Eder M, Simon C, Zyzanski S, and Kodish E (2002) Assent observed: children's involvement in leukemia treatment and research discussions *Pediatrics* **109(5)**: 806-14; Snethen JA, Broome ME, Knafk K, Deatrck JA, and Angst DB (2006) Family patterns of decision-making in pediatric clinical trials *Research in Nursing & Health* **29(3)**: 223-32. While questions of gender did not emerge as an issue in the UK-based respondents to the Working Party's consultation, the consultation with students and community representatives in Kilifi, Kenya, highlighted how protective attitudes to girls increased, rather than decreased, as they matured: Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

²²³ Young B, Ward J, Salmon P *et al.* (2011) Parents' experiences of their children's presence in discussions with physicians about leukemia *Pediatrics* **127(5)**: e1230-e8, at e1235.

²²⁴ Snethen JA, Broome ME, Knafk K, Deatrck JA, and Angst DB (2006) Family patterns of decision-making in pediatric clinical trials *Research in Nursing & Health* **29(3)**: 223-32. This view was also expressed by siblings of children enrolled in a clinical trial, for example: "I think it would have been better if the family would have told him what he had to go through and all that. I don't think he would have taken it so hard as he did when the doctors told him. That his parents actually told him, I don't know, you trust them I guess." See: Snethen JA, and Broome ME (2001) Children in research: the experiences of siblings in research is a family affair *Journal of Family Nursing* **7(1)**: 92-110, at page 101.

²²⁵ Unguru Y, Sill AM, and Kamani N (2010) The experiences of children enrolled in pediatric oncology research: implications for assent *Pediatrics* **125(4)**: e876-e83, at e880.

²²⁶ Hinds PS, Drew D, Oakes LL *et al.* (2005) End-of-life care preferences of pediatric patients with cancer *Journal of Clinical Oncology* **23(36)**: 9146-54 observed that two out of seven children with terminal cancer who enrolled in a clinical trial did so because their loved ones wanted them to, and concludes that decisions about end of life care are primarily based on relationships.

²²⁷ See: Jollye S (2009) An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials *Journal of Neonatal Nursing* **15(1)**: 18-24, at page 21, which notes that, "apart from discussing the trials amongst themselves most parents discussed the trials with family and/or friends." This will vary depending on parental relationships and decision-making styles: see, for example, Thomas M, and Menon K (2012) Consenting to pediatric critical care research: understanding the perspective of parents *Dynamics* **24(3)**: 18-24, at page 20, which compared a parent's response that "we made the consensus together" to an observation that "even my husband doesn't really know what it [the research protocol] is. I just said it was a study in ICU. He never bothers with papers anyway."

²²⁸ Jollye S (2009) An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials *Journal of Neonatal Nursing* **15(1)**: 18-24, at page 22. See also: McKenna K, Collier J, Hewitt M, and Blake H (2010) Parental involvement in paediatric cancer treatment decisions *European Journal of Cancer Care* **19(5)**: 621-30, at page 624; Miller VA, and Nelson RM (2012) Factors related to voluntary parental decision-making in pediatric oncology *Pediatrics* **129(5)**: 903-9.

²²⁹ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school*

parents would much prefer to leave the decision to doctors.²³⁰ Knowing what other parents have, or would, decide in similar circumstances may also be very reassuring for parents faced with difficult participation decisions.²³¹

Making decisions: the law and international guidance

The role of regulation

2.34 The first part of this chapter explored the empirical evidence available on how children, young people and parents experience the invitation to take part in clinical research, and the factors influencing their decision-making. The message that emerges strongly from this review is that the main influences on how children, young people and parents make decisions appear to be *situational*, depending heavily on the nature and context of the research, the situation of children or young people and their families, and the relationships they have with the researcher or research team. The question of *who* actually makes the decision, and the role of children and young people in cases where they are not the primary decision-maker, emerges relatively rarely in the published literature.

2.35 We now turn to the regulatory approaches with respect to the recruitment of children and young people into clinical research, which, by contrast, focus very much on the role and status of the decision-maker. A key protection for any research participant, found in both international statements on research ethics and in domestic legal requirements, is that participation should be *voluntary*: the free, informed, choice of the person concerned. For adults, this is usually achieved through a formal, active, process of consent.²³² The same requirement for consent applies when children and young people are being invited to take part in research; however the question then arises as to *who* provides that consent and, if not children or young people themselves, what part they may be expected to play in the decision. Below, we provide an overview of the stipulations of international ethical declarations, European law and guidance, and law and guidance within the UK with respect to:

- who gives consent;
- the role of children and young people in that process; and
- the provision of age-appropriate information for children and young people.

2.36 It is important to note that the notion of children and young people ‘participating’ in a decision-making process can be understood in very different ways. On the one hand

students in Kilifi, Kenya (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme). See also: Loue S, and Okello D (2000) Research bioethics in the Ugandan context II: procedural and substantive reform *The Journal of Law, Medicine & Ethics* **28(2)**: 165-73, at page 167.

²³⁰ See: Jollye S (2009) An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials *Journal of Neonatal Nursing* **15(1)**: 18-24, at page 22. The role of doctors in participation decisions was also noted in Deatrick JA, Angst DB, and Moore C (2002) Parents' views of their children's participation in phase I oncology clinical trials *Journal of Pediatric Oncology Nursing* **19(4)**: 114-21, at page 118, where one parent noted: "What made it so hard for me is that I'm not a doctor, and he was so well-educated. He usually guides me well with decisions, but he couldn't tell me what to do here".

²³¹ See, for example, Eder ML, Yamokoski AD, Wittmann PW, and Kodish ED (2007) Improving informed consent: suggestions from parents of children with leukemia *Pediatrics* **119(4)**: e849-e59, at e854: "I think maybe having patients or parents actually talk to other parents who either went with the clinical study or didn't. I mean, it's good to talk to the doctors, but you want, like, a regular person's point of view."

²³² There may be exceptions to this approach where research involves the 'secondary' use of information collected for other purposes, although such uses are tightly regulated. See: General Medical Council (2009) *Confidentiality*, available at: http://www.gmc-uk.org/Confidentiality___English_0914.pdf_48902982.pdf, paragraphs 40-50.

children participating in a decision may be understood to mean that they have some, however small, part in the process: the decision is not simply made on their behalf or without their knowledge. On the other hand, participation may be understood much more actively as requiring that children's views are "taken note of and may be acted upon".²³³ A requirement or recommendation that children participate in any decisions about taking part in research thus potentially captures a range of activity; from brief consultation, to giving children authority to make those decisions entirely for themselves. Full authority may not, however, always be desired. Related research in English schools exploring children's understanding of what 'children's rights' should involve, for example, found that most children interviewed conceptualised these as being respected and trusted, or as 'having a say' in decisions that affect them, but not necessarily as making these decisions on their own.²³⁴ Similar views with respect to their roles in decision-making about research were expressed by children and young people who took part in our Youth REC workshops.²³⁵

International declarations and guidance

- 2.37 The **Declaration of Helsinki**, first developed by the World Medical Association in 1964 and now in its ninth revision,²³⁶ is probably the best known and most influential international statement on the ethical principles that should be applied in "medical research involving human subjects".²³⁷ On the question of consent to research participation, the Declaration is very clear that "participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees."²³⁸ Where a potential research participant is *not* capable of giving their own consent, the Declaration requires consent instead to be sought from "the legally authorised representative". It further specifies that "when a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected."²³⁹
- 2.38 No specific reference is made in the Declaration to 'children' or 'minors': the only distinction made is between those capable, or incapable, of giving consent. It is, therefore, silent both on the extent to which children may be considered capable of giving informed consent for themselves, and on the role of parents, though parents' role as the "legally authorised representative" of their children may be implied. The

²³³ Boyden J, and Ennew J (1997) *Children in focus: a manual for participatory research with children* (Stockholm: Radda Barnen), at page 33. See also Suzanne Uniacke's distinction between "consideration respect" and "compliance respect": Uniacke S (2013) Respect for autonomy in medical ethics, in *Reading Onora O'Neill*, Archard D, Deveaux M, Manson N, and Weinstock D (Editors) (London: Routledge).

²³⁴ Morrow V (1999) 'We are people too': children's and young people's perspectives on children's rights and decision-making in England *The International Journal of Children's Rights* 7(2): 149-70.

²³⁵ Spencer G, Boddy J, and Rees R (2014) *What we think about what adults think: children and young people's perspectives on ethics review of clinical research with children* (London: Nuffield Council on Bioethics). See also the Introduction for a description of this project.

²³⁶ Including seven substantive revisions and two 'notes of clarification' in 2002 and 2004. The most recent revision dates from October 2013. See: World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>.

²³⁷ The term 'research subject' is used throughout the Declaration of Helsinki, and also in some other declarations and regulations. For the reasons discussed in Chapter 1, we prefer to use the term 'research participant', other than when directly quoting from other sources.

²³⁸ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, at paragraph 25.

²³⁹ *Ibid.*, paragraphs 28-9.

Declaration further gives no indication as to the threshold of understanding required for assent to be sought, leaving open how the concept of assent might be understood.

- 2.39 Guidance issued in 2002 (under revision at the time of writing)²⁴⁰ by the Council for the International Organizations of Medical Sciences (**CIOMS**) in association with the World Health Organization (WHO), by contrast, includes a separate guideline on children as research participants.²⁴¹ Guideline 14 specifies that research with children may only go ahead if “a parent or legal representative of each child has given permission”, and if “the agreement (assent) of each child has been obtained to the extent of the child’s capabilities”. A child’s refusal to participate or continue in the research should be respected.
- 2.40 These headline principles are discussed further in CIOMS’ commentary on the guideline, where it is noted that the age at which children become legally competent to give consent differs substantially between jurisdictions, and that many children who have not reached the relevant age for their jurisdiction can still understand the implications of informed consent and “knowingly agree” to take part. The term ‘assent’ is used to refer to this ‘knowing agreement’, and hence younger children who are not able to provide such agreement are, by implication, not regarded by CIOMS as capable of giving assent, although the commentary states that “the willing cooperation of the child” should be sought. The ‘deliberate objection’ of children of any age should always be respected unless they need treatment that is not available outside the context of research. The commentary on the guideline further suggests that, while children over 12 or 13 may usually be capable of understanding what is required for informed consent, their agreement (described as “consent (assent)”) should usually be complemented by parental permission, even if local law does not require this.
- 2.41 In general, the CIOMS guideline thus requires the agreement of both parent and child where older children are being invited to participate in research, while encouraging the willing cooperation of younger children, and recognising their right to object.²⁴² However, the commentary also highlights that, for some forms of research (such as research among adolescents regarding sexuality or use of illegal drugs, or research concerning domestic violence or child abuse), it may be appropriate for ethics committees to waive the need for parental permission. It also recognises that, in some countries, children may be deemed ‘emancipated’ before the age at which their domestic law would generally recognise adulthood: for example, because they are married, already parents, or living independently, and may hence be able to consent without the permission, or even knowledge, of their parents.

The law and guidance in Europe

- 2.42 Within the European Union, for the past decade, the **Clinical Trials Directive** of 2001 has set requirements for the conduct of clinical trials of investigational medicinal products which all member states are required to transpose into their national laws

²⁴⁰ See: CIOMS (2013) *CIOMS Working Group on the revision of the 2002 CIOMS Ethical Guidelines for Biomedical Research*, available at: <http://www.cioms.ch/index.php/12-newsflash/232-cioms-working-group-of-the-revision-of-the-2002-cioms-ethical-guidelines-for-biomedical-research>.

²⁴¹ CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf, Guideline 14.

²⁴² By implication the CIOMS guidance would see the threshold between being ‘older’ or ‘younger’ as around 12, but measured in terms of understanding rather than necessarily chronological age.

(see paragraph 2.51 on implementation in the UK).²⁴³ While, at the time of writing, the Directive is still in force, it is due to be superseded by the **Clinical Trials Regulation** which was adopted in April 2014 and is likely to become effective in 2016 (see paragraph 2.46). There are no European Union requirements with respect to other forms of clinical research with children and young people, and hence the requirements summarised below apply only to the minority of research studies that relate to ‘investigational medicinal products’ such as new medicines and vaccines.

- 2.43 Article 4 of the 2001 Directive specifies that trials involving minors may only be undertaken if the consent of the parents or a legal representative has been obtained. The Directive leaves the definition of ‘minor’ to national governments to determine, although the EU Paediatric Regulation (see paragraph 3.12) defines the paediatric population as encompassing those under 18. Many European countries, although not the UK, similarly interpret minors as being under 18.²⁴⁴ The term ‘assent’ is not used in the Directive, but it is specified that the parent’s consent “must represent the minor’s presumed will”. Minors must also receive information, appropriate to their ability to understand, from staff with paediatric experience regarding the trial, its risks and its benefits. The explicit wish of minors, who are capable of forming an opinion and assessing this information, to refuse participation or to withdraw from the trial must be “considered” by the investigator. Thus the Directive emphasises the importance of children and young people receiving appropriate *information* about the trial, but is silent with respect to the role they could or should play in the actual decision about research participation.
- 2.44 The European Commission has published additional **guidance**, produced by an *ad hoc* working group, on the ethical considerations that should be taken into account with respect to the Directive.²⁴⁵ This guidance notes that the Directive itself does not use the term ‘assent’, but that the term does appear in the Declaration of Helsinki. The guidance attempts to provide a bridge between the Directive and the Declaration by specifying that it will use the term ‘assent’ to mean “the expression of the minor’s will to participate”, thus referring back to the requirement in the Directive that a parent’s consent should “represent the minor’s presumed will”. It goes on to emphasise the importance of children participating in the consent process with their parents wherever appropriate, and specifies that researchers should provide age appropriate information, and give families enough time to make their decision.
- 2.45 The guidance further notes how “some authors”²⁴⁶ use the term “knowing agreement” to “reflect the outcome of the process of providing age appropriate information, obtaining assent, and whenever possible obtaining written confirmation from the child”.²⁴⁷ However, it goes on to use the term ‘assent’ in a very different sense from the CIOMS guidance. CIOMS uses the terms ‘assent’ and ‘knowing agreement’ with reference to young people who are legally minors within their own jurisdiction but nevertheless able to understand the implications of informed consent (see paragraph 2.40). However, the European Commission guidance suggests that, in some cases,

²⁴³ Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

²⁴⁴ European Commission (2008) European Union ethical considerations for clinical trials on medicinal products conducted with the paediatric population *European Journal of Health Law* 15(2): 223-50, at paragraph 5.4.

²⁴⁵ European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf.

²⁴⁶ The document does not specify which authors are being referred to here, but it seems likely that this is a reference back to the CIOMS guidance.

²⁴⁷ European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf, at paragraph 5.7.

assent may be obtained from children as young as three who have “the emergent capacity to agree”.²⁴⁸ The guidance further firmly recommends that assent should be obtained in writing as soon as children have reached school age and are able to read and write. We summarise these very different understandings of what assent might involve in Box 2.3 below on pages 60-1 after our discussion of the law in the UK.

- 2.46 The **Clinical Trials Regulation**, which repeals and replaces the Clinical Trials Directive, was adopted on 16 April 2014, and is due to become effective at some point after 28 May 2016, once the necessary new systems have been put into place.²⁴⁹ Unlike Directives (which member states transpose into their own legal systems), Regulations have ‘direct effect’, and so the text of the Clinical Trials Regulation will automatically become law in all EU countries as soon as it comes into force, without further interpretation. However, the regulatory structure established by the Clinical Trials Regulation falls into two parts: Part I of an application to carry out a clinical trial will be handled by any one member state on behalf of all member states (and the assessment by this ‘receiving’ member state will be binding on all others); while Part II of the application must be submitted to each individual member state where the research will be taking place (see paragraphs 3.53 and 3.61 for other requirements set out in the Regulation). Detailed requirements for consent fall within this second category, and hence may differ between EU countries, although the Regulation itself sets out various minimum requirements.
- 2.47 The Regulation follows the example of the Directive in deferring to individual member states to define ‘minors’, thus leaving intact the present scope for difference across the EU as to the age at which young people are treated as legally competent to make their own decisions about research.²⁵⁰ The requirement for informed consent from research participants should, in the case of minors, be understood as “an authorisation or agreement from their legally designated representative” (presumably usually a parent).²⁵¹ The Regulation also sets requirements regarding the information that both children and their legally designated representatives should be given about the proposed research, notwithstanding the provision for more specific requirements by individual member states. Thus:
- information for the participant or for the legally designated representative must “be kept comprehensive, concise, clear, relevant and understandable to a lay person”;²⁵² and

²⁴⁸ Ibid., at paragraph 7.1.2.

²⁴⁹ European Parliament and Council of the European Union (2014) *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>, Articles 83 and 99. See also: Lexology (11 August 2014) *Clinical trials - greater transparency and uniformity across Europe*, available at: <http://www.lexology.com/library/detail.aspx?g=0902d376-0c4e-443f-8100-527099b69ff3> for a useful summary of the provisions of the Regulation.

²⁵⁰ European Parliament and Council of the European Union (2014) *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>, Article 2(18): “‘Minor’ means a subject who is, according to the law of the Member State concerned, under the age of legal competence to give informed consent.”

²⁵¹ Ibid., Article 2(21) (in definitions) and Article 32(1)(a) (requirement for such consent). No direct reference to parents is made in the Regulation.

²⁵² Ibid., Article 29(2)(b). The requirement that the information should be ‘comprehensive’ was added in as a later amendment to the Article.

- minors must receive information about the study “in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children”.²⁵³

2.48 Similarly, the Regulation sets out minimum requirements with respect to the way in which minors should be involved in a decision to take part (or not take part) in research, while also leaving scope for variation in approach between member states:

- a minor should “take part in the informed consent procedure in a way adapted to his or her age and mental maturity”,²⁵⁴
- it is open for national laws to specify that “a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial”,²⁵⁵ and
- “the explicit wish of a minor who is capable of forming an opinion and assessing the information” provided to refuse participation in, or to withdraw from, the clinical trial at any time, should be “respected” by the investigator.²⁵⁶

2.49 As the summary above indicates, there are a number of significant differences between the 2001 Directive and the 2014 Regulation, even without considering the scope for individual member states to make their own (additional) requirements with respect to both consent and assent processes (see Table 2.1 below). The Regulation specifically requires that children and young people should “take part” in the consent process, as well as retaining the earlier requirement to ensure that age-appropriate information is provided by professionals with the necessary skills. The opaque reference in the 2001 Directive to parental consent reflecting their child’s “presumed will” has disappeared. Parents (or other legal representatives) are described as providing “authorisation” or “agreement” rather than ‘informed consent’, drawing attention to the significant difference between a person consenting to a procedure for themselves, and authorising that procedure on another person. Finally, the role of the child (albeit restricted to one “capable of forming an opinion and assessing the information”) in determining their involvement in research is significantly strengthened: the wish of such a child should be “respected” rather than simply “considered”.

Table 2.1: Comparing the Clinical Trials Directive and Clinical Trials Regulation

	2001 Directive	2014 Regulation
Definition of minor?	Depends on member state	Depends on member state
Information for minors?	Yes, appropriate to age of child, from skilled professional	Yes, appropriate to age of child, from skilled professional
Minors take part in consent process?	Not specified	Yes, in a way adapted to their age and maturity
Reference to assent	None	Member state may require
Dissent of minors able to form an opinion	To be ‘considered’ by investigator	To be ‘respected’ by investigator

²⁵³ Ibid., Article 32(1)(b).

²⁵⁴ Ibid., Article 32(2).

²⁵⁵ Ibid., Article 29(8).

²⁵⁶ Ibid., Article 32(1)(c).

2.50 Finally, many European states (both members and non-members of the EU) are signatories to the Council of Europe's Convention on Human Rights and Biomedicine, generally known as the **Oviedo Convention**.²⁵⁷ Many European researchers are thus also bound by the provisions of the Convention and its additional protocol concerning biomedical research.²⁵⁸ The Convention follows the example of the Declaration of Helsinki in that it implicitly includes children and young people within a general category of "persons not able to consent to research", without reference to the threshold at which children might be regarded as able to consent for themselves. Consent should be sought from a "legal representative" or from "an authority, person or body provided for by law".²⁵⁹ However, the Convention differs from the Declaration of Helsinki in making specific reference to 'minors' when specifying how those deemed unable to consent should be involved in the decision about taking part in research. Recognising the developmental nature of childhood, it requires that "the opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity".²⁶⁰

The law in the UK

Clinical trials

2.51 The law relating to the role of children in making decisions about research involvement in the UK differs, depending on whether the research in question is a "clinical trial of an investigational medicinal product", and hence subject to the EU rules described above. Where the research falls into this category, it is currently governed by the 2004 *Clinical Trial Regulations* which apply across the UK, and age is the deciding factor.²⁶¹ **Young people aged 16 or above** are regarded as adults and are entitled to give or withhold consent for themselves. Their parents are not given any special role: if 16 or 17 year olds lack capacity to make the decision for themselves, they are treated on the same basis as adults without capacity, and consent must be sought from a legal representative (who may be, but need not be, their parent). Where **children aged under 16** are invited to take part in a clinical trial governed by the Regulations, consent must be sought from a parent, and children's own consent will not be legally valid, regardless of how capable they are of understanding and weighing the issues at stake. While these 2004 Regulations will require revision once the 2014 EU Clinical Trials Regulation comes into force, individual EU member states will retain their entitlement to define the age of majority and to specify the manner in which children should be involved in the decision to participate in research (see paragraphs 2.46 to 2.48).

²⁵⁷ 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*, available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>. The UK, however, is not a signatory.

²⁵⁸ Council of Europe (2005) *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*, available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>. The UK, however, is not a signatory to the Convention.

²⁵⁹ *Ibid.*, Article 15(1)(iv).

²⁶⁰ 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*, available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>, Article 6(2).

²⁶¹ The Medicines for Human Use (Clinical Trials) Regulations 2004, SI 2004/1031, as amended. Note that these Regulations implement the provisions of the 2001 Clinical Trials Directive (in addition to other functions relating to medicines safety), and that therefore some of the provisions will be superseded once the Clinical Trials Regulation comes into force.

Research other than clinical trials: England and Wales

- 2.52 For research that does not constitute a clinical trial of an investigational medicinal product (and in practice, most clinical research comes into this second category²⁶²), the legal position in the UK is much less clear. In England and Wales, under the Mental Capacity Act 2005, **young people aged 16 and 17** are treated as adults and presumed to have capacity to make their own decisions unless the opposite is demonstrated.²⁶³ This would include the decision to participate in clinical research. Similarly, the Family Law Reform Act 1969 makes clear that 16 and 17 year olds with capacity can provide their own, legally valid, consent to their own medical *treatment*, although the Act is silent on the (distinct) question of consent to clinical research.²⁶⁴ However, under the common law in England and Wales, parents do not lose their power to give consent to treatment on behalf of their children until the latter reach the age of 18: parents' and children's powers to consent thus coexist up to that point. If a 16 or 17 year old refused to consent to treatment, a valid consent could potentially still be obtained from their parents, or from a court, if treatment was held to be in their best interests.²⁶⁵ When considering such a case, courts would take account of the welfare principle and statutory 'welfare checklist' set out in the Children Act 1989²⁶⁶ and the provisions of the Human Rights Act 1998.
- 2.53 Returning to the question of consent to research, then, while the provisions of the Mental Capacity Act offer assurance to young people and health professionals that consent from a 16 or 17 year old to take part in clinical research is legally valid, it remains unclear whether a young person's *refusal* to participate in research could be overridden by their parents or by a court. In practice, however, it seems highly unlikely that a 16 or 17 year old would be compelled to take part in research against their will, unless the research in question represented the only way of accessing a particular experimental treatment that was strongly believed to be the best option for the young person's condition, and a court agreed. In such a case, the decision would effectively relate to the young person's treatment, with the research element being viewed as peripheral.²⁶⁷

²⁶² 17 per cent (820 out of 4,832) of applications to RECs in England from April 2013 to March 2014 were for clinical trials of investigational medicinal products. See: Health Research Authority (2014) *Health Research Authority annual reports and accounts for the year to 31 March 2014*, available at: <http://www.hra.nhs.uk/documents/2014/07/annual-report-2013-2014.pdf>, at page 89.

²⁶³ The Mental Capacity Act (MCA) 2005 applies to those over 16 (section 2(5)), and capacity is presumed unless there is evidence otherwise (s 1(2)). Under the Act, a person is held to have capacity if they can understand, retain, and use or weigh information relevant to the decision, and communicate that decision (sections 2(1) and 3(1)). If a 16 or 17 year old is deemed to lack capacity under the MCA 2005 then other provisions of the Act must be met in order for them to be involved in 'intrusive research', including that the research is approved by the appropriate body and their carers are 'consulted' (section 30). For young people under 18, this may include those with parental responsibility for them. The MCA covers England and Wales.

²⁶⁴ Family Law Reform Act (FLRA) 1969, section 8(1).

²⁶⁵ *Re W (a minor) (medical treatment: court's jurisdiction)* [1993] 1 FLR 1; *Re R (a minor) (wardship: medical treatment)* [1992] 1 FLR 190. These cases have been the subject of considerable academic debate: see, for example, Gilmore S, and Herring J (2011) No is the hardest word: consent and children's autonomy *Child & Family Law Quarterly* **23**(1): 3-25; Cave E, and Wallbank J (2012) Minors' capacity to refuse treatment: a reply to Gilmore and Herring *Medical Law Review* **20**(3): 423-49; Gilmore S, and Herring J (2012) Children's refusal of treatment: the debate continues *Family Law* **42**(8): 973-8. For a recent defence of the 'asymmetry' between entitlement to consent and refuse, see: Manson N (2014) Transitional paternalism: how shared normative powers give rise to the asymmetry of adolescent consent and refusal *Bioethics* **29**(2): 66-73.

²⁶⁶ The welfare principle is set out in section 1(1), and the checklist in section 1(3) of the Children Act 1989. These must be applied when making an order under section 8 of the Act, one way in which courts could get involved in decisions about medical treatment or research with children. In deciding whether to make an order, a number of considerations must be taken into account, including "the ascertainable wishes and feelings of the child concerned" (section 1(3)(a)).

²⁶⁷ See, for example, *Simms v. Simms and another*; *PA v. JA and another* [2002] EWHC 2734, where the English High Court granted a declaration that it was lawful and in their best interests for two young people (16 and 18 years old) suffering from probable variant Creutzfeldt-Jakob disease to receive a 'treatment' (Pentosan Polysulphate (PPS)) which had not yet been clinically tested, and where its effects on CJD were unknown. In the judgment, PPS was viewed as 'pioneering treatment',

- 2.54 For **children under the age of 16** who lack the capacity to decide for themselves whether or not to take part in a particular research study, the law is clear: consent can be given, or withheld, by those with parental responsibility for them. In general, consent is only required from one person with parental responsibility, and researchers would not ordinarily be required to obtain consent from both parents.²⁶⁸ However, the courts have defined a “small group of important decisions” that should not be taken by one parent against the wishes of another, including immunisation and non-therapeutic male circumcision.²⁶⁹ If a child’s parents actively disagreed with each other with respect to their child’s involvement in research, researchers might hesitate to proceed on the basis of the consent of just one parent unless authorised by a court to do so.
- 2.55 Where children are under 16 but *do* have the capacity to decide for themselves whether they wish to take part in a particular research project, a further degree of uncertainty exists. Case law has established that children who have “sufficient understanding and intelligence to enable them to understand fully what is proposed” (often described as ‘Gillick competent’ children) may provide a legally-valid consent for their own *treatment*.²⁷⁰ However, there is no case law on whether or not the concept of Gillick competence should also be applied to research decisions. Hence, in practice, researchers are likely to request parental consent in addition to the consent of children under 16, however capable they may appear to be of making their own decision about whether to take part in the research.²⁷¹ Guidance issued by the UK’s Royal College of Paediatrics and Child Health (RCPCH) in 2014 reiterated this position as follows: “As there is no direct case or statute law in the UK covering non-clinical trial research, it has been presumed that the test of Gillick competence applies. In most instances, the child’s assent or consent should be underpinned by parent consent, but this can be problematic where sensitive subjects, such as sexual health, contraception, and adolescent behavioural studies are involved, and there is a duty to preserve confidentiality. In such cases, the need for parental assent or consent should be carefully considered.”²⁷²

rather than as an offer to be involved in clinical research. However, the judgment included reference to the fact that the young people concerned were not competent to consent. It is unclear what approach the court would have taken if the young people had been competent and had withheld their consent. For discussion of this decision, see: Fovargue S (2013) The (ab)use of those with no other hope? *Cambridge Quarterly of Healthcare Ethics* **22(2)**: 181-91.

²⁶⁸ Department of Health (2009) *Reference guide to consent for examination or treatment: second edition*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138296/dh_103653__1_.pdf, chapter 3, paragraphs 23 and 28.

²⁶⁹ Re J (child’s religious upbringing and circumcision) [1999] 2 FLR 678 and Re B (a child) [2003] EWCA Civ 1148.

²⁷⁰ Gillick v. West Norfolk and Wisbech Area Health Authority [1986] 1 AC 112 (House of Lords decision). As in the case of 16 and 17 year olds, parents retain concurrent powers to consent until their child reaches the age of 18, and so may potentially override the refusal of a Gillick-competent child, based on their perception of their child’s ‘best interests’: see Re R (A Minor: Wardship Consent to Treatment) [1991] 3 WLR 592. It is, however, emphasised in *Gillick* that practitioners should do their best to persuade children to inform and involve their parents, implying that such involvement is the optimum approach.

²⁷¹ See, for example, guidance from the British Medical Association that “parental consent may also be required, even if the child is competent”: British Medical Association (2010) *Children and young people tool kit*, available at: http://bma.org.uk/-/media/files/pdfs/practical%20advice%20at%20work/ethics/children%20and%20young%20people%20toolkit/childrenyoungpeopletoolkit_full.pdf, at page 53. The Medical Research Council similarly encourages “parental involvement” in the decision: Medical Research Council (2004) *MRC ethics guide: medical research involving children*, available at: <http://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/>, at page 23. The General Medical Council takes a more tentative approach, suggesting “if they are able to consent for themselves, you should still consider involving their parents, depending on the nature of the research”: General Medical Council (2007) *0-18 years guidance*, available at: http://www.gmc-uk.org/static/documents/content/0-18_0510.pdf, at paragraph 38.

²⁷² Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99(10)**: 887-91. The question of the confidentiality owed to minors who do not wish to involve their parents in aspects of their healthcare has been further considered in the case of R (on the application of Axon) v. Secretary for State for Health and Another [2006] EWHC 37.

Research other than clinical trials: Scotland

2.56 In Scotland, young people are formally treated as adults from the age of 16, and parental rights and responsibilities cease at this point.²⁷³ The law is therefore clear that when young people aged 16 or 17 are invited to take part in research, consent must be sought from them, and not from their parents. Children and young people under the age of 16 who are judged to have the capacity to make their own decisions about *treatment* may also provide a legally valid consent for themselves.²⁷⁴ However, as in England and Wales, the law is silent on whether this provision also applies to decisions about *research*, and as the RCPCH guidance cited above suggests, it is therefore usual practice additionally to obtain parental consent.

Research other than clinical trials: Northern Ireland

2.57 In Northern Ireland, pending the enactment of mental capacity legislation (under consultation at the time of writing), the Age of Majority Act 1969 specifically enables 16 and 17 year olds to provide valid consent to their own treatment, but is silent on the question of research. However, guidance issued by the Department of Health, Social Services and Public Safety suggests that the standard of Gillick competence may be used to permit young people aged 16 and 17 to consent for themselves to research. The same standard should be used to enable children under 16 to consent to research for themselves where they have the capacity to do so, although parental involvement should always be encouraged.²⁷⁵ As in England and Wales, parental powers to provide consent continue until their children reach the age of 18, and may coexist with their children's powers (see paragraphs 2.52-2.53).

Examples from other jurisdictions

2.58 Given the extent of cultural diversity with respect to perceptions of childhood (see paragraph 1.15), it is unsurprising that there is considerable variation between jurisdictions, both with respect to the general age of majority, and to specific legislative provisions enabling minors to provide consent in particular circumstances. Examples in Box 2.2 provide an indication of that diversity.

Box 2.2: Diverse approaches to consent for children and young people

In **Finland**, young people aged 15 and over can provide consent for research themselves, as long as the research is likely to be of direct benefit to their health. If no direct benefit is expected, then parental consent is required up to the age of 18.²⁷⁶ In **Norway**, parental consent is required for young people up to the age of 18 for research that involves bodily intervention or medicinal products. However, the Norwegian Ministry of Health has the power to pass regulations to enable children to consent for themselves

²⁷³ Age of Legal Capacity (Scotland) Act 1991, section 1; Children (Scotland) Act 1995, sections 1 and 2.

²⁷⁴ Age of Legal Capacity (Scotland) Act 1991, section 2(4).

²⁷⁵ Department of Health, Social Services and Public Safety (2003) *Reference guide to consent for examination, treatment or care*, available at: <http://www.dhsspsni.gov.uk/consent-referenceguide.pdf>, Chapter 3, paragraphs 2.2 and 3.1.

²⁷⁶ Finnish Medical Research Act 1999, section 8. See also: European Forum for Good Clinical Practice (2012) *The EFGCP report on the procedure for ethical review of protocols for clinical research projects in Europe and beyond: question 33 - how is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?*, available at: <http://www.efgcp.eu/Downloads/EFGCPRReportFiles/EFGCP%20ECs%20Report%202012%20-%20Question%2033%20Updated.pdf>.

from the age of 12 for research involving their personal health data.²⁷⁷ In **Sweden**, if young people “realise what the research entails” they may consent for themselves to any form of research from the age of 15.²⁷⁸

In **Singapore**, by contrast, consent to participate in a clinical trial must be obtained from a parent or guardian until a young person reaches the age of 21, unless they are already married. Consent must also be sought from children and young people themselves if they have sufficient understanding.²⁷⁹ Draft legislation covering all forms of biomedical research will, if enacted, require consent to be given by both a young person (where they have sufficient understanding of what is involved) and at least one parent, until young people reach the age of 21. However institutional review boards will be authorised, in limited circumstances, to waive the consent of parents, where young people have the understanding to consent for themselves.²⁸⁰

In **Kenya**, the KEMRI Ethics Review Committee currently advises that children and young people up to the age of 18 years (the age of legal majority) should only be involved in research with consent from at least one parent. There are, however, exceptions. A category of young people described as mature minors (understood as individuals under the age of 18 who are “married, pregnant, a mother or a household head”) may give consent for themselves and for their children, but not for their siblings. For research involving greater than minimal risk and where there is no direct benefit to the individual, it is advised that both parents consent.²⁸¹

Regulatory approach to the role of children and young people

2.59 The sections above summarise a number of regulatory requirements (whether international or domestic, legally-binding or professional good practice advice) with respect to the recruitment of children and young people into clinical research. As will be clear, the general underpinning assumption is that, until the young person reaches the age specified by law²⁸² in their own country, consent to participate in research will be required from a parent or other legally designated representative. However, there may be added complexities, as found, for example, in the law of England and Wales which recognises the age of 16 for young people to consent for themselves in many matters, while retaining coexisting parental entitlements in some circumstances to make decisions on behalf of their children up to the age of 18. English case law has also

²⁷⁷ Norwegian Act on Medical and Health Research (the Health Research Act), section 17. See: University of Oslo Library (2008) *Act 2008-06-20 no. 44: Act on Medical and Health Research (the Health Research Act)* available at: <http://www.ub.uio.no/ujur/ulovdata/lov-20080620-044-eng.pdf>.

²⁷⁸ Nordforsk (2014) *Legislation on biotechnology in the Nordic countries: an overview*, available at: http://www.nordforsk.org/en/publications/publications_container/legislation-on-biotechnology-in-the-nordic-countries-2013-an-overview-2014; section 18 of The Act Concerning the Ethical Review of Research Involving Humans (2003) (Sweden) (see: Central Ethical Review Board (Sweden) (2003) *The Act Concerning the Ethical Review of Research Involving Humans*, available at: http://www.epn.se/media/75686/the_ethical_review_act.pdf).

²⁷⁹ Singaporean Medicines (Clinical Trials) Regulations, section 11. See: Singapore Statutes Online (2000) *Singaporean Medicines (Clinical Trials) Regulations*, available at: <http://statutes.agc.gov.sg/aol/search/display/view.w3p;page=0;query=DocId%3A%2230491174-f2a3-49ef-9fee-d989473cabac%22%20Status%3Ainforce%20Depth%3A0;rec=0>.

²⁸⁰ Human Biomedical Research Bill (2014), section 8. See: Ministry of Health Singapore (2014) *Human Biomedical Research Bill*, available at: https://www.moh.gov.sg/content/dam/moh_web/PressRoom/Press%20releases/Press%20Release%20Annex%20A%20-%20Human%20Biomedical%20Research%20Bill%20-%20Draft%20for%20Public%20Consultation%20-%20November%202014.pdf.

²⁸¹ KEMRI Wellcome Trust Research Programme (2009) *SOP 7: review of the informed consent process and document* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

²⁸² This may either be a general age of majority, or a lower age specifically designated with respect for consent.

developed the concept of competence to consent to treatment (and arguably also to research) based on children's maturity and ability to understand what is required, even where they have not yet reached the age of 16. Such an approach is, by definition, decision-specific, since decisions about different forms of research, in different circumstances, may make very different demands on a child's intellectual abilities or emotional maturity.

2.60 As we note in paragraph 2.36, however, the question of 'who decides' whether children and young people take part in research clearly extends well beyond the question of who is legally entitled to *authorise* participation. Each of the regulatory instruments described above makes some reference to the extent to which children and young people should themselves be involved in that decision. Most cite the need for age-appropriate information to be provided by skilled professionals so that children can be helped to understand what the research entails. In some cases it is clearly spelled out that children and young people should be involved, to the extent appropriate to their age and level of understanding, in making the decision about taking part in research. However, despite this broad consensus on the value to be placed on including children and young people in the decision-making process, there is considerable variation in interpretation, in particular with respect to the use of the term 'assent'. As Box 2.3 demonstrates, the term is used to mean anything from the "emergent capacity to agree" of a three year old, to the "knowing agreement" of a young person able to understand what the research is entitled, and only prevented by age from providing a legally-valid consent.

Box 2.3: Requirements for 'assent'

The term 'assent' is used widely within both international statements on research ethics, and in domestic legislation. However, there is no consensus on how the term should be used:

- The **Declaration of Helsinki** requires researchers to obtain assent from potential research participants who are deemed "incapable of giving informed consent" but "able to give assent". No further detail is given as to what 'giving assent' might mean, or the capacities required to give it.
- The **CIOMS/WHO guidelines** use the term assent to refer to the "knowing agreement" of children "who have not yet reached the legally established age of consent" but who "can understand the implications of informed consent and go through the necessary procedures." By implication, the capacities required for giving assent are the same as those for consent: the only difference is that in the case of assent, domestic law does not recognise the child as legally competent, regardless of the level of their understanding. It is suggested that children over the age of 12 or 13 years of age will usually fall into this category.
- The **EU Commission guidance on the 2001 Clinical Trials Directive** defines assent as "the expression of the minor's will to participate", and suggests that assent may be obtained from children as young as three who have "the emergent capacity to agree". The guidance further firmly recommends that assent should be obtained in writing as soon as children reach school age and are able to read and write.
- The 2014 EU **Clinical Trials Regulation** makes no binding requirements with respect to assent, but leaves it open for national laws to specify that "a minor who is capable of forming an opinion and assessing the information given to him or her, shall also assent in order to participate in a clinical trial". No further detail is given as to how assent should be understood.

- The 2014 guidance issued by the UK **Royal College of Paediatrics and Child Health** defines assent as “the child’s active affirmative agreement”, and states that it should be sought from the age of seven.
- The 2001 EU **Clinical Trials Directive**, the Council of Europe’s **Oviedo Convention** and the 2004 **UK Clinical Trials Regulations** do not use the term ‘assent’ at all.

2.61 There is further variation in approach with respect to the relevance of children’s dissent or “explicit wish... to refuse participation”.²⁸³ The 2001 EU Clinical Trials Directive requires only that such a wish be “considered”, while the replacement 2014 EU Regulation takes a stronger line in specifying that it should be “respected”. In both cases, however, this requirement only appears to apply to “a minor who is capable of forming an opinion and assessing the information provided”, thus implying an older child. The CIOMS guidance, in comparison, takes the view that the “deliberate objection” of young children to take part in research should be respected, unless this would be detrimental to their own health. The RCPCH guidance notes that, while in the UK it might be lawful to go ahead on the basis of parental consent against the wishes of a child, researchers should not do so.²⁸⁴

Box 2.4: Dissent

- The 2001 EU Clinical Trials Directive requires that the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation should be ‘considered’.
- The 2014 EU Regulation specifies that the explicit wish of a minor who is capable of forming an opinion and assessing the relevant information to refuse participation should be ‘respected’.
- The CIOMS guidance states that the ‘deliberate objection’ of young children to take part in research should be respected, unless this would be detrimental to their own health.
- The RCPCH guidance notes that, while in the UK it might be lawful to go ahead on the basis of parental consent against the wishes of a child, researchers should not do so.

2.62 Finally, there is a general lack of clarity as to what professionals should do if children neither assent nor dissent: some instruments, for example, require professionals to ‘seek’ assent (implicitly focusing on the process rather than the outcome), while others specify that assent should be ‘obtained’. The RCPCH guidance is firm in stating that assent should be understood as “active affirmative agreement”, and that “lack of objection should not be construed as assent”.²⁸⁵ It is far from clear, however, how a “lack of objection” should be handled by researchers. There would appear to be a significant distinction between such lack of objection and the “explicit wish not to participate” described above. We return in Chapter 6 (see paragraphs 6.4–6.13) to our

²⁸³ The European Parliament and the Council of the European Union (2001) *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>, Article 4(c).

²⁸⁴ Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99(10)**: 887-91, at page 888.

²⁸⁵ *Ibid.*, at page 888.

own view on how the concepts of assent and dissent should be understood, and the practical implications for children's involvement in decisions about taking part in research.

Comparisons from policy areas outside healthcare

- 2.63 We commented in Chapter 1 that many of the assumptions underlying the way children's participation in research is regulated seem at odds with approaches to children's lives *outside* the research setting (see paragraph 1.25). We have noted, for example, that in many countries, children who are thought too young to make decisions about being involved in research for themselves, are nonetheless expected to take on potentially much more onerous responsibilities: for example, with respect to caring for younger siblings (see paragraph 1.15) or by working to help support their family.²⁸⁶ The age of criminal responsibility also provides an interesting point of comparison: in England and Wales, for example, it is currently set at age ten and in Scotland at age eight.²⁸⁷ Young children in the UK are thus deemed capable, in the context of criminal behaviour, of assuming a level of responsibility with respect to their own actions at a time when it is implicitly assumed they cannot take responsibility for even very minor decisions about research that may have few if any long-term consequences for them.
- 2.64 Where the regulation and guidance cited above make explicit reference to children's age as an approximation for ability to understand what is involved in research, there is a broad consensus that, for most children, this threshold is reached by around the age of 12 to 14.²⁸⁸ However, the fact that, in many jurisdictions, children are not deemed *legally* competent to consent until they are 18 suggests that there are seen to be concerns at stake other than the intellectual ability required to make a decision. One factor that is likely to be relevant in this reluctance to permit children to authorise research participation themselves is the risk of harm that research may potentially pose. Yet examples from outside healthcare again suggest a lack of consistency in this respect. In the UK, young people cannot buy alcohol or tobacco, or gamble, for example, until the age of 18, but may elect to join the army at 16 with their parents' consent.²⁸⁹ The high risk that young drivers may present both to themselves and others is reflected in higher insurance premiums up to the age of 25 or beyond,²⁹⁰ but nevertheless, young people are allowed to start learning to drive on public roads from the age of 17. Children are also encouraged, even required, to take part from a relatively young age in contact sports, such as rugby, where risk of injury is certainly not negligible.²⁹¹ While for many children and young people the risks of such sports may be offset by the benefits such as enjoyment that participation offers, this will not always be the case, particularly in the case of compulsory school sports. We return to

²⁸⁶ Cheah PY, and Parker M (2014) Consent and assent in paediatric research in low-income settings *BMC Medical Ethics* **15**(1): 22. High numbers of orphans in many countries also lead to 'child-led families' where a child as young as 12 may head a household of younger siblings. In Kenya, for example, the number of orphans in 2013 was estimated at 2.5 million, and in Malawi at over 1.2 million: UNICEF (2015) *State of the world's children 2015: country statistical information*, available at: http://www.data.unicef.org/corecode/uploads/document6/uploaded_pdfs/corecode/SOWC_2015_all-countries-update_214.xlsx.

²⁸⁷ Section 50 of the Children and Young Persons Act 1933, as amended, and section 41 of the Criminal Procedure (Scotland) Act 1995. See also discussion of 'responsibility' in James A, and James A (2012) *Key concepts in childhood studies*, Second Edition (London: Sage), pp102-4.

²⁸⁸ See, for example, CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf, at page 68; Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99**(10): 887-91, at page 888.

²⁸⁹ Ministry of Defence: Army (2015) *How to join*, available at: <http://www.army.mod.uk/join/How-to-join.aspx>.

²⁹⁰ See: Brake (2014) *Young drivers*, available at: <http://www.brake.org.uk/too-young-to-die/15-facts-a-resources/facts/488-young-drivers-the-hard-facts>; Young Driver Factbase (2014) *Homepage*, available at: <http://www.youngdriverfactbase.com/>.

²⁹¹ Carter M (2015) The unknown risks of youth rugby *BMJ* **350**: h26.

this point when considering the challenges that those responsible for reviewing the ethical acceptability of research proposals face in determining what is an ‘acceptable’ degree of risk posed by a research study (see paragraphs 5.19–5.21).

- 2.65 In this chapter, we have focussed on what is known about the individual interactions between researchers, potential participants, and their families; and on what is required by law or guidance with respect to those interactions. As the references above to risk indicate, however, the role of regulation is not limited to requirements relating to decision-making and consent, but is also concerned with the wider question of the circumstances in which research with children and young people is permitted at all. We turn in the next chapter to this bigger picture: to the influences and requirements that determine which research studies receive both the funding and the approvals necessary to proceed.

Chapter 3

Developing research
proposals: law and
practice

Chapter 3 – Developing research proposals: law and practice

Chapter 3: overview

This chapter provides an overview of the often extended process by which research studies reach the point of recruitment described in the previous chapter, covering both the 'drivers' of research, and the mechanisms designed to ensure the quality of research studies.

What research takes place and why?

Clinical research studies may be funded by the commercial sector, charitable foundations or public money. Some charitable and public sector funders set out high level priorities for the kind of research they wish to fund, but in practice most funding is allocated in response to the perceived quality of researchers' proposals. Organisations such as the James Lind Alliance argue for a more targeted approach to research prioritisation, and involve both patients and professionals in their 'priority setting partnerships' (PSPs) which identify the most urgent research questions in particular areas of care. Examples include PSPs in neonatal care and teenage cancer.

Where research is funded by the commercial sector, governments may use regulatory requirements and incentives ('sticks and carrots') to influence their agenda. In the specific area of research on medicines, the EU Paediatric Regulation 2006 has increased the information available on medicines used for children and young people by requiring companies to develop 'paediatric investigation plans' (PIPs) to include children and young people whenever they carry out trials of new medicines. New medicines are exempted from this requirement if they target conditions that do not arise in children, although the way these 'class waivers' operate in practice has been criticised. Incentives to encourage further research on off-patent medicines have not so far proved effective.

Action has also been taken at EU level to encourage collaboration, which is particularly important in research with children where conditions may be very rare and hence cohorts of potential research participants very small.

Scrutiny of research proposals

In order to protect potential research participants, international declarations and national guidance set a number of 'threshold' criteria that studies must meet, relating to the value of the research, the balance between benefits and burdens, and the management of risk. The design of research studies is subject to a detailed scrutiny process, involving both scientific ('peer') and ethical review, to ensure that these requirements are met. The valuable contribution that children, young people and parents can make, both in commenting on study design, and ensuring information about the study is suitable for children and young people, is increasingly being recognised, although is not unchallenged.

While many challenges arising in peer and ethical review processes apply to all research scrutiny, regardless of the age of potential participants, concerns specific to the ethical review of research involving children and young people were raised with the Working Party. These included anxieties that, the younger the potential participants, the more research ethics committees (RECs) tended to lean towards a protective or 'parentalist' approach. It was also argued that RECs must have access to specialist expertise in relation to relevant areas of children's and young people's healthcare in order to make a fair judgment about the risks and benefits of the proposed study.

Introduction

- 3.1 In Chapter 2, we considered the experience of children and young people who are invited to take part in a research project, looking first at how in practice they and their families make decisions about participation, and then at the legal and ethical requirements relating to consent for their participation. For many potential research participants, this approach will be their first contact with the research protocol, and may indeed be the first time they have come across clinical research at all. However, for the researchers, the point at which they are able to begin recruiting participants for a study marks an important milestone in what has already been an extended process.
- 3.2 For any research to reach this point of recruitment, researchers will first need to have obtained funding to develop their proposed research and meet the costs of undertaking it, which will involve some element of peer or scientific review of their proposed protocols. Second, a prolonged period of practical preparation is required to move from an idea to a working research project supported by a protocol, documentation for study staff, and information materials for potential participants. Increasingly, the role that children, young people and parents can play at this preparation stage is being recognised. Third, researchers will need to submit their proposals for ethical review before any research involving human participants may go ahead. In some cases, depending on the context of the research, the study will be subject to additional layers of review: for example, in the UK, specific ‘R&D approval’ is required from NHS Trusts before research can go ahead in the NHS.²⁹² Research constituting a clinical trial of a new medicine must meet specific regulatory requirements for review and authorisation (see paragraph 3.35).
- 3.3 The overarching aim of these various review and development processes is to ensure the quality of a research study, before researchers are permitted to recruit children and young people to take part in it. The factors influencing the initial *selection* of research topic, on the other hand, are more complex, with the quality of the research proposal being only one factor. This chapter begins with a consideration of these ‘drivers’ of research, in order to understand the factors underpinning which research proposals actually start their journey through the development and review processes listed above. It then goes on to provide an overview of how these systems currently work (primarily focusing on the picture in the UK but drawing in examples from further afield where possible). A brief summary of some of the main criticisms to which they have been subject is also included, in order to provide background for the Working Party’s own commentary on these issues in Chapter 5.

²⁹² See: National Institute for Health Research (2015) *Clinical trials toolkit: R&D consultation*, available at: <http://www.ct-toolkit.ac.uk/routemap/r-and-d-consultation> and Health Research Authority (2014) *NHS/HSC R&D review or permission*, available at: <http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review>. The main focus of this process is to determine whether the study can feasibly take place at that site: for example whether it has the capacity to support the study and is likely to be able to recruit the proposed number of participants.

What research takes place and why?

Who sets priorities for research?

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

Dr Daniel E Lumsden, responding to the Working Party’s call for evidence

“... charities set targets that they wish to achieve through their research funding activity, identifying gaps in knowledge and capacity and finding the most appropriate way to address them.”

Association of Medical Research Charities (AMRC), responding to the Working Party’s call for evidence

“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, responding to the Working Party’s call for evidence

- 3.4 We noted in Chapter 1 (see paragraph 1.12) that clinical research may be funded through public money, by charitable sources ranging from large foundations to small fundraising charities, or by the commercial sector from large pharmaceutical companies to small biotechnology start-up businesses. Inevitably, funding policies and priorities in the commercial sector will be influenced by financial considerations, taking into account both the research directions that seem most likely to generate a good financial return, and those areas of research on which regulatory incentives have been targeted (see paragraphs 3.11–3.15).²⁹³ The approach taken to research priorities funded by the public or charitable sectors, however, is less obvious.
- 3.5 A survey of funding practices among UK charitable and government funding bodies published in 2008 by the James Lind Alliance (JLA) found that most research funders at the time “operate[d] in a responsive mode”, relying on researchers to submit ideas rather than themselves identifying priorities.²⁹⁴ Fewer than half of the organisations who took part in the survey identified specific priorities for research, and most of those who did were willing to accept applications from researchers that fell outside these priority areas. Moreover, where priorities were set, these tended to be at a high, strategic level, which in practice were so broad that they had little effect on what research received funding. The report noted that some researchers are opposed to formal priority setting by funders because of the difficulties in predicting the outcomes and usefulness of research at the outset, particularly in basic science. Nevertheless, the JLA argued that a systematic approach to identifying and addressing priorities in research was crucial, in order to ensure that the value of research to end-users is properly considered alongside scientific merit. While the JLA survey has not been updated since 2008,

²⁹³ For small start-up businesses, with close links to academic science and medicine, initial research directions may be driven more by science than finance: however, such research is likely to depend on external sources of finance (and hence perceived commercial viability) in order to progress further.

²⁹⁴ The James Lind Alliance (2008) *Scoping research priority setting (and the presence of PPI in priority setting) with UK clinical research organisations and funders*, available at: http://www.lindalliance.org/pdfs/JLA%20Internal%20Reports/TwoCan%20JLA%20report%20March%2009_with%20appendices.pdf, pp6-7.

there does, however, appear to be an increasing focus in both the publicly and charitably funded research sector on the active identification and prioritisation of research topics.²⁹⁵

- 3.6 The JLA's 2008 report concluded that a "robust mechanism" is required to identify the research most likely to benefit patients and clinicians in making decisions about treatment. Such a mechanism should identify gaps in research, and commission research to fill them; increase capacity to conduct research in areas where it is lacking; dedicate funds to these areas; and involve patients and clinicians in all stages in the process. The JLA's own 'priority setting partnerships' (PSPs) are a practical example of this approach in practice: "these bring patients, carers and clinicians together to identify and prioritise for research the treatment uncertainties that they agree are the most important."²⁹⁶ Examples in the area of research with children and young people included an exercise involving 26 organisations and nearly 400 individual contributors to identify the 'top 15' priorities for improving the care of pre-term babies.²⁹⁷ A similar approach is planned with respect to teenage cancer.²⁹⁸
- 3.7 The involvement of children, young people and parents in this prioritisation process recognises that they will have insights into how their conditions affect them, which may differ from clinicians' perceptions and may lead them to take a different view on what forms of research are more pressing.²⁹⁹ The potential success of this collaborative approach does, of course, depend on the existence of effective networks, both of young people and their families, and of clinicians. The role that patient and parent groups may exercise is complex: they may have dual roles, both as advocates of the 'lay' perspective, and also in some cases as research funders in their own right; and concerns are sometimes expressed that the concerns of patients or parents may be vulnerable to manipulation by the commercial research sector.³⁰⁰ On the other hand, in order to play their role appropriately, networks must have sufficient influence for recommendations to be followed through in practice.
- 3.8 Similar initiatives to those promoted by the JLA are found at both European and international level, although the extent to which they draw on the expertise of children, young people and parents rather than relying primarily on the input of professionals, varies. The World Health Organization (WHO), for example, has recently involved 600 researchers in identifying and prioritising key areas for neonatal research.³⁰¹ In the

²⁹⁵ See, for example, The Association of Medical Research Charities (AMRC), responding to the Working Party's call for evidence, and the transition of the work of the JLA in April 2013 into the NIHR's Evaluation, Trials, Studies and Coordination Centre: Evaluation, Trials and Studies Coordinating Centre (8 April 2013) *NETSCC becomes the new home for the management of the JLA PSPs*, available at: <http://www.netscc.ac.uk/news/item/08042013.asp>.

²⁹⁶ The James Lind Alliance (2014) *How the James Lind Alliance works*, available at: <http://www.lindalliance.org/Introduction.asp>.

²⁹⁷ Gale C (2014) *Preterm birth priority setting partnership*, available at: http://www.cm.nihr.ac.uk/wp-content/uploads/children/4_CG_Imperial%20Preterm%20PSP%20140514.pdf.

²⁹⁸ Teenagers and Young Adults with Cancer (2014) *Working together: a celebration of TYAC's first decade 2004-2014*, available at: <http://www.tyac.org.uk/utilities/download.FA0CFB7B-A712-417D-A43A2C1965FA7301.html>, at page 23.

²⁹⁹ See: Johansson V (2014) From subjects to experts - on the current transition of patient participation in research *The American Journal of Bioethics* **14**(6): 29-31.

³⁰⁰ The Guardian (21 July 2013) *Big pharma mobilising patients in battle over drugs trials data*, available at: <http://www.theguardian.com/business/2013/jul/21/big-pharma-secret-drugs-trials>; Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics); Woods S, and McCormack P (2013) Disputing the ethics of research: the challenge from bioethics and patient activism to the interpretation of the Declaration of Helsinki in clinical trials *Bioethics* **27**(5): 243-50.

³⁰¹ WHO invited 200 "of the most productive researchers in the field in the past five years and 400 programme experts" to contribute. 132 people in total submitted their three best research ideas online which were then collated into 205 research

specific context of medicines research, the European Medicines Agency (EMA) undertakes ongoing work on an ‘inventory of paediatric research needs’ across a range of conditions affecting children.³⁰² The Agency’s website notes that these inventories should be of value both to the pharmaceutical industry when identifying “opportunities for business development” and by the Agency’s own Paediatric Committee (PDCO) when considering whether research with children is required as part of the development of new medicines or new uses of existing medicines (see paragraphs 3.12–3.13).

- 3.9 PDCO has been exploring for some time how children and young people could be involved in its activities,³⁰³ and these discussions have explicitly included the proposal that children and young people should have input into this area of defining significant therapeutic needs.³⁰⁴ The results of a survey with PDCO members found that 86 per cent of those responding saw a benefit to involving children and young people in PDCO’s activities, although a minority thought it was too difficult for practical reasons, or that children would not be interested.³⁰⁵ A survey carried out in 2013 by the European Network for Paediatric Research (Enpr-EMA, a European umbrella organisation bringing together individual clinical research networks concerned with research in children from across Europe) found that just four out of 17 responding networks currently involved young people and family members in priority-setting.³⁰⁶ It would therefore appear that such involvement is possible, but far from widespread at present. Enpr-EMA has since set up working groups to develop proposals both for how networks can contribute to prioritising therapeutic needs, and for how children and parents can be involved in those discussions.³⁰⁷
- 3.10 While the approach advocated by the JLA provides a practical model for identifying priorities in the context of individual childhood conditions, or within specialties such as neonatal care, challenges remain with respect to how priorities for research might be agreed *across* children’s specialities, or indeed between childhood and adult conditions. How, for example, should the relative priority to be given to research in childhood cancers, eating disorders, or cystic fibrosis, be determined, and how might these then compete for funding against the need for research into conditions that arise only in adulthood, such as dementia? While there is no simple consensus on the basis for such prioritisation, an attempt has been made in the context of neonatal medicines

questions which were then sent for scoring to the 600 experts first approached: Yoshida S, Rudan I, Lawn JE *et al.* (2014) Newborn health research priorities beyond 2015 *The Lancet* **384(9938)**: e27–e9.

³⁰² This work is mandated by Article 43 of the Paediatric Regulation, see: European Medicines Agency (2014) *Inventory of paediatric needs*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000096.jsp&mid=WC0b01ac05800260a1.

³⁰³ 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/ema/doc_index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500132555&murl=menus/document_library/document_library.jsp&mid=0b01ac058009a3dc.

³⁰⁴ European Medicines Agency (2013) *Involvement of children/young people in PDCO activities*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143651.pdf.

³⁰⁵ European Medicines Agency (2014) *Results from the questionnaire to PDCO members* (London: European Medicines Agency).

³⁰⁶ Pelle B, Helms P, Drabwell J *et al.* (2014) O-168a Young people and family involvement in paediatric research networks: outcomes of a survey among Enpr-ema networks *Archives of Disease in Childhood* **99 (supplement 2)**: A88–A9. Enpr-EMA is the ‘European Network of Paediatric Research at the European Medicines Agency’. Included in these four are the UK-based groups discussed later in this chapter (see paragraphs 3.37–3.39).

³⁰⁷ Enpr-EMA (2014) *Mandate of the Enpr-EMA working groups*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163382.pdf.

research to identify ‘generic’ criteria to guide prioritisation decisions that could potentially be applied more widely.³⁰⁸ These include:

- features of the condition: how severe it is; how common it is; the extent to which it is specific to childhood (thus limiting the scope for learning from adult research); and the extent to which evidence-based treatments currently exist;
- factors relating to existing or potential treatments: whether effective treatments exist for adults (or for older children); what is known about their off-label use in children; whether age-appropriate formulations have been approved; whether treatment will be needed over prolonged periods (adding to risks of adverse outcomes);
- the feasibility of research, including whether it is likely that enough participants can be recruited, and whether relevant outcome measures can be identified and reliably measured; and
- ethical factors influencing the possibility of research, such as whether likely benefits exceed potential harms, and if there are likely to be sufficient benefits over existing therapies.

Some health departments also publish regular reviews of the ‘state of the public health’ in their own countries, which provide a basis for discussion of areas of priority need for research in individual countries or regions.³⁰⁹

The use of regulatory incentives

- 3.11 While commercial organisations are free to set their own research agendas as they see fit, these can, nevertheless, be influenced by the use of regulatory incentives, whether positive or negative (‘carrots and sticks’). Governments thus have some power to influence not only the research directly funded through public money, but also the targets or direction of research funded by industry. The use of such incentives to date has primarily focused on clinical trials, perhaps reflecting both the particular value placed on the development of medicines over other forms of research, and the high cost (and hence often commercial nature) of such research.³¹⁰
- 3.12 In recognition of the need for much better data on medicines used for children (see paragraphs 1.1–1.2), there have been a number of legislative developments in recent years that have either set requirements to conduct paediatric clinical trials or provided incentives to encourage their practice. In the EU, the 2006 Regulation on Paediatric Medicines (commonly known as the Paediatric Regulation) aims to increase both the availability of medicines specifically formulated and licensed for paediatric use, and the

³⁰⁸ Ward RM, Benitz WE, Benjamin DK, Jr. *et al.* (2006) Criteria supporting the study of drugs in the newborn *Clinical Therapeutics* **28(9)**: 1385-98.

³⁰⁹ See, for example, the annual series of reports on the state of public health by the English Chief Medical Officer: Department of Health (2014) *Annual report of the Chief Medical Officer: surveillance volume, 2012 - on the state of the public's health*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/298297/cmo-report-2012.pdf. A companion ‘advocacy’ volume focussed specifically on children’s health, see: Department of Health (2013) *Annual report of the Chief Medical Officer 2012: our children deserve better - prevention pays*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/255237/2901304_CMO_complete_low_res_accessible.pdf.

³¹⁰ The RCPCH, for example, noted in 2012 that there were no commercial studies in the National Institute for Health Research Paediatric Non-Medicines Portfolio, while 62 per cent of the studies in the parallel Medicines portfolio were commercially sponsored. See: Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>, at paragraph 3.8.

level of information available to prescribers on medicines that are taken by children.³¹¹ For companies wanting to market a new medicine, it is now a standard requirement that data from paediatric studies must be included in the application. These studies must be carried out in accordance with a pre-agreed 'paediatric investigation plan' (PIP). Age-appropriate formulations of medicines, such as syrups for young children, should also be developed. These requirements potentially apply to *all* new medicines, and also to certain changes to marketing authorisations (which specify the purposes for which medicines may routinely be used), but may be deferred or waived where appropriate. Waivers, for example, may be granted 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.

- 3.13 Information about clinical trials with children, including those carried out as part of a PIP in countries outside the EU, must, further, be entered into the EU Database on Clinical Trials (EudraCT) for use by national medicines regulators, with some of the information to be made publicly available through the open-access EU Clinical Trials Register.³¹² The information that must be made publicly available includes details of the protocol, the sponsor, the source of funding, the trial design and rationale, and a discussion and interpretation of the study results (including interruption or termination of the trial).³¹³ These requirements to submit information about clinical trials with children also apply to information derived from paediatric studies undertaken *before* the 2006 Regulation came into force, under the 'data-sharing' arrangements set out in Articles 45 and 46 of the Regulation, with the aim of creating a central repository of all such information.³¹⁴
- 3.14 In addition to these requirements, the 2006 Regulation also provides financial incentives to pharmaceutical companies to reward them for carrying out trials with children. Where a PIP has been completed as part of the development of a medicine, then research sponsors will be granted a six months' extension of the 'supplementary protection certificate', thus extending the financial benefit of the patent by six months. For orphan medicinal products (those targeting rare serious diseases), 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.³¹⁵ For off-patent products, a new category of marketing authorisation called the 'paediatric use marketing authorisation' (PUMA) was developed with the aim of encouraging the

³¹¹ Council Regulation (EC) 1901/2006 on medicinal products for paediatric use, as amended by Council Regulation (EC) 1902/2006, coming into force on 26 January 2007. Note, however, that some of provisions only came into force a further 18 months after the main Regulation. See also: European Commission (2014) *Medicines for children: major developments*, available at: http://ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm for a general overview of recent developments in EU policy with respect to medicines for children, and MHRA (2014) *Legal requirements for children's medicines*, available at: <https://www.gov.uk/government/publications/legal-requirements-for-childrens-medicines>.

³¹² EU Clinical Trials Register (2015) *Clinical trials*, available at: www.clinicaltrialsregister.eu. The EudraCT database was first established by Article 11 of the 2001 Clinical Trial Directive (2001/20/EC) for use by national competent authorities to record clinical trial data. Subsequently, Article 57 of the 2004 EU Pharmaceutical Regulation (EC 726/2004) and Article 41 of the Paediatric Regulation (1901/2006) required part of the information to be made public.

³¹³ European Commission (2009) *Guidance on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMA), in accordance with Article 41 of Regulation (EC) No. 1901/2006*, available at: http://ec.europa.eu/health/files/eudralex/vol-10/2009_c28_01/2009_c28_01_en.pdf.

³¹⁴ European Medicines Agency (2014) *Submitting results of paediatric studies*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000038.jsp. The EMA notes on its website that, owing to the large amount of information on nationally authorised medicines, "the assessment [of study results] is processed in several waves."

³¹⁵ Regulation EC No 1411/2000 on orphan medicinal products, Article 8. For more information on the regulation of orphan medicinal products, see: European Commission (2015) *Orphan medicinal products*, available at: http://ec.europa.eu/health/human-use/orphan-medicines/index_en.htm.

development of new formulations, suitable for children, of older medicines. A PUMA, if granted, provides ten years' market protection.³¹⁶

- 3.15 In the US, similar approaches have been in place for some time. Since 1997, the 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.³¹⁷ 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.³¹⁸ Other countries are yet to follow suit in developing such specific initiatives to encourage medicines' research with children,³¹⁹ although international cooperation is promoted through a 'paediatric cluster' involving the EMA, FDA, and regulators in Japan and Canada.³²⁰ The EU and US incentives available to industry could, of course, potentially lead to results of relevance in other countries; however a review published in 2012 concluded that unfortunately companies "do not seem to be making the results of these trials available to all countries if there is no financial incentive to the company."³²¹

Effectiveness of these measures

Overall impact

- 3.16 In 2013, the European Commission published a report reviewing the impact of the first five years of the Paediatric Regulation.³²² While emphasising that it would take at least ten years for the full effects of the Regulation to become apparent, the five-year report nevertheless identified a number of areas where significant progress had been made:

³¹⁶ See: European Medicines Agency (2015) *Paediatric use marketing authorisations*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000413.jsp.

³¹⁷ The Food and Drug Administration Modernization Act (FDAMA; 1997) Paediatric Exclusivity Provision; later reauthorised as the Best Pharmaceuticals for Children Act (2002). See: FDA (2011) *Drug research and children*, available at: <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm>.

³¹⁸ FDA (2003) *Paediatric Research Equity Act 2003*, available at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM077853.pdf>.

³¹⁹ See, for example, Smit-Marshall P (2010) Paediatric trials: a worldview *Applied Clinical Trials* **19**(1): 32-7; Hoppu K, Anabwani G, Garcia-Bournissen F *et al.* (2012) The status of paediatric medicines initiatives around the world: what has happened and what has not? *European Journal of Clinical Pharmacology* **68**(1): 1-10; Council of Canadian Academies (2014) *Improving medicines for children in Canada*, available at: http://www.scienceadvice.ca/uploads/eng/assessments%20and%20publications%20and%20news%20releases/therapeutics/therapeutics_fullreporten.pdf. See also: Sharma A, Jacob A, Tandon M, and Kumar D (2010) Orphan drug: development trends and strategies *Journal of Pharmacy and Bioallied Sciences* **2**(4): 290-9 for a useful summary of orphan drug incentives (potentially relevant to children) around the world.

³²⁰ European Medicines Agency (2012) *5-year report to the European Commission: general report on the experience acquired as a result of the application of the Paediatric Regulation*, available at: http://ec.europa.eu/health/files/paediatrics/2012-09_paediatric_report-annex1-2_en.pdf, pp35-6.

³²¹ Hoppu K, Anabwani G, Garcia-Bournissen F *et al.* (2012) The status of paediatric medicines initiatives around the world: what has happened and what has not? *European Journal of Clinical Pharmacology* **68**(1): 1-10, at page 2.

³²² European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>. See also: European Medicines Agency (2013) *Successes of the paediatric regulation after five years*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500143984.pdf.

- More than 600 PIPs, covering a range of different conditions, had been agreed by PDCO, thus ensuring that information would be collected about the efficacy and safety of these medicines in children.
- Previously unpublished data on around 2,200 medicines had been submitted by companies to regulators.
- 221 changes to product information relating to safety and efficacy had been made, along with 89 additions to dosing information for children.
- A total of 132 new medicines, or new uses of existing medicines, had been licensed or adapted for children.³²³

The parallel ‘carrot and stick’ approaches in the US have had similar results, leading to the introduction of over 350 labelling changes to children’s medicines by 2010.³²⁴

3.17 More generally, the European Commission suggested that the Regulation had led to a “fundamental change of culture” in pharmaceutical companies, with the development of medicines for children now seen as “an integral part of the overall development of a product”. While the number of clinical trials involving children had remained fairly constant at an average of about 350 per year over the five years since the Regulation came into force, this in fact represented a small increase in the *proportion* of clinical trials involving children, as the total number of trials taking place had been falling. Moreover, there had been an “evident increase” in the actual number of children participating in clinical trials, in particular for babies and children under two years of age who, in the past, had been almost entirely excluded from trials. The availability of free advice on paediatric trials from PDCO, and the development of Enpr-EMA were both cited as means by which expertise in paediatric research was increasingly being shared, and collaboration encouraged.³²⁵

Areas where more needed to be done

3.18 The Commission’s report, however, also noted a number of areas where the Regulation had been less successful than had been hoped. Only one PUMA had been granted (see paragraph 3.14), suggesting that the incentive offered to encourage companies to develop suitable children’s formulations for off-patent medicines was insufficient,³²⁶ although ear-marked European funding had initially been made available to encourage such research.³²⁷ Moreover, because the research related to older medicines, it was not necessarily particularly attractive to academics.³²⁸ An additional problem may arise where publicly funded research is carried out by academics, who do

³²³ European Medicines Agency (2013) *Successes of the paediatric regulation after five years*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500143984.pdf; European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children – from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>.

³²⁴ Hoppu K, Anabwani G, Garcia-Bournissen F *et al.* (2012) The status of paediatric medicines initiatives around the world: what has happened and what has not? *European Journal of Clinical Pharmacology* **68**(1): 1-10, at page 2.

³²⁵ European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, pp6-8.

³²⁶ *Ibid.*, at paragraph 5.2.

³²⁷ Article 40 of the Paediatric Regulation, implemented through Framework 7 research grants (see: European Commission (2013) *Research and innovation: FP7*, available at: http://ec.europa.eu/research/fp7/index_en.cfm); Ruggieri L, Giannuzzi V, Baiardi P *et al.* (2014) Successful private-public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines *European Journal of Pediatrics*: 1-11, at page 2.

³²⁸ Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics); European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, at paragraph 5.2.

not necessarily have the same ‘regulatory’ mindset as their industrial colleagues, and may be less alert to what is required by the regulators.³²⁹

- 3.19 A more fundamental challenge was noted in the Commission’s report that, despite the significant increase in the amount of data being collected on the effect of medicines on children, it is not necessarily the case that the research most urgently needed with respect to *children’s* healthcare was being targeted. The methods used by the Regulation to incentivise children’s research still take as their starting point adult health needs: the commercial sector will inevitably target their research on conditions that are common in adults, since these are most likely to bring in the best financial return.³³⁰ Companies are not required to prioritise research targeting the specific health needs of children, but rather simply to ensure that when they undertake research addressing adult conditions, they also, where applicable, include children and young people in the research.³³¹
- 3.20 The Commission’s concern that clinical research with children may not always be targeted where it is most needed received some support from a 2013 review comparing the number and focus of clinical trials worldwide³³² with the WHO data on the global burdens of disease.³³³ This analysis found only a “moderate” association between burden of disease in children and clinical trials in countries across all income levels, with least association in low-income countries. At a Working Party factfinding meeting concerned with ‘setting the research agenda’, however, it was argued that this lack of clear alignment between children’s research priorities and research carried out should not be overstated, at least in the European context, and that in some areas, such as new antibiotics, clear progress was being made.³³⁴
- 3.21 The use of waivers, exempting industry from the requirement to collect data from children on the basis that the trial medicine is for adult use only, has also been contested. In 2010, the EMA published a list of conditions where a waiver would automatically be granted (‘class waivers’) on the basis that the specific condition being targeted by the trial medicine, for example lung cancer, does not occur in children.³³⁵ Waivers may, additionally, be granted on a case-by-case basis. However, in some

³²⁹ The issue of ‘regulatory mindset’ emerged as a strong theme in the EFGCP (2014) *Joint EFGCP/DIA/EMA better medicines for children conference 2014 on explor[ing] ways to enhance collaboration between key players*, available at: <http://www.efgcp.eu/Downloads/confDocuments/Final%20Programme%20-%20EFGCP-DIA-EMA%20Medicines%20for%20Children%20Conference.%2030%20September%20&%201%20October.%20London.pdf>.

Ruggieri L, Giannuzzi V, Baiardi P *et al.* (2014) Successful private-public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines *European Journal of Pediatrics*: 1-11, at page 9, also highlight how trial approval processes call for a “need to address specific regulatory and organisation activities that are usually outside the fields of competence of the academic and not-for-profit research groups.”

³³⁰ European Medicines Agency (2013) *Report of the workshop on paediatric investigation plans in type 2 diabetes mellitus*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143022.pdf, at page 2.

³³¹ European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, at page 10.

³³² Calculated on the basis of all trials registered on the ClinicalTrials.gov registry from 2006 onwards.

³³³ Bourgeois FT, Olson KL, Ioannidis JPA, and Mandl KD (2014) Association between pediatric clinical trials and global burden of disease *Pediatrics* **133(1)**: 78-87.

³³⁴ Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics): see Appendix 1. (For a more critical view on antibiotics, see: Garazzino S, Lutsar I, Bertaina C, Tovo P-A, and Sharland M (2013) New antibiotics for paediatric use: a review of a decade of regulatory trials submitted to the European Medicines Agency from 2000 - why aren’t we doing better? *International Journal of Antimicrobial Agents* **42(2)**: 99-118.) This discussion was in the context of European policy and practice, and did not address the question of inequalities between high and low income countries.

³³⁵ European Medicines Agency (2010) *European Medicines Agency decision P/345/2010*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500011500.pdf.

cases where a class waiver applies, the way in which the trial medicine works (its 'mechanism of action') may be highly relevant to other conditions that *do* occur in children. It has therefore been strongly argued by organisations such as the Institute for Cancer Research (ICR) that waivers should not be granted if there is a possible *related* use of the trial medicine in children.³³⁶ As an example of how this might affect cancer research in particular, the ICR notes that 26 of the 28 cancer medicines that have been authorised in Europe since 2007 have a mechanism of action that is relevant for childhood cancers; nevertheless, 14 of these medicines received waivers.³³⁷

- 3.22 The Working Party was told that the EMA was considering what action might be taken to adjust the way waivers were granted, with one possible approach being to grant a waiver only if the mechanism of action of the trial medicine was clearly inapplicable to children.³³⁸ Minutes of the PDCO meeting in November 2012 noted "a trend for an opinion to revoke the waivers".³³⁹ However, a review of the conditions covered by the existing waivers, initiated by PDCO, was subsequently suspended in June 2013,³⁴⁰ before being restarted in April 2014.³⁴¹ At the time of writing, no formal changes in policy have been announced. It was, however, noted at the EMA's 2014 annual paediatric conference that some research sponsors do choose to develop PIPs, on a voluntary basis, even where a relevant class waiver is in place.³⁴²

Encouraging collaboration and transparency

- 3.23 The question of how well different 'players' in the research field are able and willing to collaborate in research involving children and young people (and the extent to which this can, in fact, be encouraged or mandated by regulators) is also an ongoing issue. Such collaborations are particularly important in research involving children and young people: both because clinical research with children is often concerned with relatively rare conditions, thus making it more difficult to recruit sufficient participants (or avoid repeatedly approaching the same small group of children and young people); and because of the need to ensure that children are only invited to take part in research, with its potential burdens as well as benefits, if the research study is genuinely likely to add to existing knowledge, and not simply duplicate other work elsewhere.³⁴³ Thus, initiatives to promote and improve collaboration are one important way in which the challenge to encourage more 'children-only' research may be met (see paragraphs 3.19–3.20). Such collaboration is relevant not only to researchers and industry, as

³³⁶ Institute of Cancer Research (10 February 2014) *EU rules are denying children latest cancer drugs*, available at: <http://www.icr.ac.uk/news-archive/icr-scientists-call-for-changes-to-eu-rules-on-children%27s-cancer-drugs>.

³³⁷ *Ibid.* For example, the ICR notes that medicines have been approved for treating adult cancers with mutations in the ALK or EGFR genes, but that manufacturers were not obliged to test these medicines in children, even though ALK and EGFR mutations have been shown to play a role in some childhood cancers. For a contrary view on the implementation of the 2006 Regulation: Rose K (2014) European Union pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer *Clinical Therapeutics* **36(2)**: 163-77.

³³⁸ Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics): see Appendix 1.

³³⁹ European Medicines Agency (2012) *Paediatric Committee (PDCO): minutes of the 7-9 November 2012 meeting*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2012/12/WC500136449.pdf, at page 5.

³⁴⁰ European Medicines Agency (2013) *Paediatric Committee (PDCO): minutes of the 12-14 June 2013 meeting*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/07/WC500146772.pdf, at page 5.

³⁴¹ European Medicines Agency (2014) *Paediatric Committee (PDCO): minutes of the 23-25 April 2014 meeting*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2014/06/WC500168239.pdf, at page 13.

³⁴² EFGCP (2014) *Joint EFGCP/DIA/EMA better medicines for children conference 2014 on explor[ing] ways to enhance collaboration between key players*, available at: <http://www.efgcp.eu/Downloads/confDocuments/Final%20Programme%20-%20EFGCP-DIA->

[EMA%20Medicines%20for%20Children%20Conference,%2030%20September%20&%201%20October,%20London.pdf](http://www.efgcp.eu/Downloads/confDocuments/Final%20Programme%20-%20EFGCP-DIA-EMA%20Medicines%20for%20Children%20Conference,%2030%20September%20&%201%20October,%20London.pdf)

³⁴³ See, for example, Salman RA-S, Beller E, Kagan J *et al.* (2014) Increasing value and reducing waste in biomedical research regulation and management *The Lancet* **383(9912)**: 176-85, at page 178, which notes the inefficiencies of duplicating effort for both researchers and regulators.

discussed below, but also to non-commercial funders: in 2012, the Royal College of Paediatrics and Child Health (RCPCH) called for further cooperation between charitable and public funders of children's research in order to maximise impact and avoid duplication.³⁴⁴

- 3.24 While the European Commission's 2013 report highlights the way that European mechanisms established by the Paediatric Regulation have fostered collaboration both within and beyond Europe,³⁴⁵ collaboration and transparency were contested topics at the EMA's 2013 annual paediatric conference. Industry delegates recognised the value of collaborative trials, particularly with respect to recruiting participants with rare conditions, but expressed anxieties about competition.³⁴⁶ Similar concerns have been expressed across the wider clinical research sector in the context of recent European initiatives³⁴⁷ to require more openness about clinical trial protocols and the publication of negative results as well as positive ones.³⁴⁸ However, it is interesting to note that these 'new' requirements, being implemented through the Clinical Trials Regulation 2014 and through transitional action by the EMA, in fact act primarily to bring other areas of clinical research in line with *existing* practice required for those carrying out clinical trials with children where information-sharing has been mandated for some time (see paragraph 3.13).
- 3.25 Although commercial concerns were raised by delegates at the 2013 EMA conference, examples of good practice in collaboration were also presented. A workshop held by the EMA earlier in 2013, specifically on research in type 2 diabetes mellitus in children and young people, for example, identified the potential value of 'multi-arm' trial designs, where a number of new medicines, each being developed by a different company, could be tested simultaneously against a single agreed control group, thus reducing the number of participants needed and avoiding over-burdening potential participants.³⁴⁹ A similar approach has been taken for treatment for Gaucher disease.³⁵⁰ These collaborative approaches were actively encouraged by the regulator, as was a plan to

³⁴⁴ Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>, pp40-1.

³⁴⁵ European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, pp7-8.

³⁴⁶ Develop Innovate Advance (2013) *7th DIA/EFGCP/EMA medicines for children conference*, available at: http://www.diahome.org/Tools/Content.aspx?type=eopdf&file=%2Fproductfiles%2F2276204%2F13115_pgm.pdf. See also: European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, at page 12.

³⁴⁷ European Medicines Agency (28 May 2014) *European Medicines Agency welcomes publication of the Clinical Trials Regulation*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/05/news_detail_002112.jsp&mid=WC0b01ac058004d5c1.

³⁴⁸ See, for example, The Guardian (21 July 2013) *Big pharma mobilising patients in battle over drugs trials data*, available at: <http://www.theguardian.com/business/2013/jul/21/big-pharma-secret-drugs-trials>. The All Trials initiative, by contrast, has campaigned "for all past and present clinical trials to be registered and their full methods and summary results reported": AllTrials (2013) *All trials registered / all results reported*, available at: <http://www.alltrials.net/find-out-more/all-trials/>. In April 2015, the World Health Organization also published a statement on disclosure of clinical trial results. See: Public Disclosure of Clinical Trials Results: World Health Organization (2015) *WHO statement on public disclosure of clinical trial results*, available at: <http://www.who.int/ictrp/results/reporting/en/>. The statement notes, for example, that "unreported clinical trials conducted in the past are to be disclosed in a publicly available, free to access, searchable clinical trial registry."

³⁴⁹ European Medicines Agency (2013) *Report of the workshop on paediatric investigation plans in type 2 diabetes mellitus*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/05/WC500143022.pdf; Karres J, Pratt V, Guettier J-M *et al.* (2014) *Joining forces: a call for greater collaboration to study new medicines in children and adolescents with type 2 diabetes* *Diabetes Care* **37(10)**: 2665-7.

³⁵⁰ European Medicines Agency (2014) *Gaucher disease: a strategic collaborative approach from EMA and FDA*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2014/05/WC500166587.pdf

develop a diabetes/endocrinology network across Europe, hence facilitating the sharing of expertise.

- 3.26 The Commission's 2013 report similarly noted the value of such networks, while commenting that "well-developed research networks capable of facilitating the necessary research to fulfil the commitments included in paediatric investigation plans do exist in some but not all member states".³⁵¹ All four parts of the UK have such networks: the Clinical Research Network: Children (CRN: Children) in England,³⁵² ScotCRN in Scotland,³⁵³ the Children and Young People's Research Network Wales,³⁵⁴ and the NICRN (Children's) in Northern Ireland.³⁵⁵ The English and Scottish networks also include active young persons' advisory groups whose members are involved both in advising on individual study design and documentation, and also in commenting on national policies relating to children's research (see paragraphs 3.37–3.39).³⁵⁶
- 3.27 The increasing recognition of the contribution that children, young people and parents can make in shaping the research agenda highlights how transparency in research (see paragraphs 3.13 and 3.24) is relevant not only between researchers, but also between researchers and participants, or interested members of the public. The 2014 EU Clinical Trials Regulation will specifically require lay summaries to be produced by trial sponsors, explaining the outcomes of the research in a way that is accessible to non-specialists. In the UK, the Care Act 2014 similarly requires the Health Research Authority (HRA) to promote "transparency in research", including publication and dissemination of research findings and conclusions, the provision of access to data on which research findings or conclusions are based, and the provision of information at the end of research to participants.³⁵⁷ The importance placed on access to such information, particularly by those who participated in the research, emerged clearly in responses to the Working Party's call for evidence, in meetings with our stakeholder group, in the Kenya Medical Research Institute (KEMRI) report,³⁵⁸ and in the contributions of young people who took part in our Youth REC project (see Appendices 2-4), as well as in published studies.³⁵⁹ This interest in the outcomes of the research, that is, in what researchers have learned as a result of the study, is distinct from the

³⁵¹ European Commission (2013) *Report from the Commission to the European Parliament and the Council: better medicines for children - from concept to reality*, available at: <http://www.ipex.eu/IPEXL-WEB/dossier/files/download/082dbcc53eea9c03013f75ffb4243058.do>, at page 7.

³⁵² National Institute for Health Research (2014) *About children research*, available at: <http://www.crn.nihr.ac.uk/children/about-children-research/>. The network was formerly known as the Medicines for Children Research Network, but has now expanded in scope to include paediatric non-medicines research.

³⁵³ Scottish Children's Research Network (2014) *Young persons' group*, available at: <http://www.scotcrn.org/young-people/>.

³⁵⁴ Children and Young People's Research Network Wales (2015) *Homepage*, available at: <http://www.wales.nhs.uk/sites3/home.cfm?orgid=970>.

³⁵⁵ Northern Ireland Clinical Research Network (2014) *NICRN (Children's) homepage*, available at: <http://www.nicrn.hscni.net/interest-groups/nicrn-childrens/>.

³⁵⁶ National Institute for Health Research: Children's Research Network (2014) *Young Persons' Advisory Group*, available at: <http://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/>; Scottish Children's Research Network (2014) *Young persons' group*, available at: <http://www.scotcrn.org/young-people/>.

³⁵⁷ Care Act 2014, section 110(2), available at: <http://www.legislation.gov.uk/ukpga/2014/23/part/3/chapter/2/enacted>.

³⁵⁸ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

³⁵⁹ See, for example, Snowdon C, Brocklehurst P, Tasker R *et al.* (2014) Death, bereavement and randomised controlled trials (BRACELET): a methodological study of policy and practice in neonatal and paediatric intensive care trials *Health Technology Assessment* **18(42)**: 1-410, pp186-203, in the context of bereaved parents whose child had taken part in research.

interest of individual participants in their personal ‘results’ that may be applicable to their own healthcare.³⁶⁰

Checks and balances: promoting high quality research

Minimum threshold requirements for research involving children

3.28 The first part of this chapter has presented an overview of the factors (both commercial and non-commercial) that influence which clinical research studies with children and young people are funded, and the impact of the various recent regulatory incentives aimed specifically at including more children and young people in clinical trials of new medicines and vaccines. That, however, is only the first part of the picture from the perspective of the researcher. In order for any such research proposal to progress further, it must also meet a number of regulatory requirements designed to promote high quality research and protect research participants. International conventions such as the Declaration of Helsinki,³⁶¹ the guidelines published by the Council for International Organizations of Medical Sciences (CIOMS) in association with the WHO,³⁶² and the Council of Europe’s Convention on Human Rights and Biomedicine (the ‘Oviedo Convention’),³⁶³ all 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. Individual jurisdictions then decide whether and how to translate these requirements into their own legislative or regulatory arrangements.

3.29 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 REC for scrutiny and approval before the research may begin.

3.30 These general protections for research participants (which appear in broadly similar terms in other international statements) apply to all research, whatever the age the participants. Further protections are then imposed with respect to children, or to all ‘vulnerable groups’, a category implicitly including children and young people (see paragraph 1.26). The provisions relating to the forms of consent or permission required before children may take part in research, and the way in which children and young people should be engaged in decision-making were set out in detail in Chapter 2 (see

³⁶⁰ See, for example, Gikonyo C, Kamuya D, Mbete B *et al.* (2013) Feedback of research findings for vaccine trials: experiences from two malaria vaccine trials involving healthy children on the Kenyan coast *Developing World Bioethics* 13(1): 48-56, which distinguishes clearly between the feedback of aggregate and individual results.

³⁶¹ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>. The 1996 version, while superseded by later revisions, is cited in the EU Directive and UK Clinical Trial Regulations.

³⁶² CIOMS (2002) *International ethical guidelines for biomedical research involving human subjects*, available at: http://www.cioms.ch/publications/layout_guide2002.pdf.

³⁶³ 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*, available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>; Council of Europe (2005) *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research*, available at: <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>.

paragraphs 2.37–2.62). More fundamentally, the Declaration of Helsinki stipulates that medical research with “vulnerable groups” can *only* be justified if it relates to the health needs and priorities of that group, and if it cannot be carried out in non-vulnerable groups.³⁶⁴ Children and young people should thus only be recruited into research that cannot be carried out on adults, and that relates directly to children’s health needs and priorities.³⁶⁵

- 3.31 Such limits are based on the perception of all children and young people as ‘vulnerable’; implicitly these protections suggest that *all* research presents risks, from which children should if possible be excluded. However, as we note elsewhere (see paragraphs 1.5–1.8 and 3.48), ‘clinical research’ involving children covers a wide range of activity, with an equally wide variation in potential risk or burden. Few would dispute the idea that, where possible, early stage clinical trials (especially those using medicines with new mechanisms of action) should be tested first in adults with undoubted capacity to assess the risks and to give consent for themselves.³⁶⁶ However, the justification for excluding children and young people from very low risk research on this basis seems much less clear. Moreover, in some cases this requirement may be used to exclude young people (for example, adolescents with cancer) from ‘adult’ trials of new interventions, even where they have no other options, and there is some prospect of benefit.³⁶⁷
- 3.32 While an approach that limits the involvement of children and young people in research might be seen as highly protective, the Declaration of Helsinki also emphasises the importance of ensuring that particular populations are not *excluded* from research, stating that “groups that are underrepresented in medical research should be provided appropriate access to participation in research”.³⁶⁸ A similar point is made in the Canadian Tri-Council policy guidelines in the particular context of those unable to give valid consent for themselves. The guidelines emphasise that “those who are not competent to consent for themselves shall not be automatically be excluded from research that is potentially beneficial to them as individuals or to the group they represent.”³⁶⁹ Such an approach acts as a reminder of the positive benefits that well-conducted clinical research can bring, and the dangers of providing healthcare that is not underpinned by a solid evidence base (see paragraph 1.19).

³⁶⁴ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, at paragraph 20.

³⁶⁵ Similar limitations are imposed by the Clinical Trials Regulation 2014, with exceptions for medical conditions that only arise in minors, or where the trial is “essential” with respect to minors to validate data obtained from those able to consent for themselves: European Parliament and Council of the European Union (2014) *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>, Article 32(1)(e) and (f).

³⁶⁶ As we note in Box 1.4, however, this is not always possible: some early stage clinical trials can only be done in children, for example in conditions arising only in children, or unique to neonates.

³⁶⁷ This is a particular issue for teenagers in cancer trials, where the older children are, the less likely they are to be recruited. See: Bleyer A (2007) Young adult oncology: the patients and their survival challenges *CA: A Cancer Journal for Clinicians* **57(4)**: 242-55; Whelan JS, and Fern LA (2008) Poor accrual of teenagers and young adults into clinical trials in the UK *Lancet Oncology* **9(4)**: 306-7; Fern LA, Lewandowski JA, Coxon KM, and Whelan J (2014) Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials *The Lancet Oncology* **15(8)**: e341-e50.

³⁶⁸ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, at paragraph 13.

³⁶⁹ Cited in Menon K, Ward R, and Group ftCCCT (2014) A study of consent for participation in a non-therapeutic study in the pediatric intensive care population *Journal of Medical Ethics* **40(2)**: 123-6, at page 123. See: Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada (2010) *Tri-Council policy statement: ethical conduct for research involving humans* (Ottawa: Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada) for the full text.

3.33 The precise ways in which the requirements set by international declarations to protect research participants are implemented in different countries, and for different kinds of research, inevitably vary. The question of ‘voluntariness’ in research with children and young people, implemented through consent and assent procedures, has already been discussed in Chapter 2, in our analysis of the interactions between researchers and families at the point of recruitment to research. The remaining threshold criteria concern the design and scrutiny of the particular study *before* that point of recruitment, and the details of their implementation will again vary in different jurisdictions. However, in almost all cases they will include two critical elements: some form of ‘peer review’ of the proposed study protocol, and ‘ethical review’ by an independent REC or institutional review board (IRB). Below, we provide a brief overview of both these processes of review, before looking separately at the question of risk, which is likely to be an important factor in both stages of the review process.

Scrutiny of study design: the role of peer review

3.34 The threshold requirements described above, relating to the importance of the research, the balance between benefits and burdens, and the management of risks, set clear parameters not only with respect to the selection of research topic, but also to the detailed design of each research study. A critical part of the process by which research institutions or other sponsors decide to adopt a study proposed by one of their researchers, or external funding bodies decide which research proposals they will support, is therefore their assessment of the *quality* of the research proposal. This may include factors such as:

- the quality of the study design (for example, whether the proposed methodology is appropriate, and whether the underpinning science, where relevant, is robust);
- the feasibility and likely acceptability of the proposed study; and
- the importance of the topic.

3.35 This assessment is generally carried out through a process of ‘peer’ or ‘scientific’ review, in which the proposed research will be scrutinised by experts in relevant fields, such as clinicians, experts in methodology (such as statisticians), other relevant professionals, and members of the public (see paragraphs 3.37–3.41).³⁷⁰ Within the UK, *all* health or social care research must be subject to peer review, although the Department of Health has emphasised that this review should be in proportion to the scale of the research and the risks involved.³⁷¹ Thus, in some circumstances, an external panel of independent experts may be required, while in others, such as for student projects, review by an internal supervisor may be sufficient. Where the research constitutes a clinical trial of a new medicine, specific European regulatory requirements for review and authorisation must be met: in particular, clinical trials forming part of a PIP (see paragraph 3.12) must be scrutinised by the EMA’s PDCO,

³⁷⁰ See: National Institute for Health Research (2014) *Clinical trials toolkit: routemap - peer review*, available at: <http://www.ct-toolkit.ac.uk/routemap/peer-review> for a useful explanation of peer review.

³⁷¹ Department of Health (2005) *Research governance framework for health and social*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/139565/dh_4122427.pdf, at page 13. Note that Research governance frameworks are different for each country in the UK. See: Health Research Authority (2005) *Research governance frameworks*, available at: <http://www.hra.nhs.uk/resources/research-legislation-and-governance/research-governance-frameworks/>. A draft UK-wide policy framework was published for consultation by the HRA in the first part of 2015, see: Health Research Authority (2015) *Draft UK policy framework for health and social care research - for comment (active)*, available at: <http://www.hra.nhs.uk/about-the-hra/consultations-calls/uk-policy-framework-health-social-care-research-comment-active/>.

and the final protocols of all clinical trials must be reviewed for safety and quality by national regulatory bodies.³⁷² The EMA can offer scientific advice and assistance in developing protocols for clinical trials, and where these relate to medicines for children, this advice is provided free of charge.³⁷³

- 3.36 While the valuable role that expert scientific and methodological scrutiny may play in the development of research protocols is not disputed, there are well-recognised challenges in the systems currently used for achieving this scrutiny. These include: difficulties in recruiting reviewers as the work is generally unpaid; potential conflicts of interest on the part of reviewers who may themselves be carrying out similar work; and the fact that most reviews are provided anonymously.³⁷⁴ These issues arise across the wider research sector, and are discussed in more detail in the Nuffield Council's 2014 report on the culture of scientific research in the UK.³⁷⁵ In particular, that report emphasises the importance of funding bodies and research institutions recognising and rewarding high quality peer review.³⁷⁶

Input into protocol review by children, young people and parents

"The example of involvement in research of young people in the UK is really an inspiration for researchers in other countries."³⁷⁷

"Involving parents and children in the design of studies, wherever possible and relevant, could also help to encourage recruitment and retention."³⁷⁸

- 3.37 The Working Party received considerable input through its consultative activities on the potential role of children, young people, and parents in influencing the development of research proposals, both in terms of actual study design and in relation to the information that should be provided for potential participants.³⁷⁹ In England, the former Medicines for Children Research Network (now 'CRN: Children' – see paragraph 3.26) has placed the involvement of children and young people at the heart of its activities from its inception, establishing 'young persons' advisory groups' (YPAGs) to ensure that children's and young people's voices are heard in the development of clinical research. ScotCRN has an equivalent group of 24 young people aged between 11 and

³⁷² See Article 6 of the Paediatric Regulation (1901/2006) and National Institute for Health Research (2014) *Clinical trials toolkit: routemap*, available at: <http://www.ct-toolkit.ac.uk/routemap>.

³⁷³ European Medicines Agency (2014) *Scientific advice*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000031.jsp&mid=WC0b01ac0580025b8f.

³⁷⁴ See, for example, the discussion of peer review in The James Lind Alliance (2008) *Scoping research priority setting (and the presence of PPI in priority setting) with UK clinical research organisations and funders*, available at: http://www.lindalliance.org/pdfs/JLA%20Internal%20Reports/TwoCan%20JLA%20report%20March%2009_with%20appendices.pdf. See also: European Medicines Agency (2013) *Best expertise vs conflicts of interests: striking the right balance - workshop report*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500150985.pdf.

³⁷⁵ Nuffield Council on Bioethics (2014) *The findings of a series of engagement activities exploring the culture of scientific research in the UK*, available at: <http://nuffieldbioethics.org/project/research-culture/>.

³⁷⁶ *Ibid.*, pp35-6.

³⁷⁷ Member of the Dutch clinical research community, responding to GenerationR. See: Medicines for Children Research Network (2014) *GenerationR: young people improving research - 2013 meeting report*, available at: <http://viewer.zmags.co.uk/services/DownloadPDF?pubVersion=26&publicationID=62b8f2e9&selectedPages=all>, at page 16.

³⁷⁸ British Medical Association, responding to the Working Party's call for evidence.

³⁷⁹ See also: Fern LA, Lewandowski JA, Coxon KM, and Whelan J (2014) Available, accessible, aware, appropriate, and acceptable: a strategy to improve participation of teenagers and young adults in cancer trials *The Lancet Oncology* **15(8)**: e341-e50.

17,³⁸⁰ and similar young people's groups have since been established in Canada (KIDSCan)³⁸¹ and the US (the KIDS network).³⁸²

- 3.38 YPAGs in England consist of five regional groups based in Liverpool, Birmingham, London, Bristol, and Nottingham, each with ten to 15 members aged between eight and 19.³⁸³ Researchers from both non-commercial and commercial sectors may ask a YPAG to comment on a proposed study protocol, and the Working Party was told that group members are robust where necessary in their comments on what is, and is not, likely to be acceptable to future participants.³⁸⁴ The YPAGs hosted a highly successful conference, GenerationR, in London in September 2013, and speakers included delegates from pharmaceutical companies describing the positive input received from young people, and how this had shaped study protocols.³⁸⁵ In particular, researchers were invited to consider the impact of their proposed designs on young people's daily lives, such as school attendance, and to think hard about whether particular elements of protocols, such as repeated blood sampling at rigid times, were truly essential.³⁸⁶ Delegates commented on how input from YPAG members had both ensured their revised protocols passed very easily through the subsequent ethical review process, and had also made it easier and quicker to recruit children and young people to take part in the resulting study.³⁸⁷
- 3.39 In addition to commenting on elements of the study protocol itself, YPAG members also advise researchers on the appropriate design of patient information sheets and consent and assent forms. Examples of advice cited in the GenerationR report include suggested changes to terminology (using ordinary language, rather than medical terms for bodily functions, for example), producing different materials for different age-groups, and the use of cartoons for younger age-groups.³⁸⁸ The YPAGs have also published guidance for researchers to help them produce accessible information materials for children and young people.³⁸⁹

³⁸⁰ An equivalent group exists in Scotland: Scottish Children's Research Network (2014) *Young persons' group*, available at: <http://www.scotcrn.org/young-people/>, which involves 24 young people aged between 11 and 17.

³⁸¹ Maternal Infant Child & Youth Research Network (2014) *Young persons as research ambassadors and advisors*, available at: <http://www.micyrn.ca/CreatingAndConnectingNetwork.asp>.

³⁸² Connecticut Children's Medical Center (20 September 2013) *Connecticut Children's hosts first-of-its-kind kids' advisory group, offering hands-on, front seat approach in the development of medical innovations for children*, available at: <http://www.connecticutchildrens.org/resources/newsroom/latest-news/13-kids-advisory-group>. See also: KIDS (2013) *Concept brief*, available at: <https://www.ctsacentral.org/sites/default/files/documents/KIDS%20Concept%20Brief%2027JUN13.pdf>.

³⁸³ National Institute for Health Research: Children's Research Network (2014) *Young Persons' Advisory Group*, available at: <http://www.crn.nihr.ac.uk/children/pcpie/young-persons-advisory-group/>.

³⁸⁴ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>.

³⁸⁵ Medicines for Children Research Network (2014) *GenerationR: young people improving research - 2013 meeting report*, available at: <http://viewer.zmags.co.uk/services/DownloadPDF?pubVersion=26&publicationID=62b8f2e9&selectedPages=all>.

³⁸⁶ Nuffield Council on Bioethics (13 September 2013) *Blog: young people show adults how it's done at paediatric conference*, available at: <http://blog.nuffieldbioethics.org/?p=843>.

³⁸⁷ Medicines for Children Research Network (2014) *GenerationR: young people improving research - 2013 meeting report*, available at: <http://viewer.zmags.co.uk/services/DownloadPDF?pubVersion=26&publicationID=62b8f2e9&selectedPages=all>, at page 8; Medicines for Children Research Network (2014) *Industry study benefits from Network know-how*, available at: <http://www.crn.nihr.ac.uk/wp-content/uploads/children/Children%20-%20industry%20study%20benefits%20from%20Network%20know-how.pdf>.

³⁸⁸ Medicines for Children Research Network (2014) *GenerationR: young people improving research - 2013 meeting report*, available at: <http://viewer.zmags.co.uk/services/DownloadPDF?pubVersion=26&publicationID=62b8f2e9&selectedPages=all>, at page 8.

³⁸⁹ NIHR Children's Research Network (2014) *CRN: children - patient information guidance*, available at: <http://www.crn.nihr.ac.uk/resources/crn-children-patient-information-guidance/?h=9>. See also Preston J, Paton H and Callens C (2013) *Guidance notes for involving young people in health research design and delivery* (London: National

- 3.40 Parents are similarly included within the CRN remit,³⁹⁰ and have the opportunity to contribute to the peer review of studies, and comment on documentation.³⁹¹ They have also helped develop practical guidance for parents and carers who find themselves faced with decisions about research participation.³⁹² Organisations concerned with specific childhood conditions may also similarly have mechanisms for involving parents and young people, for example as lay members on panels scrutinising research proposals,³⁹³ or in a more *ad hoc* manner commenting on the design of research information.³⁹⁴ The first ‘Young Persons’ Mental Health Advisory Group’, involving young people aged between 16 and 24 from across England, was set up during 2014 by the NIHR’s CRN: Mental Health.³⁹⁵
- 3.41 The Working Party’s Youth REC project (see Introduction and Appendix 4) also provided valuable evidence of children and young people’s abilities to engage very rapidly with the ethical and practical aspects of study design. The children and young people involved were quick to understand both the main rationale of a mock asthma research protocol, to identify possible areas of concern in the study design presented (often, but not always, agreeing with the views of the adult REC members), and to make practical suggestions as to how the design could be improved.

Role of ethical review

- 3.42 The requirement in the Declaration of Helsinki and elsewhere that draft research protocols should be reviewed by an independent ethics committee applies to all medical research involving human participants. The Declaration specifies that:

“The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to

Institute for Health Research); Young Health Participation (2014) *Involving children and young people in research*, available at: <http://younghealthparticipation.com/involving-children-and-young-people-in-research/>.

³⁹⁰ The (M)CRN’s consumer strategy notes that, in addition to children and young people, its work also encompasses the involvement of “parents/carers with experience of, or interest in, participating in clinical research, health conditions and/or health settings. See: Medicines for Children Research Network (2012) *Medicines for Children Research Network: consumer strategy 2012-2015*, available at: <http://www.crn.nihr.ac.uk/wp-content/uploads/crnadmin/Children-2013-consumer-strategy.pdf>, at page 3.

³⁹¹ See: Clinical Research Network (2008) *Parent involvement*, available at: <http://www.crn.nihr.ac.uk/children/pcpie/parent-involvement/>, which sets out the remit of parents/carers to join clinical studies groups.

³⁹² See, for example, Medicines for Children Research Network (2011) *Toolkit for consumer representatives on MCRN clinical studies groups*, available at: <http://www.crn.nihr.ac.uk/wp-content/uploads/crnadmin/Children-2011-consumer-toolkit.pdf>.

³⁹³ See, for example, the approach used by the Muscular Dystrophy Campaign, where all applications for research funding must be submitted in both ‘lay’ and scientific form: Muscular Dystrophy Campaign (2015) *Applying for a research grant*, available at: <http://www.muscular dystrophyuk.org/information-for-professionals/researchers/apply-for-a-grant/>. In addition, the Campaign involves parents as members of its Lay Research Panel: see, for example, Muscular Dystrophy Campaign (16 July 2013) *Families and individuals come together for Becker muscular dystrophy information day*, available at: <http://www.muscular dystrophyuk.org/news/families-and-individuals-come-together-for-becker-muscular-dystrophy-information-day/>.

³⁹⁴ See: INVOLVE (2009) *Senior investigators and public involvement*, available at: <http://www.invo.org.uk/wp-content/uploads/2011/12/INVOLVESeniorInvestigatorsNov2009.pdf>, at paragraph 3.2, for a discussion of how parents have been involved in planning research with newborns with brain injury. See also: Muscular Dystrophy UK (2015) *Lay research panel*, available at: <http://www.muscular dystrophyuk.org/progress-in-research/get-involved-in-research/lay-research-panel/>.

³⁹⁵ NIHR Clinical Research Network (2014) *Young People’s Mental Health Advisory Group*, available at: <http://www.crn.nihr.ac.uk/news/young-persons-mental-health-advisory-group/> and Clinical Research Network (2014) *Young people ReThinking mental health research*, available at: <http://www.crn.nihr.ac.uk/news/young-people-rethinking-mental-health-research/?h=21>.

*be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.*³⁹⁶

- 3.43 In addition to this overarching requirement for independent ethical scrutiny of research, regardless of the age of participants, some legal instruments further specify that, in the case of research involving children and young people, the review committee must include specific expertise in children’s and young people’s healthcare. The 2014 EU Clinical Trials Regulation, for example, requires that any assessment of a clinical trial involving minors should be “on the basis of paediatric expertise or after taking advice on clinical, ethical and psychosocial problems in the field of paediatrics”,³⁹⁷ and a similar requirement was included in the earlier 2001 Clinical Trials Directive.³⁹⁸ A European survey found that member states had implemented the 2001 requirement in a variety of ways: Finland, Slovakia, the Netherlands and Italy, for example, had established ethics committees specifically devoted to research with minors, while a number of other countries including Norway, Denmark, Spain and France instead provided advice from external experts, where required.³⁹⁹ In the UK, some RECs are ‘flagged’ as including paediatric expertise, and hence as more suitable for considering research protocols.⁴⁰⁰ The importance of such expertise for proper scrutiny of research proposals with children, particularly for those involving babies and young children, was strongly emphasised to the Working Party at a factfinding meeting on the role of ethical review.⁴⁰¹ It was argued that members of RECs may be very anxious about the idea of subjecting children to any kind of invasive interventions, and that it was crucial for there to be a suitably qualified expert on the REC to advise, for example, on what was normal practice in neonatal or children’s units. Such advice might also include clarifying where the current lack of evidence base for any form of treatment might make a placebo an acceptable option in a control group.
- 3.44 Concerns were, however, expressed at the same meeting that this system of ‘flagging’ RECs which are able to deal with paediatric research proposals did not always achieve its purpose. If a REC was flagged, this only meant that the membership included at least one member with paediatric expertise: it was argued there was no guarantee that this member would be present when a proposal relating to research with children or

³⁹⁶ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, at paragraph 23.

³⁹⁷ European Parliament and Council of the European Union (2014) *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>, Article 10(1).

³⁹⁸ The European Parliament and the Council of the European Union (2001) *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>, Article 4(h)

³⁹⁹ Altavilla A, Giaquinto C, and Ceci A (2008) Chapitre 1: European survey on ethical and legal framework of clinical trials in paediatrics: results and perspectives *Journal International de Bioéthique* **19(3)**: 15-48. See also: Altavilla A, Manfredi C, Baiardi P *et al.* (2012) Impact of the new European paediatric regulatory framework on ethics committees: overview and perspectives *Acta Paediatrica* **101(1)**: e27-e32.

⁴⁰⁰ Health Research Authority (2015) *Standard operating procedures for research ethics committees: version 6.1*, available at: <http://www.hra.nhs.uk/documents/2015/01/standard-operating-procedures-version-6-1-2.pdf>, at page 35.

⁴⁰¹ Nuffield Council on Bioethics (2014) *Factfinding meeting: the role of ethical review* (London, 6 February: Nuffield Council on Bioethics): see Appendix 2.

young people was discussed (although their advice should at the least be obtained).⁴⁰² It was also noted that there were perennial difficulties in obtaining and retaining paediatric expertise on RECs, not least because many NHS employers did not see such membership as part of clinicians' core work and hence did not value it. Possible ways forward to promote active engagement with RECs by paediatricians included shifting the culture both in the profession as a whole, and among employing organisations, so that involvement in ethical scrutiny was recognised as a core professional duty.⁴⁰³

- 3.45 More generally, there was a robust discussion at the factfinding meeting as to whether RECs should see their role primarily as *protective* (with a focus first and foremost on the welfare of research participants) or *facilitative* (aiming to help ensure that research could go ahead). It was argued that a good REC should be both: their aim should be to help researchers make their research better, while still protecting potential participants.⁴⁰⁴ Clearly such discussions of the proper role of the REC extend well beyond the area of research involving children and young people to the ethical review of *all* research, as do the well-documented debates in the medical and ethical literature about the balance between the value of the REC process and the administrative burdens it imposes on researchers.⁴⁰⁵ However, it was suggested that these issues arise in acute form in the context of research involving children because of the perceived tendency of REC members to adopt a more protective or 'parentalist' approach in research involving children, especially with younger potential research participants.⁴⁰⁶ In particular, concern was expressed about how 'exposed' REC chairs may feel if adverse outcomes do eventuate in a trial with children, and their own role of providing scrutiny comes under the spotlight.⁴⁰⁷
- 3.46 In light of these concerns that RECs might be overly nervous when scrutinising studies involving children, the National Research Ethics Service (NRES) subsequently provided figures to the Working Party on the outcomes of all the 865 studies involving children and young people submitted to RECs in 2013-4. These showed that 46 of the 865 studies involving children received an 'unfavourable opinion', although of the 27

⁴⁰² Ibid. However, 2015 guidance for UK RECs makes clear that the expert's advice should be obtained: Health Research Authority (2015) *Standard operating procedures for research ethics committees: version 6.1*, available at: <http://www.hra.nhs.uk/documents/2015/01/standard-operating-procedures-version-6-1-2.pdf>, at paragraph 2.53.

⁴⁰³ Nuffield Council on Bioethics (2014) *Factfinding meeting: the role of ethical review* (London, 6 February: Nuffield Council on Bioethics): see Appendix 2.

⁴⁰⁴ Note also section 110(2)(a) of the *Care Act 2014*, where the Health Research Authority is explicitly given functions covering both these aspects: "to protect participants and potential participants in health or social care research and the general public by encouraging research that is safe and ethical".

⁴⁰⁵ See, for example, Dyck M, and Allen G (2012) Is mandatory research ethics reviewing ethical? *Journal of Medical Ethics* **39**(8): 517-20; Dunn M (2012) Getting the justification for research ethics review right *Journal of Medical Ethics* **39**(8): 527-8; Hunter D (2012) How not to argue against mandatory ethics review *Journal of Medical Ethics* **39**(8): 521-4; Israel M (2012) Rolling back the bureaucracies of ethics review *Journal of Medical Ethics* **39**(8): 525-6; Whitney SN (2012) The python's embrace: clinical research regulation by institutional review boards *Pediatrics* **129**(3): 576-8. See also: Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>, at page 60, where it is argued that "publicly funded, investigator led clinical trials designed to resolve uncertainties in treatments already in wide use should be subject to regulation that is proportionate, and not the same as that necessary for trials of novel experimental agents".

⁴⁰⁶ A 'parentalist' approach was described as taking a view on research in the same way that a concerned parent might. This approach was critiqued on the basis that there is a risk that committee members who put themselves in the place of a parent and think 'I wouldn't want my child to take part in that research' are really thinking they wouldn't want their child to have that *condition*. The emotional consequences of 'thinking the unthinkable' about one's own child's health may cause unconscious confusion so that the research becomes unthinkable. See also the discussion of 'collective equipoise' and how REC members may require higher levels of equipoise (i.e. more uncertainty) for research involving children in Mhaskar R, Bercu BB, and Djulbegovic B (2013) At what level of collective equipoise does a randomized clinical trial become ethical for the members of institutional review board/ethical committees? *Acta Informatica Medica* **21**(3): 156-9.

⁴⁰⁷ Nuffield Council on Bioethics (2014) *Factfinding meeting: the role of ethical review* (London, 6 February: Nuffield Council on Bioethics): see Appendix 2.

subsequently resubmitted all but five were then given a favourable opinion. It was noted that these figures were in line with the national average. A much larger proportion (497) of the 865 studies, however, received a 'provisional outcome' after first being scrutinised by a REC. All but eight of these went on to receive a favourable decision, after responding to the RECs' provisional opinions.⁴⁰⁸

- 3.47 It was noted at the factfinding meeting that relevant expertise with respect to children's and young people's healthcare among REC membership was particularly important to ensure that the REC considered the risks of the proposed research in light of both the levels of risk inherent in the current standard of care and the dangers of unresearched care (see above paragraph 3.43). It was also emphasised that, instead of 'second-guessing' what parents and children might think about the proposed protocol, it was crucial to obtain direct input from families with experience of the condition being researched. While the Working Party heard conflicting views at its stakeholder meeting with young people and parents as to whether it was reasonable or practical to involve children directly in REC meetings, there was broad consensus that it was crucial for RECs to ensure that, at some point in the development of the protocol, the voices of those most directly affected had been heard.⁴⁰⁹

Assessing and managing risks

Minimising risks

- 3.48 The assessment, minimisation and management of risks that might arise in a particular study, and the question of whether these are outweighed by the importance of the research question, are key issues that both those involved in peer review and those responsible for ethical review must be satisfied have been addressed in order to permit a study to proceed. As we have reiterated throughout this report, 'clinical research' encompasses an immensely broad area of potential activity, and the risks associated with that research are similarly variable, both in terms of magnitude of possible harm involved, and likelihood of that harm arising. We noted in Chapter 1 that some studies will involve little or no risk at all; some may pose risks of psychological harm; and some lead to the risk of physical harm, or even death (see paragraph 1.8). There are also multiple *causes* of possible harm during a study: risks of harm may arise directly as a result of study procedures, but they may also arise as a result of standard care (which in many cases will not be risk-free), or indeed as a result of the underlying condition. It may, therefore, sometimes be difficult to identify the cause of the harm arising in a particular case, particularly where participants suffer from serious conditions or standard treatment is liable to cause multiple side-effects.
- 3.49 In the specific context of clinical trials involving 'investigational products' such as new medicines or vaccines, there are strict legislative requirements designed to minimise risk and ensure the safety of participants. There are specific rules for phase 1 'first in human' studies to protect participants: these advise, for example, on how the starting dose should be selected, and require appropriate medical expertise to be available on

⁴⁰⁸ Personal communication from Dr Simon Woods National Research Ethics Panel Member (an advisory board for the HRA and NRES), 16 December 2014. The figures relate to the period 1 April 2013 - 31 March 2014. Twenty eight applications in total were resubmitted after receiving an unfavourable opinion, but one application was not in a valid form; hence the figure of 27 cited above.

⁴⁰⁹ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>.

site.⁴¹⁰ Other regulations relate to pharmacovigilance: the ongoing monitoring of safety throughout clinical trials.⁴¹¹ In addition to these safety measures there are also regulations related to 'Good clinical practice' (the international quality standard for clinical trials, designed to facilitate mutual acceptability by regulators in the EU, US and Japan) which must be followed for all clinical trials with investigational products for human use.⁴¹² These rules include provisions designed to protect the participants of clinical trials by ensuring, for example, that those carrying out clinical trials are qualified and trained appropriately to carry out their responsibilities.⁴¹³ Finally, both the EMA and the FDA recommend the use of an independent 'data and safety monitoring board' or 'data monitoring committee' for clinical trials in children and young people. These committees are responsible for overseeing both the safety and the conduct of the trials under their remit and providing their opinion on whether the study should continue, be amended, or stop at any point.⁴¹⁴

Communicating risks

- 3.50 In order for parents, children and young people to make their *own* assessment of whether the risks present in a study are acceptable to them, information about both potential risks and possible benefits needs to be presented in lay language. While both adults and children can find it hard to understand statistical information and make decisions about known risks, it is often believed that children experience particular difficulties with such information.⁴¹⁵ However, it has been argued that, under the right circumstances, even young children can demonstrate considerable understanding: for example, in predicting the colour of counters when drawn from a bag, five year olds can take account of new evidence and guess with some accuracy the most likely outcome.⁴¹⁶
- 3.51 The format in which information is presented can be key to helping both adults and children understand information about risks: for example, presenting risk information as natural frequencies (such as 'eight people out of every 1,000') has been found to help children and adults to understand and solve problems and thereby to make more informed decisions.⁴¹⁷ Pictorial presentations, such as icon arrays or pictographs, are

⁴¹⁰ European Medicines Agency (2007) *Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products*, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf. See also Expert Scientific Group on Phase One Clinical Trials (2006) *Final report*, available at:

http://webarchive.nationalarchives.gov.uk/20130107105354/http://dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_073165.pdf.

⁴¹¹ European Commission (2014) *The EU pharmacovigilance system*, available at: http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm.

⁴¹² International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (1996) *ICH harmonised tripartite guideline: guideline for good clinical practice - E6(R1)*, available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf, implemented in the European Union by European Commission (2005) *Commission Directive 2005/28/EC*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>.

⁴¹³ European Commission (2005) *Commission Directive 2005/28/EC*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>, Article 2 (2).

⁴¹⁴ Food and Drug Administration (2006) *Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring committees*, available at: <http://www.fda.gov/OHRMS/DOCKETS/98fr/01d-0489-gdl0003.pdf>; European Medicines Agency (2005) *Guideline on data monitoring committees*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003635.pdf. For an example of how such ongoing monitoring may be used to halt a study early, see: MedicalXpress (2015) *Morphine following common childhood surgery may be life threatening*, available at: <http://medicalxpress.com/news/2015-01-morphine-common-childhood-surgery-life.html>.

⁴¹⁵ Meder B, and Gigerenzer G (2014) Statistical thinking: no one left behind, in *Probabilistic thinking*, Chernoff EJ, and Sriraman B (Editors) (Dordrecht, Netherlands: Springer), pp127-48.

⁴¹⁶ Giroto V, and Gonzalez M (2008) Children's understanding of posterior probability *Cognition* **106(1)**: 325-44.

⁴¹⁷ Zhu L, and Gigerenzer G (2006) Children can solve Bayesian problems: the role of representation in mental computation *Cognition* **98(3)**: 287-308; Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, and Fagerlin A (2010) The effect of format on

particularly helpful. Typically these visually depict the number of people out of 100 who would have an adverse health outcome if, for example, they took a certain preventative health action, compared to the number out of 100 who would have the adverse outcome if they did not take the action. However, while this knowledge of how to present information about known risks is useful, in many situations involving research, reliable information on risks is not available and decisions have to be made under conditions of uncertainty. Some psychologists have argued that when making decisions under conditions of uncertainty, the simple heuristics or rules of thumb that people intuitively use are often more appropriate than complex strategies that involve considering and weighing all available information.⁴¹⁸

Ethical requirements relating to risk

3.52 Ethical and legal requirements relating to the management of risks in research are set at two levels. General requirements emphasising the importance of assessing, controlling and minimising risks apply to *all* research involving human participants (see, for example, paragraph 3.29). Additional, more stringent, standards may then be set for particular subgroups of participants, whether defined generally as those “incapable of giving informed consent” or more specifically, such as minors. These additional safeguards may seek to categorise risk (for example, as ‘minimal’ or ‘minor increase over minimal’), or specify a balance between risk and benefit, or both. In some jurisdictions these requirements may apply to all research involving children, while in others, they may only apply to research that is categorised as a clinical trial of an investigational medicinal product (see paragraph 1.5 and Box 1.4). Thus:

- If there is “no likelihood of benefit” to potential participants “incapable of giving informed consent”, then the Declaration of Helsinki permits only research entailing “minimal risk and minimal burden”.⁴¹⁹
- Specifically in relation to children, if there is no prospect of direct benefit to the child participant, US Regulations allow research that involves “no greater than minimal” risk or in limited circumstances “minor increase over minimal risk”.⁴²⁰
- If the research does offer the prospect of direct benefit to the child participant, the US Regulations allow risks that are “justified” by the anticipated benefits to the subjects”.⁴²¹
- The 2001 EU Clinical Trials Directive makes no additional requirements for clinical trials involving minors with respect to acceptable levels of risk, but requires that “some direct benefit for the group of patients is obtained from the clinical trial”.⁴²² ‘Group’ is not defined in the Directive.

parents’ understanding of the risks and benefits of clinical research: a comparison between text, tables, and graphics *Journal of Health Communication* **15(5)**: 487-501; Meder B, and Gigerenzer G (2014) Statistical thinking: no one left behind, in *Probabilistic thinking*, Chernoff EJ, and Sriraman B (Editors) (Dordrecht, Netherlands: Springer), pp127-48.

⁴¹⁸ Gigerenzer G, and Gaissmaier W (2011) Heuristic decision making *Annual Review of Psychology* **62(1)**: 451-82.

⁴¹⁹ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, at paragraph 28.

⁴²⁰ US Department of Health & Human Services (2009) *Code of federal regulations: 45 CFR 46.404 & 46.406*, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.406>.

⁴²¹ US Department of Health & Human Services (2009) *Code of federal regulations: 45 CFR 46.405*, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.405>.

⁴²² The European Parliament and the Council of the European Union (2001) *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use*, available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>, Article 4(e).

- Ethical guidance on the 2001 EU Directive allows clinical trials where the risks are “minimised” and where the trial offers a prospect of direct benefit to children with the same condition (not necessarily those participating in the research).⁴²³
- The UK 2004 Clinical Trials Regulations (implementing the 2001 Directive within the UK) allow clinical trials where the risks are “minimised” and where the trial offers a prospect of direct benefit to children actually participating in the study.⁴²⁴
- The 2014 European Clinical Trials Regulation (due to replace the 2001 Directive in 2016 – see paragraphs 2.46–2.49, and 3.61) requires that there should be “scientific grounds” for expecting either “direct benefit for the minor concerned outweighing the risks and burdens involved”, or “some benefit for the population represented by the minor” with only minimal risk and minimal burden compared with standard treatment.⁴²⁵
- The 2014 *Guidance on clinical research involving infants, children and young people* published by the Royal College of Paediatrics and Child Health in the UK states that “research should ideally carry no greater than minimal or low risk. However, research that involves greater than minimal risk may be acceptable if the interventions involve diagnostic procedures or treatments that are important for the individual child, and are likely to provide information that will improve understanding or treatment of the condition.”⁴²⁶

Box 3.1: Approaches to risk and benefit

Benefit as a threshold requirement

- Some direct benefit for the ‘group’ required before clinical trial permitted (2001 EU Directive), interpreted as:
 - prospect of direct benefit for children with the same condition (EU guidance on 2001 Directive)
 - prospect of direct benefit to children participating in the study (UK Clinical Trials Regulations)

Where there is likelihood or prospect of benefit

- Risks justified by the anticipated benefits (US Federal Regulations governing human subjects research)
- Risks and burdens outweighed by direct benefits (2014 EU Regulation)
- Greater than minimal risk acceptable if arising out of interventions that are important for the individual child (RCPCH guidance)

Where there is no likelihood or prospect of direct benefit

- minimal risk and minimal burden (Declaration of Helsinki)
- minimal risk or, in limited circumstances, minor increase over minimal risk (US Federal Regulations)
- minimal risk and minimal burden (2014 EU Regulation)

⁴²³ 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*, available at: ftp://ftp.cordis.europa.eu/pub/ftp7/docs/ethical-considerations-paediatrics_en.pdf, at paragraphs 11 and 12.

⁴²⁴ 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, at paragraphs 10 and 14.

⁴²⁵ European Parliament and Council of the European Union (2014) *Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC*, available at: <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>, Article 32(1)(g). Article 28(1)(e) makes general provision with respect to minimising risk, requiring that “the clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects and both the risk threshold and the degree of distress are specifically defined in the protocol and constantly monitored”.

⁴²⁶ Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99**(10): 887-91.

- 3.53 There has been considerable debate over the approach taken in the 2001 EU Clinical Trials Directive because of its focus on the concept of benefit to a ‘group’ of children, and the varied interpretations of that concept in EU member states’ own legislation. The question of how broadly or narrowly the group should be defined has been highly significant for the permissibility of particular clinical trial protocols: is it necessary for the children participating in the study to obtain direct benefit, and how can that be assured in advance given the inevitable uncertainty involved in research? Would such a requirement include those randomised to standard care? Or should the requirement be understood much more broadly as permitting research that is thought likely to offer direct benefit in the future to children with a particular condition, or even all children who might potentially develop that condition in the future?⁴²⁷ However, the 2014 European Clinical Trials Regulation (which will be directly effective in all member states) cuts through this debate by avoiding the term ‘group’ and specifically requiring instead *direct* benefit to the minor if risks are to be more than minimal. The Regulation follows the approach of the Declaration of Helsinki in permitting only minimal risk and burden where such direct benefit is unlikely. Thus, once the 2014 Regulation comes into force, there appears to be a broad consensus across the various declarations, legal instruments and guidance documents that research should *either* offer the prospect of direct benefit outweighing possible risks (for example, where it is hoped that a trial treatment will be more effective than standard alternatives), or that the procedures involved in the research pose only minimal or low risks and burdens. The exception is the US reference to “minor increase over minimal risk”.⁴²⁸
- 3.54 The rationale for these additional protective safeguards for research with children and young people, and the manner in which they should be interpreted in practice has also been the subject of longstanding debate in the ethical literature.⁴²⁹ At a Working Party factfinding meeting on the question of risk, it was argued that, in attempting to make sense of these safeguards, it was crucial to distinguish the different goals inherent in research interventions.⁴³⁰ As highlighted in Chapter 1, one research protocol may involve a number of distinct components: those that are administered with the goal of improving a patient’s health, such as a new medication or other intervention; and those that are administered in order to generate knowledge and potentially benefit future patients (see paragraph 1.10).
- 3.55 It was put to the Working Party that acceptable risks for these components similarly needed to be judged separately. The risks and burdens (known and unknown) of the new intervention should be judged in the same way of those of any other clinical intervention, and balanced against the prospect of benefit. Thus in the case of a new intervention for a serious condition for which no effective treatments exist, or only those

⁴²⁷ For an overview of these issues, see: Nuffield Council on Bioethics (2011) *Children, medicines and clinical trials: background paper*, available at: http://nuffieldbioethics.org/wp-content/uploads/Children_medicines_clinical_trials_background_paper.pdf. Following the workshop at which this background paper was discussed, the project was renamed ‘Children and clinical research: ethical issues’.

⁴²⁸ IRBs in the US may approve research with children involving minor increase over minimal risk if “the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations” and “the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition”: US Department of Health & Human Services (2009) *Code of federal regulations: 45 CFR 46.406*, available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.406>.

⁴²⁹ See, for example, the discussion of ‘minimal risks’ in: Stanford Encyclopedia of Philosophy (2012) *Minimal risks*, available at: <http://plato.stanford.edu/entries/clinical-research/#MinRis>.

⁴³⁰ Nuffield Council on Bioethics (2014) *Factfinding meeting: risk* (London, 4 November: Nuffield Council on Bioethics).

with known high risks or burdens, high risk might indeed potentially be justified by the prospect of important benefit.⁴³¹ Such an approach would be the same, whatever the age of the patient. However, it was argued that a *separate* judgment should still be made about the acceptability of the risks and burdens of the interventions carried out in order to generate knowledge, where concern for the welfare of young participants should be the dominant concern. These procedures should still be subject to the ‘minimal risk or burden’ requirement, regardless of the prospect of benefit in other aspects of the protocol. Thus the prospect of benefit offered by the intervention could not justify monitoring or data-collecting techniques carried out for research purposes that posed more than minimal risk or burden for the participant.

- 3.56 A number of different approaches have been taken to how this ‘minimal risk or burden’ requirement might be defined. These have included the risks of routine clinical investigations, such as blood pressure measurements; the risks that children are exposed to in their daily lives, such as travelling in a car, crossing the road, or helping with household tasks; and risks of charitable activities, such as mowing the lawn for a neighbour, or taking part in a sponsored event.⁴³² It was put to the Working Party that the most appropriate way of judging an acceptable threshold of risk or burden in a procedure with no potential benefit for participants was by comparison with the “daily risks of children who are not unduly burdened”, that is children who “fare well” in their ordinary lives.⁴³³ Such an approach would exclude inappropriate comparisons with children who were already unduly burdened by factors such as poverty or illness, focusing instead on the kind of risks and burdens that might form part of the usual life experiences of a child or young person living ‘good’ or ‘desirable’ lives. Such life experiences, for example, might include learning to deal with the risks of road transport as children begin to travel independently, or coping with the burden of leaving friends and school because of a family decision to move house.

Minimising risk and burden through innovative trial design

“I would be worried if something went wrong and may cause me harm – blood tests/injections; side effects – be aware – if something would be a risk; time commitment – if you have to fast for a long time; if the trial abides to all standards and regulations for research.”⁴³⁴

- 3.57 There are a number of ways in which the impact of procedures that may be particularly troubling for children and young people can be reduced, and advice is available for researchers on how to design their research with children in mind, particularly with reference to minimising pain.⁴³⁵ As highlighted above, one of the main concerns comes

⁴³¹ It was argued that this was effectively a question of whether the intervention was “consistent with clinically competent care”: ie, given the uncertainty among the community of experts as to the most effective treatment (equipose), were the potential risks and burdens judged to be outweighed by the potential benefits?

⁴³² See, for example, Westra AE, Wit JM, Sukhai RN, and de Beaufort ID (2011) How best to define the concept of minimal risk *The Journal of Pediatrics* **159**(3): 496-500; Binik A, and Weijer C (2014) Why the debate over minimal risk needs to be reconsidered *Journal of Medicine and Philosophy* **39**(4): 387-405; Wendler D (2014) Justice and nontherapeutic pediatric research *The American Journal of Bioethics* **14**(9): 13-5.

⁴³³ Binik A (2014) On the minimal risk threshold in research with children *American Journal of Bioethics* **14**(9): 3-12; Binik A, and Weijer C (2014) Why the debate over minimal risk needs to be reconsidered *Journal of Medicine and Philosophy* **39**(4): 387-405; Nuffield Council on Bioethics (2014) *Factfinding meeting: risk* (London, 4 November: Nuffield Council on Bioethics).

⁴³⁴ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people’s responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴³⁵ See, for example, European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf; Sammons H, and Starkey E (2012) Ethical issues of clinical trials in children *Paediatrics and Child Health* **22**(2): 47-50.

from invasive procedures, especially blood tests. However, local anaesthetics can be used for blood taking, while sedation, such as nitric oxide (laughing gas) or midazolam (a medicine that makes children feel sleepy, and affects memory on a temporary basis) can be used for more invasive procedures such as lumbar puncture. Sampling techniques can also reduce burden: for example, researchers can sometimes take blood samples for research at the same time as those needed for care; make use of clinical samples 'left over' from the laboratory; and use dry blood spots and laboratory techniques that need the smallest sample volume possible.⁴³⁶ Techniques using urine and breath samples, instead of blood samples, can also be considered.⁴³⁷

3.58 There are also techniques for limiting the number of blood samples needed from each individual child, and hence reducing any distress caused. These include the use of techniques such as population pharmacokinetics, where smaller numbers of samples are taken from more children; their data is then analysed together by a computer program to give the same results.⁴³⁸ The statistical technique of Bayesian analysis can also be used to identify the point at which results show significance: this enables the trial to be stopped at the earliest point possible, and so limits the number of children recruited.⁴³⁹ Developments in 'adaptive licensing', in which new medicines may be given provisional approval for use with a limited patient population, with further studies taking place to allow for the possibility of the approval being extended to a broader patient population, may also be valuable for research with children and young people.⁴⁴⁰

Practical constraints on research

"At the minute they [the current regulations] often appear balanced towards making clinical research in children difficult, with multiple layers of overlapping bureaucracy."⁴⁴¹

3.59 The previous section of this chapter has described the various forms of scrutiny that research protocols receive during their development, and the ways in which study designs may be adapted to minimise the impact on children and young people. While the primary aim of these scrutiny processes is to improve the quality of the final research protocol, and to ensure that research participants are appropriately protected, at times the way in which these 'checks and balances' operate in practice may be experienced by researchers as barriers or hindrances in their work. In response to such concerns, there have been a number of recent initiatives aiming to streamline governance processes and minimise regulatory burdens on researchers.

⁴³⁶ Patel P, Mulla H, Kairamkonda V *et al.* (2013) Dried blood spots and sparse sampling: a practical approach to estimating pharmacokinetic parameters of caffeine in preterm infants *British Journal of Clinical Pharmacology* **75**(3): 805-13.

⁴³⁷ Oshikoya KA, Smith K, Sammons H, and Choonara I (2015) Decreased metabolism of 13C-caffeine via hepatic CYP1A2 in marasmus and kwashiorkor based on breath test *Journal of Basic and Clinical Physiology and Pharmacology* **26**(1): 105-13.

⁴³⁸ Long D, Koren G, and James A (1987) Ethics of drug studies in infants: how many samples are required for accurate estimation of pharmacokinetic parameters in neonates? *The Journal of Pediatrics* **111**(6, part 1): 918-21.

⁴³⁹ Sammons H (2009) Ethical issues of clinical trials in children: a European perspective *Archives of Disease in Childhood* **94**(6): 474-7.

⁴⁴⁰ See: MHRA (2014) *Early access to medicines scheme (EAMS)*, available at: <http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm>; TaylorWessing (2014) *Adaptive licensing: a model approach?*, available at: http://www.taylorwessing.com/synapse/regulatory_adaptivelicense.html; WebMD UK Health News (27 May 2014) *Duchenne muscular dystrophy drug approval*, available at: <http://www.webmd.boots.com/children/news/20140527/duchenne-muscular-dystrophy-drug>.

⁴⁴¹ Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI), responding to the Working Party's call for evidence.

- 3.60 In the UK, the role of the HRA has recently been restated in legislation, with an explicit remit of “encouraging research that is safe and ethical”.⁴⁴² The HRA’s functions include those “relating to the co-ordination and standardisation of practice relating to the regulation of health and social care research”, as well as oversight of RECs. The HRA must also publish guidance on principles of good practice in the management and conduct of health and social care research, to which NHS trusts and foundation trusts must have regard. The Care Act 2014 further requires the HRA to ensure that RECs “provide an efficient and effective means of assessing the ethics of health and social care research”.⁴⁴³ Work undertaken so far by the HRA has included the publication of guidance on consistency in REC review.⁴⁴⁴
- 3.61 At European level, the new EU Clinical Trials Regulation is putting in place a revised system for approval of clinical trials including a single centralised application procedure via a new EU portal. Applications will be divided into two parts: Part I will be handled on behalf of multiple member states (where approval is being sought for multi-country trials) by a single ‘receiving’ country; Part II, on the other hand, will be assessed by each member state separately, as it will concern aspects of the trial, such as those relating to consent and ethical review, for which member states are able to set their own requirements. Tight timeframes have been set for assessment of the applications, including ethical scrutiny, and failure to respond within these timeframes will be treated as tacit agreement.⁴⁴⁵ While the Regulation is silent on how ethical scrutiny should be carried out, other than with respect to required timescales, Enpr-EMA has set up a Working Group to gather examples of “good practice when ECs [ethics committees] consider trials related to children and young people” and to develop proposals to disseminate those examples.⁴⁴⁶
- 3.62 Finally, it is important to recognise that there are also a number of administrative and other factors, entirely unconnected with concerns about ethical and scientific acceptability, that may hinder or even prevent research taking place. While such barriers are not intrinsically ‘ethical’ in nature, the Working Party has approached its task from the premise that “scientifically valid and ethically robust research, addressing questions of importance to the health of children and young people, should be seen as intrinsically good, and as a natural and necessary part of a healthcare system” (see paragraph 1.19). It is therefore useful to note briefly here initiatives that have sought to identify, and reduce, such administrative barriers to research with children and young people. In 2012, the RCPCH published the results of its investigation into precisely this issue in the context of the UK NHS.⁴⁴⁷ Barriers to research identified by the RCPCH included:

⁴⁴² Care Act 2014, section 110(2)(a), available at: <http://www.legislation.gov.uk/ukpga/2014/23/part/3/chapter/2/enacted>.

⁴⁴³ Care Act 2014, section 110(1)(a), available at: <http://www.legislation.gov.uk/ukpga/2014/23/part/3/chapter/2/enacted>.

⁴⁴⁴ Health Research Authority - National Research Ethics Advisors’ Panel (2014) *Consistency in REC review*, available at: <http://www.hra.nhs.uk/documents/2014/10/consistency-rec-review-2-may-2014.pdf>.

⁴⁴⁵ For example, European Commission (2014) *Clinical trials: Regulation EU No. 536/2014 - general information*, available at: http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm#ct1; Lexology (11 August 2014) *Clinical trials - greater transparency and uniformity across Europe*, available at: <http://www.lexology.com/library/detail.aspx?g=0902d376-0c4e-443f-8100-527099b69ff3>.

⁴⁴⁶ Enpr-EMA (2014) *Mandate of the Enpr-EMA working groups*, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163382.pdf, Working Group on Ethics, at page 4.

⁴⁴⁷ Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>. See also: National Institute of Health Research (2014) *Delivering neonatal studies on the NIHR portfolio*, available at: <http://www.crn.nihr.ac.uk/wp-content/uploads/children/DRAFT%20NN%20PDM%20Event%20Report%202014%20BRANDED%20v3%2020141208%20%282%29.pdf> as an example of CRN: Children initiatives to tackle some of the many practical challenges that may hinder

- a rigid postgraduate training system that offered little opportunity for clinicians in training to develop research skills or knowledge of research governance;
- a decline in children’s research capacity in the UK, with fewer child-health researchers being appointed by universities;
- very patchy support and infrastructure for research within the NHS, particularly in areas such as primary care, health technologies and health systems research (in contrast with the well-established infrastructure for medicines research);⁴⁴⁸ and
- a simple lack of time for consultants to devote to research.

3.63 In response to these identified concerns, the RCPCH issued a ‘call for action’ for improvements, aimed both at the RCPCH itself and at other interested parties. Recommendations included:

- promising improvements in training in research skills as part of paediatricians’ general training requirements, as set by the RCPCH;
- recommending collaborative work on the part of the NIHR and other academic research funders to increase academic research capacity in the UK; and
- emphasising the important role that NHS organisations play in facilitating research, both in terms of the provision of appropriate facilities, and of recognising the value of paediatricians’ involvement in research “whether as users, contributors or leaders”.⁴⁴⁹

3.64 At the same time, the RCPCH also noted many of the positive features of the UK research environment. These included the excellent support offered to children’s medicines research provided through the MCRN (subsequently re-named – see paragraph 3.26); multiple funding streams for children’s research; governmental commitment to the biosciences; enthusiastic and dedicated support for research from charities, parents and children; and “sterling examples” of consultants and trainee paediatricians eager to be involved in research. The Working Party similarly heard from many such enthusiastic children and young people, parents, health professionals, researchers, and regulators who were inspiring in their commitment to clinical research with children and young people. Having summarised the evidence we heard from those many contributors, along with the legal and regulatory background, we now turn to the Working Party’s own analysis of the ethical issues.

research. For a critique of related infrastructure challenges in the US, see Hay WW, Gitterman DP, Williams DA *et al.* (2010) Child health research funding and policy: imperatives and investments for a healthier world *Pediatrics* **125(6)**: 1259-65.

⁴⁴⁸ Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>, at page 11, recommended that the NIHR establish “a unified Children’s Research Network to support the delivery of medicines and non-medicines children’s studies”. This recommendation was followed in 2014 with the creation of the new Clinical Research Network: Children.

⁴⁴⁹ Royal College of Paediatrics and Child Health Commission for Child Health Research (2012) *Turning the tide: harnessing the power of child health research*, available at: <http://www.rcpch.ac.uk/child-health/research-projects/research-opportunities/turning-tide/turning-tide-harnessing-power-chi>, at page 12.

Chapter 4

An ethical approach to
children's involvement in
research

Chapter 4 – An ethical approach to children’s involvement in research

Chapter 4 overview

Diversity of childhood

We identify three scenarios in which a child’s or young person’s potential for input into a decision about research raises distinct ethical questions:

- **Case One:** children who are not able to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are very unwell or are unconscious.
- **Case Two:** children who are able to form views and express wishes, but who are clearly not yet able to make their own independent decisions about research.
- **Case Three:** children and young people who potentially have the capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered minors in their domestic legal system.

Role of parents

Ethical considerations that parents should take into account when making decisions with or on behalf of their children include:

- **Respect for children as individuals**, regardless of their age or capacity, expressed, for example, through consideration of children’s wishes.
- **Recognition of children’s developing capacity** for autonomous agency, and parents’ supportive role in helping their child to develop decision-making skills and confidence.
- **Concern for children’s immediate and longer-term welfare.** Longer-term welfare is concerned with children’s and young people’s future ‘good’ including, but not limited to, what is best for them in terms of their physical health or personal interests. Parents also have a responsibility to seek to influence the values that their child acquires as they grow up, and to ‘shape’ the adult they become.

How different parents balance these considerations will depend on many contextual factors including the situation of their child at the time (which of the three cases is applicable), the nature of the decision, and the nature of family relationships.

Understanding welfare

- An understanding of a child’s longer-term welfare should encompass the possibility of contributing to wider social goods, such as participation in properly regulated clinical research.
- The language of ‘best interests’ is often used to capture this general concern for children’s welfare, but is misleading in the context of research. Parental consent to research should be based on their confidence that participation in the proposed research is *compatible* with their child’s immediate and longer term interests.

Challenging vulnerability

- Concerns about the potential vulnerability of children and young people in research should be treated as an alert, and not as an automatic brake on research: a prompt to researchers to ask themselves: ‘Does this research raise particular ethical challenges and what can I do about them?’ Researchers need to work in partnership with children, young people and parents throughout the whole endeavour of research.

Introduction: scope and methodology

- 4.1 In Chapter 1 of this report, we set out the ethos that has underpinned the Working Party's consideration of these issues, both in terms of our approach to the value of research (see paragraph 1.19), and in our emphasis on children's and young people's capacity to engage with the research process and the wider world (see paragraphs 1.20–1.26). In Chapter 2, we looked at how, in practice, children and young people, their families, and professionals approach the option of research involvement, and at the approaches taken by law to the role of children and young people in such decision-making. We then, in Chapter 3, analysed the factors underpinning the initial prioritisation and selection of research topics, the 'threshold requirements' governing clinical research set by international ethical conventions to protect potential participants, and the various means of scrutiny through which research proposals pass in order to ensure the quality of a research study, before researchers are permitted to recruit children and young people to take part in it.
- 4.2 In this chapter, we now draw on our underpinning ethos, on the available empirical evidence, and on our overview of existing regulatory approaches, to analyse the ethical issues at stake in seeking to involve children and young people in clinical research. We will then go on, in the final chapters, to consider the implications of this analysis for ethical conduct by research professionals. As we discussed in our Introduction, our approach has been to root our analysis in the reality of children's and young people's lives, aiming to understand how they and their parents experience the 'offer' of taking part in research in the context of their day-to-day lives. To achieve this, we have drawn both on the published literature, and on the direct contribution of children, young people and their parents to the Working Party's considerations: in stakeholder meetings, through our open consultation in the UK and beyond, and in school workshops in the UK and Kenya (see Introduction and Appendices 2-4).
- 4.3 Thus, rather than beginning with the values and principles set out in international ethical or legal conventions on research and considering how these fit with children's and young people's experiences, we have taken the opposite approach: that of starting with the experiences, concerns, and implicit values, arising out of families' practical experience of research involvement, and considering the extent to which these correlate with, or challenge, traditional thinking about the ethical acceptability of research with children and young people. In particular, we have resisted starting from the assumption that an ethical approach to research with children and young people will necessarily be an adapted version of an ethical approach to research with adults. Children and young people are not simply 'small adults', and we should start our consideration with *their* experiences and concerns.
- 4.4 Inevitably, our consideration of 'what matters' ethically to children and young people, families, and research professionals will touch on issues of wider research governance, applicable to all forms of research involving human participants, whatever their age. However, our central focus of concern, both in this chapter, and in the practical policy recommendations that follow, will be on the specific ethical challenges that arise out of the involvement of children and young people in research. We therefore begin with a consideration of what it is that is ethically different about involving children and young people in clinical research.

What is (ethically) different about children and young people?

Who do we mean by ‘children’?

4.5 As we noted in Chapter 1, the terms ‘children’ or ‘minors’ are used in research guidelines and conventions to refer to a far from homogenous group: from newborn babies to adolescents approaching young adulthood (see paragraphs 1.14–1.15). In order to consider what it is that is potentially different, ethically speaking, about children and young people in research, it is necessary to make some further distinctions within this broad concept of ‘childhood’. The use of simple age categorisations is problematic because of the diversity of children’s intellectual abilities and speed of development, maturity, and experience, including experience of illness (see paragraph 2.30). We therefore suggest the use of three ‘paradigm’ or ‘example’ cases of childhood which raise distinct ethical issues with respect to decision-making in research. These draw not only on the capacities associated with particular stages of childhood development, but also on the complexity of the decision to be made, and on situational and temporal factors (such as emotional turmoil or ill-health) which may affect how children and young people experience, and are able to engage with, the research process.

- **Case One:** children and young people who are not able at this time to contribute their own view as to whether they should take part in research. This case covers all babies and very young children, but may also apply on a temporary basis to older children or young people if they are unconscious, or very unwell. Children in Case One may, of course, express physical and emotional reactions to the *procedures* involved in research, but cannot actively participate in an initial decision as to whether they should undertake them.
- **Case Two:** children and young people who *are* able at this time to form views and express wishes, but who are clearly not yet able to make their own decisions about research involvement without assistance. Many children will be able to express wishes and preferences in this way from a relatively young age. The sophistication of their views will vary significantly.
- **Case Three:** children and young people who potentially have the intellectual capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered to be ‘minors’ in their domestic legal system. ‘Capacity’ to make a particular decision should be understood both in terms of the intellectual capacity to understand what is involved and the emotional maturity and experience to understand the wider picture – for example, the likely impact on their future life.

4.6 All children, at the beginning of their lives, will fall into Case One, and most (although not all) will progress over time through Case Two to Case Three. Some children with learning disabilities, for example, may not reach Case Three, although this should never be assumed simply on the basis of a diagnostic label. Although the developmental aspect of childhood means that most children, most of the time, will progress in a linear way through these three paradigm cases, it is nevertheless impossible to suggest meaningful age ranges for each case. This is because the case that is relevant to the situation of a particular child or young person will depend not only on their own maturity and development (combined with other factors such as temporary diminution of capacity), but also, critically, on the *nature* of the proposed research, and hence the nature of the decision to be taken. Thus, Case One might potentially cover

an unconscious 14 year old whose parents are asked to consent to involvement in emergency research; or a frightened seven year old in severe pain whose parents need to make an immediate decision about commencing participation in cancer research on the day of diagnosis; as well as all babies. Case Two might cover a three year old who is a potential participant in a vaccine trial; a 12 year old who is not used to being trusted with his own decisions in a study about his levels of physical activity; or a 15 year old with a life-limiting condition faced with the prospect of participating in a phase 1 trial.⁴⁵⁰ Finally, Case Three might cover a confident and articulate eight year old invited to participate in research about her experiences of using a particular health service; a 13 year old taking part in a study concerned with use of tobacco and alcohol; or a 14 year old used to accepting responsibility to take part in a cognitive study including brain scans.

- 4.7 The primary purpose of these paradigm cases is thus not to provide simple answers to how children at particular ages should be treated in clinical research, but rather to indicate three quite distinct *situations* in which a child's or young person's potential for input into a decision about research raises distinct ethical questions, both for their parents and for professionals involved in research. We return to these cases at different points throughout this chapter.

The role of parents

- 4.8 This **developmental** aspect of childhood, from the complete helplessness of a baby in Case One to the relative self-sufficiency of a young person in Case Three, provides a pointer in identifying what it is that is distinct or 'special' about childhood. A factor that unites all three cases, correlating directly with this developmental nature of childhood, is that children have **parents** (understood in the broadest possible sense of one or more adults taking on a role of parental responsibility whether or not they have a biological connection with their child) who play an important role, from both legal and ethical perspectives, with respect to making decisions on their behalf.⁴⁵¹ While it is certainly the case that some children, such as those in child-headed households,⁴⁵² or street children, do not have any such adult taking a protective interest in their welfare, we suggest that such circumstances should be regarded as exceptional (in the sense of being problematic, even if not necessarily rare) and deserving of separate analysis (see paragraphs 6.37–6.41 for a discussion of researchers' responsibilities in such circumstances).⁴⁵³ We therefore suggest that these two factors – the developmental nature of childhood, and the complementary role of the parent – help explain why it is important to consider the ethical challenges that arise in research with children

⁴⁵⁰ For an illustration of children's capacity to understand and engage, see Myra Bluebond-Langner's work with dying children: "[all] of the leukemic children whom I studied faced death with a great deal of understanding about the world of the seriously ill and their place in it. They knew the institution and disease as well as any lay adult." See: Bluebond-Langner M (1978) *The private worlds of dying children* (Princeton: Princeton University Press), at page 135.

⁴⁵¹ As we noted in Chapter 1, we use the term 'parent' in this report to cover all those with 'parental responsibility' for a child: that is, those who are legally entitled to make decisions for and with the child. In the UK context, for example, this will include legally appointed guardians and also many others, such as grandparents, who have acquired parental responsibility through a parental responsibility order or residence order.

⁴⁵² It was reported at the Global Health Bioethics Network summer school in Malawi (July 2014) that in Malawi alone over a million children live in such households.

⁴⁵³ See: Clacherty G and Walker J (2011) *Including street children: a situational analysis of street children in Durban, South Africa*, available at: <http://www.streetchildrenresources.org/wp-content/uploads/2013/01/including-street-children-south-africa.pdf> who highlight the ethical imperative of ensuring that these particularly excluded groups of children and young people *are* appropriately included in research, especially given that the distinct threats to their health and safety posed by their living conditions.

separately from those challenges that may arise in research with others considered as vulnerable in some way, such as adults who lack capacity.

- 4.9 The nature of the parenting role is in a constant state of change and evolution throughout children's development, from the starting point of children's complete vulnerability and dependence on others, until the points when in practice and/or in law they are regarded as sufficiently mature to take responsibility for their own actions in particular spheres (see paragraph 2.64). Even when children formally reach the age of majority in their own jurisdiction, parents do not stop being parents: young adults may depend on their parents (both practically and emotionally) long into adult life, and in most cases emotional ties between parent and child will continue to evolve during the lifetime of both parties.⁴⁵⁴ However, at the point when children become legally adult, the powers and responsibilities inherent in the parenting role alter fundamentally. We therefore suggest that a starting point for considering what is *ethically* distinct about children is a consideration of the role of the parent towards their minor child (legally defined), both in general, and in specific application to decision-making in research. Such an analysis will also help us understand the role of others who may, in particular contexts and at particular times, have recognised responsibilities towards children: for example, teachers, health professionals and researchers.
- 4.10 Drawing on the input the Working Party received directly from children, parents and professionals in consultation responses, the published literature on decision-making in research with children (see Chapter 2), and ethical analysis of 'good' parenting decisions,⁴⁵⁵ we identified at least three distinct ethical considerations that parents should take into account when making decisions with or on behalf of their children:
- respect for children as **individuals**, regardless of their age or capacity;
 - recognition of children's **developing capacity for autonomous agency** and the supportive or educational role of parents in helping their child develop and 'practise' decision-making skills and confidence; and
 - concern for children's immediate and longer-term **welfare**.

In addition to ethical considerations that will inform the way parents make decisions on behalf of, or with, their children, parents need also to take account of any **practical constraints** that might influence what options are genuinely open to them with respect to a particular decision. These practical constraints may also at times have ethical importance. We consider the three ethical considerations, and the issue of practical constraints, in more detail below.

Children as individuals

"Well, you should let your parents maybe give an opinion but it is your choice!"⁴⁵⁶

⁴⁵⁴ See, for example, Arnett J (2004) *Emerging adulthood: the winding road from the late teens through the twenties* (Oxford: Oxford University Press). See also: Kuther TL, and Posada M (2004) Children and adolescents' capacity to provide informed consent for participation in research *Advances in Psychology Research* **32**: 163-73, at page 168 where they note: "parents remain influential through young adulthood. It appears that the voluntary element of consent is complex."

⁴⁵⁵ See, in particular, Rosati C (2006) Preference-formation and personal good *Royal Institute of Philosophy Supplement* **59**: 33-64.

⁴⁵⁶ Comment by year four child (aged 8-9), reported in Nuffield Council on Bioethics (25 November 2013) *Blog: what do you mean - ask children?!*, available at: <http://blog.nuffieldbioethics.org/?p=907>.

*"You're your own person and you don't have to do something if you don't want to."*⁴⁵⁷

*"Children [taking] part in research should be treated as research participants and not just a means to research findings."*⁴⁵⁸

- 4.11 The notion of respecting children as individuals, regardless of their age or capacity, is described by the philosopher Connie Rosati as "regard for the child as the distinct individual that she is".⁴⁵⁹ This regard for children as distinct individuals was expressed by consultation respondents both in terms of consideration of children's wishes, and respect for their bodily integrity. One parent, for example, commented that "even at five my child knows what he will and won't do",⁴⁶⁰ while a young person put the view forcefully that "it's your body and you shouldn't be forced to agree to doing something you don't want to or aren't comfortable with."⁴⁶¹ Such consideration of children's preferences does not, however, necessarily entail giving children a *veto*, whether in connection with research participation or with respect to other aspects of parental decision-making.⁴⁶² As we discuss below (see paragraphs 4.18–4.33), parents must also take into account questions of their child's welfare which may, at times, run directly counter to their immediate preferences. The preferences of a very young child with respect to participation in research elements of cancer treatment, for example, are unlikely to be the only factor in parental decision-making. Moreover, as we saw in Chapter 2, there is considerable evidence of the value placed by many children and young people (including those approaching adulthood) on shared decision-making with their parents (see paragraphs 2.30–2.32). However, regard for children and young people as individuals and respect for their sense of self provides a powerful reason for ensuring that they are *involved* in any decision that affects them.
- 4.12 Regard for children and young people as individuals should not, however, be understood as respect for 'partial capacity'. Clearly, as children develop and mature, their ability to make decisions on their own also evolves, and part of the parental role is to support that process (see paragraph 4.13). Decisions, whether about research participation or anything else, vary in complexity, and children will have the capacity to make some decisions long before they have the capacity to make others. The role of parents where their minor children *do* have capacity to make a particular decision about research involvement is discussed below (see paragraphs 4.42–4.50). However, where children make a choice or express a preference *without* that capacity and maturity, it is not meaningful to regard their choice as 'partially capacitous' but rather as

⁴⁵⁷ Fifteen year old, responding to the Survey Monkey questionnaire for young people. See: Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people's responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁵⁸ Fasela Emmanuel, NIMR, Lagos, Nigeria, responding to the Working Party's call for evidence.

⁴⁵⁹ Rosati C (2006) Preference-formation and personal good *Royal Institute of Philosophy Supplement* 59: 33-64, at page 38.

⁴⁶⁰ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁶¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people's responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁶² See, for example, Uniacke S (2013) Respect for autonomy in medical ethics, in *Reading Onora O'Neill*, Archard D, Deveaux M, Manson N, and Weinstock D (Editors) (London: Routledge), pp94-110.

an expression of will or value that should be given appropriate consideration because of their intrinsic value as an individual (see paragraphs 4.39–4.40).⁴⁶³

Developing capacity

“I would always ensure my child was involved in decision-making processes, recognising her level of maturity and development.”⁴⁶⁴

“... those from eleven onward, aah, those should make their own decision... Ours as parents is to try to help them...”⁴⁶⁵

- 4.13 An important part of the parenting role, as children mature, is to support them in their development into increasingly autonomous decision-makers. As young participants at the Working Party’s stakeholder day told us, children need the “*chance to learn, and to make their own mistakes*”.⁴⁶⁶ At the same time, it is clearly not the role of responsible parents to abandon children to the consequences of their own decision-making if they lack the understanding or experience to recognise the likelihood or gravity of adverse consequences. As we emphasised in our description of the three paradigm cases (see paragraph 4.5), capacity to make a decision independently includes not only the intellectual ability to understand what is involved, but also the maturity and experience necessary to foresee how the implications of what is involved might affect one’s future life (or indeed that of others), and to feel confident in asking others for help in thinking things through.⁴⁶⁷
- 4.14 This role of parents in supporting their children’s emergent ability to make their own decisions and direct their own lives, while ensuring that this exploration of autonomous agency takes place in a relatively safe environment, has been described as one of ‘mediation’ between children’s wishes and what is practically feasible, socially acceptable, or safe in the wider world. The family lawyer, John Eekelaar, for example, suggests that “a primary role of parenting is, indeed, to mediate between the developing personality of the child and the social world”.⁴⁶⁸ The philosopher Garrath Williams similarly describes the “breadth and depth of institutional experience” required to understand the “terms of cooperation” inherent in the social world, and argues that “above all [children] gain this experience under the authority of their parents, who guide them into the fraught world of adult institutions”.⁴⁶⁹ Parents who responded to the Working Party’s consultation made similar claims in connection with their role in guiding

⁴⁶³ See, for example, Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* **26(8)**: 422-30, which argues for the importance of seeing children as ‘ends in themselves’, and the compatibility of this approach with children’s participation in research.

⁴⁶⁴ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁶⁵ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

⁴⁶⁶ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>.

⁴⁶⁷ See, for example, the discussion in Nedelsky J (1989) Reconceiving autonomy: sources, thoughts and possibilities *Yale Journal of Law and Feminism* **1**: 7-36, at page 11, where Nedelsky argues that “the capacity to find one’s own law can develop only in the context of relations with others (both intimate and more broadly social) that nurture this capacity”.

⁴⁶⁸ Eekelaar J (1994) The interests of the child and the child’s wishes: the role of dynamic self-determinism *International Journal of Law, Policy and the Family* **8(1)**: 42-61, at page 52.

⁴⁶⁹ Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* **26(8)**: 422-30.

and sharing decision-making with their children with respect to research, suggesting: "It should be [an] informed choice and all must be involved to achieve this".⁴⁷⁰

- 4.15 Families will, of course, take a wide range of approaches to the question of how much their children should be encouraged to 'practise' making decisions for themselves and how much opportunity they should have to make their own mistakes. There will be great diversity of approach both between and within different cultural traditions with respect to parenting, and the extent to which children expect to have their voices heard within their families will differ widely around the world.⁴⁷¹ However, we suggest that an inevitable part of any child's development towards adulthood involves increasing responsibility and agency; and that part of the parental role is to support their capacity to handle those responsibilities. The *form* this support may take will vary considerably: it may be highly verbalised, encouraging children to express views and make choices from an early age; or it may be indirect, in placing children in a position where they are expected to take responsibility for themselves or others, such as younger siblings. Whatever form the parental influence may take, children in any culture will be aware of different expectations placed upon them in terms of accepting and managing responsibility between their early childhood and their adolescence.
- 4.16 In general, it is hard to see why any individual child or young person should be treated as *less* responsible in the context of research decisions than he or she is in their daily life.⁴⁷² There are, of course, exceptions to this claim – for example, where children are simply too ill or distressed at the time a research decision is required, or where the responsibilities that they are normally expected to bear are already excessive. We return to these points later (see paragraphs 6.21 and 6.37–6.41).
- 4.17 Recognition of developing capacity includes, by implication, the recognition that the point will come where children can, and will, 'take over' from adults, in the sense of being able to provide their own legally valid consent to proposed research involvement.⁴⁷³ As we discuss below (see paragraph 4.42), this does not necessarily mean that parents will be excluded from a part in decision-making if the young person wishes to involve them, just as adults may find it supportive for a partner or friend to be

⁴⁷⁰ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁷¹ See, for example, Abebe T (2009) Multiple methods, complex dilemmas: negotiating socio-ethical spaces in participatory research with disadvantaged children *Children's Geographies* **7**(4): 451-65, which discusses challenges to research in rural Ethiopia where children are not necessarily seen as having 'private views' as subordinate members of the household. The complexity of the picture, however, is demonstrated by Twum-Danso A (2010) The construction of childhood and the socialisation of children in Ghana: implications for the implementation of Article 12 of the CRC, in *A handbook of children and young people's participation: perspectives from theory and practice*, Percy-Smith B, and Thomas N (Editors) (Abingdon: Routledge), pp130-40, who found in her work in Ghana that children commented in group discussions that it was better not to express opinions, but in practice expressed their views privately to their mothers. Family dynamics may also affect parents' decision-making: see, for example, Sun L, and Lin Y (2015) Homogenous mothers-in-law, different daughters-in-law: in-law relationship comparison between Vietnamese and Taiwanese daughters-in-law *Asian Social Science* **11**(4): 252-8, which notes how, in Vietnam, "the position of the mother-in-law is supreme, and she can dominate over, demand, force and even scold the daughter-in-law."

⁴⁷² Cheah PY, and Parker M (2015) Research consent from young people in resource-poor settings *Archives of Disease in Childhood* **100**(5): 438-40; Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>, at page 16.

⁴⁷³ See, for example, Ross LF (1998) *Children, families and healthcare decision-making* (New York: Oxford University Press); Manson N (2014) Transitional paternalism: how shared normative powers give rise to the asymmetry of adolescent consent and refusal *Bioethics* **29**(2): 66-73.

involved.⁴⁷⁴ However, in such circumstances, the role of a parent will cease to be that of a ‘mediator’ between their child and the world, and become more like that of an equal; offering support, as needed. This shift into capacitous decision-making should not, of course, be seen as a single transition point but as a series of such points, depending on the complexity of the decision: a young person may be capable of making their own decisions in some, but not all, areas and may value more or less support at different times and in different circumstances.

Welfare: moving on from ‘best interests’

“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.”⁴⁷⁵

“It... offers flexibility in that there can be a number of legitimate views as to what is in the best interests of a child.”⁴⁷⁶

“[‘Best interests’] is not helpful at all. Even for therapeutic trials, the treatments are given not primarily that the child should get well, but to objectively evaluate if the medicine works.”⁴⁷⁷

“‘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.”⁴⁷⁸

4.18 A crucial part of the parents’ role is to promote their child’s welfare: taking care of their child both in terms of protecting them from possible harms and in doing what is ‘good’ for them. This role is often captured in the language of ‘acting in a child’s best interests’ although, as we argue below, the use of the word ‘best’ may, at times, create more confusion than clarity. Concern for a child’s welfare may usefully be separated into concern for their *immediate* welfare at the time of the research (such as any pain, anxiety, distress, or enjoyment associated with participation in research) and for their *longer-term* welfare (their future ‘good’, including, but not limited to, questions of what is ‘best’ for them in terms of their physical health or personal interests – see paragraph 4.27). Parents who responded to the Working Party’s survey highlighted factors such as the burden of invasive procedures and discomfort as examples of immediate concerns they might have in connection with research, along with anxiety about the risks of more permanent physical and emotional harm, or invasions of privacy. They also noted possible ways in which participation could be good for their child: for example, in terms of their child’s own health (“better care from their medical team” or “potential to get access to an innovative treatment”); enjoyment (“children like to take part in new things, and might enjoy the experience”); and more broadly in terms of inculcating the value of benefitting others (“encouraging my child to help others”).⁴⁷⁹

⁴⁷⁴ See, for example, Hart RI, Foster HE, McDonagh JE *et al.* (2015) Young people’s decisions about biologic therapies: who influences them and how? *Rheumatology*: Published online first (5 February 2015) which found that mothers play a supporting role in treatment decisions well into their children’s early adulthood.

⁴⁷⁵ Anonymous respondent to the Working Party’s call for evidence.

⁴⁷⁶ Professor Jo Bridgeman, responding to the Working Party’s call for evidence.

⁴⁷⁷ Roma Chilengi, responding to the Working Party’s call for evidence.

⁴⁷⁸ Health Research Authority, responding to the Working Party’s call for evidence.

⁴⁷⁹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

Children and young people raised a similar range of possible benefits and concerns with respect to taking part in research (see paragraphs 2.20–2.23).

- 4.19 While individual children and young people may have very different feelings about particular procedures, such as the prospect of a blood sampling, judgments about whether their immediate welfare is affected by the proposed research are likely to be relatively uncontested. Something that distresses children or makes them anxious will be a matter of concern with respect to their welfare. Conversely, if children show interest or enjoyment in taking part, parents will be reassured that participation is having a positive effect on their short-term welfare.
- 4.20 What constitutes children's or young people's longer term welfare, on the other hand, may be more hotly contested. As we noted at the beginning of this report (see paragraph 1.10), the primary purpose of research is an attempt to derive generalisable new knowledge that may benefit others in the future. While a research protocol may include elements of treatment such as a novel medicine or intervention, procedures undertaken for research purposes (whether these are additional tests to collect data, or the randomisation of patients to one or another arm of a comparative study) do not directly aim to *benefit* participants. On the other hand, one of the most important tasks of the peer and ethical review processes described earlier is that of protecting potential participants from unjustified *harm* by ensuring that any risks and burdens involved in these research-related procedures are reduced to an acceptable minimum, and the risks involved in any therapeutic element are proportionate to the hoped-for benefits (see paragraphs 3.48–Box 3.1).
- 4.21 Thus, in considering how children's longer term welfare might be understood, we have to confront directly the question of whether parents may, ethically or legally, consent to something 'being done' to their child that does not have the primary aim of benefiting them (even if, in the event, their child happens to derive some benefit from it, whether emotional or physical). Children, like adults, may of course be *willing* to take part in research for altruistic reasons (see paragraphs 2.20–2.21), but if it is the case that parents can only consent to what is 'best' for their child, it is difficult to see how such a requirement would permit, for example, invasive procedures that are not directly associated with their child's healthcare. Indeed, legal advice given to the Medical Research Council (MRC) in the 1960s suggested that no 'non-therapeutic' medical research with children under the age of 12 could be lawful precisely because such research could not be in their best interests.⁴⁸⁰
- 4.22 We suggest that these concerns as to the scope of parental decision-making are misplaced for two reasons. First, in the specific legal context of the UK, we argue that parents are not obliged (and could not practically or ethically *be* obliged) to act at all times in the 'best' interests of their children, since interests within families will often compete, and will have to be balanced. Second, from a broader ethical perspective, we suggest that the notion of *promoting* children's longer-term welfare should be understood in a more holistic way than that implied by the terminology of 'best' interests.

⁴⁸⁰ See: Kennedy I (2001) *Treat me right: essays in medical law and ethics* (Oxford: Clarendon Press), at page 5. Kennedy traces how this approach has shifted to a focus on the importance of limiting the degree of risk to which children are potentially exposed.

- 4.23 The language of ‘best’ interests is widely deployed in the context of children’s research⁴⁸¹ for at least two reasons. For clinicians, there is an inevitable crossover between research and treatment, and despite the central ethical and legal importance of parental consent for the care of children (see paragraph 4.25), clinicians treating children will always *recommend* the care that they believe to be ‘best’ for a particular child in light of his or her medical condition and the treatment options available. Moreover, the legal and ethical requirement in the UK for health professionals to treat *adult* patients who lack capacity in their own best interests is well established.⁴⁸²
- 4.24 The term ‘best interests’ is also commonly used in a legal context, when courts are called upon (for example, by health authorities) to determine what action will best promote the welfare of a child when this is contested.⁴⁸³ Disagreements leading to court determinations may arise either between parents (for example, in the family courts when determining the living arrangements of children whose parents are divorcing), or between parents and health or social care professionals (if significant disagreement exists between what parents want, and what professionals believe to be the best course of action for a child). There are many cases where the opportunity for a court to consider, independently, what course of action would be ‘best’ for a child has been highly valuable in finding a way forward in areas where there are genuine and sincerely-held differences of opinion. Such differences may particularly arise in connection with decisions about treatment near the end of a child’s life.⁴⁸⁴ Similar considerations might also arise in cases where access is desired to unlicensed treatment that is only available in the context of research, and where there is no consensus on its appropriateness.⁴⁸⁵ In such cases, however, the decisions as to what is ‘best’ for a child would relate first and foremost to his or her own *treatment* needs, and not to procedures undertaken for research purposes, even though at times the treatment might only be available within the ‘package’ of research.
- 4.25 Although such legal procedures exist to resolve parental and professional differences of opinion, it is important to note that challenges of this kind will only be brought to court where parents’ actions are believed to fall *outside* a wide spectrum of acceptable decision-making by parents. They will not be brought simply because a health professional takes a different view from that held by a parent. Nor, other than in emergency, may a health professional simply ignore parental decisions and act in what they believe to be a child’s best interests without first seeking court authorisation.⁴⁸⁶
- 4.26 The breadth of this spectrum of ‘acceptable’ parental decision-making derives both from an understanding that what is ‘good’ for children extends well beyond their physical well-being (a point to which we return in more detail below), and also from the impossibility, on a practical level, of the interests of one person in a family always

⁴⁸¹ See, for example, use of the term by respondents to our call for evidence: Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>, pp38-43.

⁴⁸² Mental Capacity Act 2005, and formerly in case law.

⁴⁸³ See section 1(1) of the Children Act 1989. ‘Best interests’ and ‘welfare’ are regularly used interchangeably in the case law: see, for example, *Re Wyatt (a child) (medical treatment: continuation of order)* [2005] EWCA Civ 1181 at 79 and 87; and *Re A (children) (conjoined twins: surgical separation)* [2001] 2WLR 480 at 512.

⁴⁸⁴ See, for example, the case of *NHS Trust v. Baby X and others* [2012] EWHC 2188. Ian Kennedy, however, has criticised the use of the language of ‘best interests’ also in this context, on the basis that it simply serves to legitimise decisions based on instinct (a form of ‘*ad hocery*’) with the “empty rhetoric of best interests”: Kennedy I (2001) *Treat me right: essays in medical law and ethics* (Oxford: Clarendon Press), at page 395.

⁴⁸⁵ See, for example, the case of *Simms v. Simms and another*; *PA v. JA and another* [2002] EWHC 2734, although it should be noted that in this case the proposed intervention was described as “pioneering treatment”, rather than treatment provided in the context of research.

⁴⁸⁶ English judges are able to hear urgent applications concerning medical treatment at very short notice: see *Glass v. United Kingdom* [2004] 1 FLR 1019.

taking precedence (see paragraph 4.34). Parents also have responsibilities to take into account the interests of other children in their family, of adult family members for whom they may have caring responsibilities, and indeed of each other and themselves.⁴⁸⁷ On a mundane level, this may mean children being unwillingly 'dragged along' to their sibling's sporting or other leisure activities; on a more serious level, parents may exceptionally be forced to confront the question of whether they should consent to one child being a bone marrow donor for a sibling. At times, children's immediate interests may need to be subordinated to adult or wider family interests, such as where adult illness or other difficulties in the family temporarily dominate family decision-making.

- 4.27 While this constraint on parents' ability to act always in their child's 'best' interests may seem, at first sight, primarily a *practical* one, the practical demands placed on parents by others also serve to illuminate our second claim in paragraph 4.22: that what is 'good' for a child *must* extend beyond what is easy or enjoyable or nice for them, or that which is needed to promote their physical or emotional well-being. As we argued in Chapter 1, children are able, and expected, to begin to take their place in the social world around them from an early age (see paragraphs 1.21–1.25). While one part of the parental role, as we suggest, is to have regard to the unique individual that their child is (see paragraphs 4.11–4.12), this parental function is complemented by a responsibility to seek to influence the values that their child acquires as they grow up: that is, to shape the kind of person their child becomes. This 'shaping' includes influencing how children understand their responsibilities to others, as social beings.⁴⁸⁸ Thus, as Garrath Williams argues: "first... each of us is duty-bound to contribute to social goods in *some* ways, and second... this duty is one that we are duty-bound to lead our children into. We do so partly by our own example, and partly by requiring them to undertake it."⁴⁸⁹
- 4.28 **We therefore suggest that an understanding of children's long-term welfare should encompass the possibility of contributing to wider social goods. Such a contribution could take the form of participation in properly regulated clinical research in order to contribute to the knowledge base necessary to improve healthcare for all children in the future.** Any desire to make such a social contribution may, of course, go alongside many other factors also relevant to the welfare of particular children, such as the prospect of improvements in healthcare that could directly benefit them in future; or indirect benefits such as greater attention from clinicians and researchers; or enjoyment in taking part. However, such prospect of (or belief in) personal benefit for child participants should not be regarded as an ethical prerequisite for parents to consent to participation.
- 4.29 This is not, of course, to say that either adults or children have a specific *duty* to take part in research; rather that, in determining what is good for their children, parents are not only permitted but *required* to take into account the fact that their children are

⁴⁸⁷ See, for example, Ross LF (1998) *Children, families and healthcare decision-making* (New York: Oxford University Press) for a description of families as having 'group goals' which are distinct from the individual goals of family members; and Buchanan A, and Brock D (1990) *Deciding for others: the ethics of surrogate decision making* (Cambridge: Cambridge University Press) for a justification of why parents may take into account both their own self-interests and their obligations to their other children. For an overview of ethical arguments in this field, see: McDougall RJ, and Notini L (2014) Overriding parents' medical decisions for their children: a systematic review of normative literature *Journal of Medical Ethics* **40(7)**: 448–52.

⁴⁸⁸ See, for example, Herring J, and Foster C (2012) Welfare means relationality, virtue and altruism *Legal Studies* **32(3)**: 480–98.

⁴⁸⁹ Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* **26(8)**: 422–30, at page 426.

growing up in a particular social context, and need to learn to take their adult place in that society. Participation in properly regulated research offers one possible opportunity for expressing social solidarity, and hence may be regarded as 'good' for the child.⁴⁹⁰

- 4.30 Returning, then, to the question of terminology: in the context of court proceedings in the UK concerned with children's welfare, the courts' focus on what is 'best' for one child is understandable, given that such proceedings arise precisely because of significant levels of disagreement over the right course of action in a particular case.⁴⁹¹ It is also important to note that the terminology of 'best' interests has, in fact, increasingly been interpreted by judges in the broader way described above, with many factors other than a child's physical well-being taken into account in judging what is best for that child, both in cases relating to medical care,⁴⁹² and those relating to wider aspects of a child's upbringing.⁴⁹³ However, it was clear from our consultation responses that, in the very different context of day-to-day parental and clinical decision-making with respect to children's participation in research, the language of 'best' interests was deeply problematic. Indeed respondents used the term in directly conflicting ways. Some saw it as clearly objective, suggesting an understanding based on children's personal medical needs. Others argued it was entirely subjective, by implication recognising the very disparate attitudes different parents might take to what constituted their children's welfare, and equally the diversity of children's and young people's *own* attitudes.
- 4.31 Other respondents suggested that the term should be understood with reference to the needs of *all* children and young people to receive evidence-based healthcare, thus eliding the interests of individual child participants and the interests of all potential beneficiaries of the research.⁴⁹⁴ There is clearly an important distinction to be made between what is 'good' or 'best' for children as a class, and what is 'good' or 'best' for a *particular* child. The bioethicist Seema Shah, for example, highlights how vaccination programmes are 'good' for children, because the benefit/risk ratio is highly favourable for children as a group, but that nevertheless it may be in the 'best interests' of some particular children *not* to be vaccinated, because of their particular health conditions. In such examples, describing vaccination as being in 'children's best interests' may in fact be dangerous because of the risk that the particular needs of children for whom vaccination is contraindicated may be overlooked.⁴⁹⁵ One way of avoiding this confusion may be to avoid the term 'best interests' altogether when considering the interests of a group, and to use instead the language of likely 'benefits and harms' of a procedure.
- 4.32 Given the various difficulties described above, the Working Party does not believe that, in the specific context of participation in research, the terminology of children's or

⁴⁹⁰ See also: Lyons B (2012) Solidarity, children and research *Bioethics* **26(7)**: 369-75 for a discussion of research participation by children as an example of social solidarity.

⁴⁹¹ Note, however, that where courts are asked to consider the interests of siblings, they have explicitly considered the sets of interests together, rather than making two separate 'best interests' judgments: see, for example, *Re T and E* (proceedings: conflicting interests) [1995] 1 FLR 581, a case involving care and adoption proceedings, where the court took both children's welfare into account and balanced them against each other. If an order would greatly benefit one child and slightly disadvantage the other, then the order should be made.

⁴⁹² See, for example, *Re Wyatt* (a child) (medical treatment: continuation of order) [2005] EWCA Civ 1181.

⁴⁹³ See, for example, *Re G* (children) [2012] EWCA Civ 1233 at 29 where Munby LJ took the view that a child's happiness "can include such things as the cultivation of virtues and the achievement of worthwhile goals, and all the other aims which parents routinely seek to inculcate in their children", and should not be understood as "pure hedonism".

⁴⁹⁴ Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁴⁹⁵ Shah S (2013) Does research with children violate the best interests standard: an empirical and conceptual analysis *Northwestern Journal of Law & Social Policy* **8(2)**: 121-73. See also: Huxtable R (2004) *Re C* (A Child) (immunisation: parental rights) [2003] EWCA Civ 1148 *Journal of Social Welfare and Family Law* **26(1)**: 69-77.

young people's 'best' interests is particularly helpful either to those responsible for making decisions about their research participation, or those responsible for designing or reviewing research protocols. We note that research guidance issued by bodies such as the MRC and the Royal College of Paediatrics and Child Health (RCPCH) already avoids its use: in its 2004 guidance, the MRC requires that research should not be "contrary to the child participant's interests";⁴⁹⁶ while the RCPCH, in its 2014 update to its earlier guidance, uses the terminology of children's 'interests' only in the context of the collective interests of all children to be able to receive healthcare "assured by research".⁴⁹⁷

- 4.33 However, in inviting children and parents to contribute to the social goods of research, researchers must, of course, be confident that the study protocol does not pose undue risks or burdens for children and young people. Thus, alongside participation in research understood as "an act of care for others", as characterised by one of our consultation respondents, there must, of course, be concern for the physical and emotional well-being of every child participant. **We therefore suggest that parental consent to research should be based on their confidence that participation in the proposed research is compatible with their child's immediate and longer term interests.** An emphasis on the compatibility of children's interests with the demands of research participation both maintains the interests of the individual participant rightly at the forefront of consideration, while avoiding the misleading implication that participation may only be acceptable if it is the 'best' (which may be understood as the 'only') option for a particular child or young person. We return later to the associated responsibilities of both researchers and those responsible for the review of research proposals in this respect (see Chapters 5 and 6).

The relevance of practical constraints

- 4.34 Finally, in addition to these three ethical considerations (that is, respect for children's individuality, respect for their developing autonomy, and concern for their welfare), consultation respondents also echoed the findings of our literature survey in emphasising the *practical* constraints that may hinder participation (see paragraphs 2.14–2.15). Parents who responded to the Working Party's online survey highlighted factors such as the convenience of the location; whether travel, parking and accommodation expenses were covered; and the extent to which participation coincided with treatment schedules, as important logistical constraints that might prevent children taking part in research even if they and their parents actively wished to participate. While such constraints are essentially practical in nature, they do, nevertheless, illustrate further an ethical factor influencing decision-making within a family that emerged in our earlier discussion of best interests: the fact that other family members will also have legitimate needs that at times will take precedence (see paragraphs 4.26–4.27). In the context of research participation, these familial considerations are, primarily, likely to be relevant in *refusing* participation that might otherwise have been accepted. These considerations also raise the issue of the extent of research professionals' responsibilities to seek to keep these constraints to a

⁴⁹⁶ Medical Research Council (2004) *MRC ethics guide: medical research involving children*, available at: <http://www.mrc.ac.uk/documents/pdf/medical-research-involving-children/>, at paragraph 4.3.

⁴⁹⁷ Modi N, Vohra J, Preston J *et al.* (2014) Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees *Archives of Disease in Childhood* **99(10)**: 887–91, at page 887. The guidance uses the concept of what is "important for the individual child" when considering whether risks that are more than minimal or low can be justified.

minimum. We return to the wider question of professionals' responsibilities in Chapter 5.

Decision-making in the paradigm cases

4.35 We have emphasised earlier in this report that clinical research covers a wide range of possible activity (see paragraphs 1.5–1.9 and 3.48). Children, young people and their families also differ significantly. We were reminded by our stakeholder group that “families operate in very different ways, and researchers need to be aware of that”.⁴⁹⁸ Thus, the way in which these three ethical factors, along with any practical constraints, will be weighed in practice will be different – depending, for example, on the individual child or young person, their parents, the context of the research, and the circumstances of the family. No ethical guidance or regulation with respect to the involvement of children in research can hope to specify precisely the ‘right’ weight to be given to respecting a child’s worth as an individual, encouraging their developing capacity, and protecting and promoting their welfare in any individual case. However, a consideration of how the balance is likely to *shift* as children progress through the three cases described in paragraphs 4.5–4.7 casts light on some of the most contested areas of ethical debate described in earlier chapters of this report: those of children’s own ‘say’ in research decisions, and the question of how parents may justify exposing their children to potential discomfort, if not risk, through research participation.⁴⁹⁹ In turn, this will help us to clarify the ethical basis of *researchers’* responsibilities to the children whom they seek to recruit into research.

4.36 In **Case One**, the feature that distinguishes a child’s position from that of children and young people in Cases Two and Three, and from adults, is the inability of the child or young person to take part in a decision about whether they should participate in the research (as opposed, for example, to indicating physical or emotional responses to any procedures involved in that research). Hence the sole focus is on the role of *others* (first and foremost children’s parents) in making decisions on behalf of their child. We discuss later in this chapter some of the problems that arise when children are automatically assumed to be ‘vulnerable’ in research in a way that adults are not (see paragraphs 4.53–4.61). However, the babies, children, and young people falling within this case, whether on the basis of their stage of development or because of temporary incapacity, are very clearly ‘vulnerable’ in a way that children in Cases Two and Three may not be, in that at this point they are entirely dependent on others to make decisions for them.⁵⁰⁰

4.37 Parents’ primary concern in such circumstances will be for the *welfare* of their children. However, this will not be a question with a single right answer: parents of children in similar positions may come to different conclusions about the acceptability of particular procedures. Such differences in judgment will arise because of the diversity of parental views as to what constitutes their child’s welfare, both in the immediate present, and in the longer term. There may be particular diversity with respect to the value placed on

⁴⁹⁸ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>.

⁴⁹⁹ In recognising this as an important concern for many of those involved in research with children and young people, the Working Party is also alert to the evidence that, in practice, many parents give consent to research at least partially because of a belief or hope that it will be of direct benefit to their own child: see paragraph 2.22.

⁵⁰⁰ See, for example, Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme), where very young children’s “fragility”, dependency and inability to express or defend themselves was felt to raise very different questions with respect to research participation, compared with those arising in connection with the participation of older children.

contributing to wider social goods, such as the knowledge obtained through research (see paragraph 2.21). Differences in judgment will also arise out of respect for their child as an *individual*, however young: for example, in terms of the potential for distress caused by the research interventions to *this* particular child. Such considerations are clearly also encompassed under the banner of concern for their child's immediate welfare interests – but the fact that children can and do have quite disparate reactions to the same procedures highlights the personal and individual nature of such responses and needs.⁵⁰¹

4.38 Finally, as we discussed above (see paragraphs 4.26–4.27), parents may legitimately take into account their *own* needs and values in making a decision about research participation, or indeed may simply be unable to make a decision because of the stress of the situation. As the quotations in Box 4.1 illustrate, in some cases being asked to take part in research that is unlikely to be of direct benefit to their own child may simply be one burden too many for parents to bear at a difficult time. Much is assumed about the 'vulnerability' of children: but parents too may be placed in impossible circumstances where they may feel highly anxious and unsupported.⁵⁰² We return to the implications of the difficult, sometimes impossible, situations in which parents may find themselves in our analysis of the concept of vulnerability (see paragraph 4.61) and in our consideration of the implications for professional responsibilities (see paragraph 6.26 and Box 6.4).

Box 4.1: Examples of decision-making in Case One

"You just think 'Oh God, something else, another thing to have to think about' when you've got this little baby and all you can think about is if he's going to be ok."⁵⁰³

"I was thinking, the longer I take to make this decision, the longer [he] has to wait for something to help him. You know if I took like twenty four hours to decide... he might have deteriorated so much that the nitric oxide might not have [worked] on him."⁵⁰⁴

"Would I want to go on an in-depth interview during that period [after premature birth]? No, I don't think so. I don't think I'd have the sanity or patience to do something like that."⁵⁰⁵

"My son has recently been diagnosed with an incurable and life-limiting condition and one that will result in profound physical disabilities, so taking part in clinical research into a treatment or cure could be hugely significant for him."⁵⁰⁶

"She is a small child, under five years, she cannot tell you where she hurts. She can tell you the hand is hurting only to find that it's hurting inside there, so expressing herself becomes a problem."⁵⁰⁷

⁵⁰¹ See, for example, Alderson P, Hawthorne J, and Killen M (2005) The participation rights of premature babies *The International Journal of Children's Rights* 13: 31-50.

⁵⁰² See, for example, Kodish ED, Pentz RD, Noll RB *et al.* (1998) Informed consent in the children's cancer group *Cancer* 82(12): 2467-81.

⁵⁰³ Jollye S (2009) An exploratory study to determine how parents decide whether to enrol their infants into neonatal clinical trials *Journal of Neonatal Nursing* 15(1): 18-24, at page 20.

⁵⁰⁴ Snowden C, Elbourne D, and Garcia J (2006) "It was a snap decision": parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials *Social Science & Medicine* 62(9): 2279-90, at page 2286.

⁵⁰⁵ Ward FR (2010) Parents' views of involvement in concurrent research with their neonates *Journal of Empirical Research on Human Research Ethics: JERHRE* 5(2): 47-55, at page 50.

⁵⁰⁶ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

4.39 In **Case Two**, the feature that distinguishes the position of children or young people (and potential parental response) from the other two cases is their ability to form and express views about the invitation to take part in research, or particular aspects of the research. However, this ability falls short of the intellectual capacity and emotional maturity required to make the decision about research participation on their own.⁵⁰⁸ In this case, in addition to making judgments about their child's immediate and longer term welfare, parents will need to determine how these factors should be balanced both against the respect due to their child's own views and feelings on taking part in the research, and their general educational obligation to develop their child's decision-making capacity. As we note above (see paragraph 4.35), there can be no simple calculus as to *how* these factors should be weighed in the balance against each other where they are in potential conflict. Relevant considerations for parents who are making decisions with children or young people in Case Two include:

- the potential for their child to derive direct or indirect benefit from the proposed research, and the likelihood and severity of any associated risks;
- the burden of research participation for their child – for example, whether they have particular anxieties about any of the procedures involved;
- their child's own views and feelings about the proposed research;
- the maturity and understanding of their child;
- the value placed by the parents on the role of participation for their child's longer term welfare;
- the relative strength of their views with respect to the various welfare considerations listed above, and their child's feelings; and
- the likely impact on their child's immediate and longer term welfare of overriding their preferences: for example, the degree of immediate distress and the risk of future lack of trust in clinicians or researchers if they are required to take part against their will.

4.40 The way in which these factors will be balanced will depend on the particular parents, the individual children/young people, and the nature of the decision to be made. As we saw in our review of the evidence, in many circumstances, parents and children will come to a shared decision as to whether or not to participate in a particular study (see paragraphs 2.30–2.33). Where, for example, the research involves no prospect of direct benefit, such as survey-based research about health behaviours or experiences of health services, parents may adopt a 'gate-keeping' role: they may first make their own judgment on whether the burdens involved are acceptable and the research worthwhile, and then, if that judgment is positive, may allow a relatively young child to decide for themselves whether or not to take part.⁵⁰⁹ Alternatively, they may take a view

⁵⁰⁷ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

⁵⁰⁸ Note Williams' discussion of research involvement as a form of social contribution, where he emphasises the relevance of children's emotional maturity (experience of "the game" of social relations), rather than intellectual capacity: Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* **26(8)**: 422-30.

⁵⁰⁹ Such an approach could be compared to giving a young child a 'choice' between alternatives that are all acceptable to the parent, such as choices relating to (already approved) meal options, or activities.

that the research is a 'good thing to do', and more actively encourage their child to participate, even if there is initial resistance. In contrast, if the study in question relates to their child's care, such as the prospect of a clinical trial of a new intervention, parents' dominant concern will be for the welfare of their child, their perception of what will be 'best' for them, and their assessment of any additional burdens imposed by procedures related to the research. However, even in these cases, the other factors cited above will be important. Given that, by definition, there will *always* be a degree of uncertainty as to whether an intervention that is the subject of research will be better than any alternatives, then the enthusiasm, or reticence, of children or young people with respect to the proposed study should always play some part in the decision, to a greater or lesser extent depending on all of the other factors in play.

- 4.41 Where parents and their child initially disagree, then, as in other areas of family life, there is likely to be some degree of negotiation within the family. Parents who believe that there are good reasons for their child to participate in research may engage with an initially hesitant or reluctant child in a variety of ways: these may include encouraging, persuading, cajoling, distracting or indeed bribing them to take part. As Garrath Williams notes in his justification of the involvement of children in research: "As children we learn very early that we have to do things we dislike or did not expect as part of acting together with others."⁵¹⁰ Children's *anxieties* about taking part in research, particularly with respect to pain or discomfort, should, however, always be taken very seriously (see case study of vaccine research in Box 6.2 on page 154). If a child remains clearly opposed to participation, then there would have to be strong reasons relating to welfare (longer-term good) in order to justify overriding their preferences and sense of self-worth.

⁵¹⁰ Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* **26**(8): 422-30. See also: John T, Hope T, Savulescu J, Stein A, and Pollard AJ (2008) Children's consent and paediatric research: is it appropriate for healthy children to be the decision-makers in clinical research? *Archives of Disease in Childhood* **93**(5): 379-83, at page 380, where children were invited to take part in a follow-up to a vaccine study which involved blood tests. When asked whether they would respect their child's decision not to participate, the majority of parents said they would, but half would use a variety of methods in persuasion first.

Box 4.2: Examples of decision-making in Case Two

“We should talk about it and decide, but because I am 13 I should have a lot of say.”⁵¹¹

“I’m not really a fan of having blood taken.”⁵¹²

“Usually when they want me to know something they usually tell my mom, and if she thinks that I should know then she tells me. Because I get overwhelmed with things really easy, she doesn’t tell me until the last minute so I don’t have any other choice. That makes me mad. But I think she... she knows that now, and I don’t think she’ll do that anymore... I think she was afraid that I would refuse to go through with it.”⁵¹³

“Yeah. We told her what was going on. You really can’t hide too much from her. She was seven going on 14.”⁵¹⁴

“I always think it’s best to be upfront with your kids, no matter what, to a level of their understanding... I mean, at nine, he’s old... he is old enough to say, well, you know, I don’t really fancy it.”⁵¹⁵

“I think that if the child is over the age of 11 or they have a long-term condition, they should be able to voice that they wish to be a part of the research regardless of what their parents or guardians may say.”⁵¹⁶

“I believe that my child has a right to be part of any decisions regarding his treatment and the risks they may be exposing themselves to.”⁵¹⁷

“... you’re working towards adulthood and I think if you are not comfortable with the decision, you are going to, not going to have the best psyche with your treatment and if your parents say ok this is what we are doing you’re going to get this treatment, you are already so out of control. I mean this cancer is coming and taking control of your body.”⁵¹⁸

“The 9, 10 year olds there they just understand, somehow they do understand themselves, so they should also, if the parents have agreed they should go for that research, they also should be asked if they want to, and then they should be told the benefits of having this kind of research, they should be educated somehow. Somehow they will end up understanding and making a decision also.”⁵¹⁹

⁵¹¹ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people’s responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁵¹² Ibid.

⁵¹³ Snethen JA, Broome ME, Knafel K, Deatrick JA, and Angst DB (2006) Family patterns of decision-making in pediatric clinical trials *Research in Nursing & Health* **29**(3): 223-32, at 227.

⁵¹⁴ Ibid., at 228.

⁵¹⁵ Woolfall K, Shilling V, Hickey H *et al.* (2013) Parents’ agendas in paediatric clinical trial recruitment are different from researchers’ and often remain unvoiced: a qualitative study *PLoS ONE* **8**(7): e67352.

⁵¹⁶ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people’s responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁵¹⁷ Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents’ responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>. See also: paragraph 2.20.

⁵¹⁸ Snethen JA, Broome ME, Knafel K, Deatrick JA, and Angst DB (2006) Family patterns of decision-making in pediatric clinical trials *Research in Nursing & Health* **29**(3): 223-32, at page 228.

⁵¹⁹ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

- 4.42 In **Case Three**, by contrast, the distinctive feature is children's or young people's potential capacity to make the decision for themselves whether to participate in research. Thus, the particular challenges faced by both families and researchers in this case arise first with respect to the judgment as to whether children or young people in fact have the capacity to make this particular decision; and second with the question of how the potential for any conflict with the views of their parents may be managed. As we note in Chapter 2 (see paragraphs 2.51–2.57), the legal position in the UK with respect to children's decision-making powers in the context of research involvement is highly complicated, and in some cases uncertain. However, our primary focus here is on an *ethical* analysis of the respective roles of children and their parents in making decisions about research participation in circumstances where children or young people arguably have the intellectual capacity to make the decision in question (for example, by reference to the 'capacity test' for adults in the English Mental Capacity Act 2005⁵²⁰), but where the society in which they live does not grant them full 'adult' decision-making powers. We return in Chapters 5 and 6 to the legal and professional implications of our analysis.
- 4.43 We set out clearly in Chapter 1 (as part of the ethos of this report) two critical attitudes to children and young people that have underpinned the Working Party's approach throughout to the difficult issues that arise when contemplating clinical research with children and young people. First, we argued that children should be regarded as active participants in research from a very early age. Second, we took the view that it is always essential to consider children in the context of their family and the life they share with that family (see paragraph 1.23). Similarly, we saw in our review of the empirical evidence in Chapter 2 that the way in which decisions about research participation are made is heavily influenced by family circumstances and by the nature of family relationships. This ethos, supported by the empirical evidence available, provides the basis for our ethical analysis of the role of competent young people and children in making decisions about research involvement.
- 4.44 We therefore suggest that, instead of seeking primarily to identify *who* (children or their parents) are entitled to provide a legally effective consent or veto on research participation in Case Three, the ethical focus should be on obtaining agreement within the family unit concerned. Thus, the starting assumption in any discussion as to whether children or young people in Case Three should take part in a research study should be that this should normally be a shared family decision. Such an approach both reflects the experiences of supportive family decision-making described in the literature, and obviates the need for anxious calculations as to whether or not the young person in question meets a competence threshold – which itself is often likely to be contested. Clearly, however, such an approach will not always be possible: there will be cases where meaningful research results may only be obtainable without parental involvement (for example, where research relates to sexual behaviour or illegal drug use). There will also be cases where young people and their parents take opposing views on the appropriateness of participation. Young people, parents and professionals all need guidance on how to handle such cases, and we return to this below (see paragraphs 6.24–6.25). Similarly, we consider later the very specific challenges that face children and young people in all our cases who do not have any form of parental support, whether from an actual parent, or from other adults taking on this role (see paragraphs 6.31–6.41). However, we argue that, in the majority of cases,

⁵²⁰ Broadly the ability to understand the relevant information, and retain it long enough to make a decision.

a consensual or negotiated approach will reflect the reality of family life, and the way that young people and their parents make decisions in many other domains.

- 4.45 This claim – that the default approach within Case Three should be for consensus decisions within the family with respect to research participation – is implicitly built on a further claim about the *nature* of parental responsibility. It is uncontroversial to argue that parents continue to have an interest in the welfare of their children, even when those children are competent to make their own decisions. As we note in paragraph 4.9, emotional and caring relationships between parents and their children continue into adulthood, and a parent’s concern for the welfare of their child does not simply evaporate at the point when their child is able to take on decision-making responsibility for themselves. However, it is far from self-evident to claim that these parental interests in their children’s welfare should continue to have an effect in the public, as well as in the private, sphere once children are competent to make their own decisions. Indeed, if parental responsibility and power to make decisions on behalf of their minor children is understood as deriving *only* from children’s inability to make those decisions for themselves, then it follows quite straightforwardly that those responsibilities and powers fall away as soon as children are capable of making the decision in question.
- 4.46 We argue, however, that this is too ‘thin’ an account of parental responsibility. Drawing on our earlier analysis of what is special about childhood, we suggest that parental responsibilities do not derive solely from children’s initial inability to make their own decisions. Rather they derive from the particular developmental character of childhood (see paragraphs 4.8–4.9) which, we have suggested, underpins the threefold responsibilities of parents to respect their child as an individual; help them to develop as independent decision-makers; and promote their immediate and longer-term welfare. In particular, we have argued that parents’ role in promoting their child’s welfare includes seeking to influence and steer the kind of adult their child becomes (see paragraphs 4.18–4.28). These responsibilities are certainly connected with the inability of younger children to make decisions for themselves, but even a brief consideration of the relationship between parents and teenagers illustrates how this is only a partial picture. Teenagers are commonly required by their parents to do many things that they may not want to do, often in connection with the way they treat others (for example, with respect to particular standards of courtesy, or giving up time to visit older family members). On the whole we think it appropriate for parents to have a role in influencing the kind of behaviour they believe to be acceptable in their family: not because their child is unable to understand the consequences of behaving otherwise, but because it is a parent’s job to promote what they see as desirable attitudes and behaviours.
- 4.47 In other words, **we are making the claim that there *is* a morally significant difference between ‘competent children’ and ‘adults’, which may potentially justify differential treatment. Children, however intellectually capable, do not have full adult powers – and the corollary of that is that they also do not have full adult responsibilities.**⁵²¹ Parents are there, both ethically and legally, to share

⁵²¹ See, for example, the discussion in Manson N (2014) Transitional paternalism: how shared normative powers give rise to the asymmetry of adolescent consent and refusal *Bioethics* **29(2)**: 66-73: Manson uses the concept of a child’s acquisition of “unshared, unconstrained, adult power” as the point at which parental powers should fall away, and argues that parents and children up to that point should have a “joint bank account” approach to decision-making where either can ‘make withdrawals’ (i.e. consent), and hence neither can veto. A statutory example of the distinction between an adult and a competent child in England is found in the Care Act 2014 where ‘adults’ are defined as those aged 18 and above (section 2(8)), but where section 58(3) makes provision for children who have “capacity or [are] competent to consent” to make decisions for themselves about an assessment in connection with transition to adult services. Section 58(4) goes on to state that if a competent child refuses, the local authority is still empowered to go ahead “if the child is experiencing, or is at risk of,

that responsibility until the agreed threshold of adulthood is reached. In making this claim, it is crucial to acknowledge that childhood is, at least in part, a social characterisation that will vary from society to society. The law in each country will set a norm judged appropriate for this parental power and responsibility to end: that is, the age of majority. It will vary around the world, and move over time; some jurisdictions may also choose to specify different ages for particular aspects of parental power to end.⁵²² However, it is always drawn *somewhere*. In practice, the question of when parental power really ends will depend on the nature of a family's relationship: in some cases parental influence (or even active control) over behaviour will persist well past the legal age of majority. Thus, 'house rules' may apply to young people over the age of 18 who still live at home, and parents may continue to seek to influence their children throughout their life. In other families, parental powers may, in practice, cease to be effective long before the age defined by law.

- 4.48 This approach to parental responsibility in childhood helps explain why, intuitively, it may seem right for parents to be able to override the wishes of an apparently competent child or young person where major risks are at stake. Such cases may arise, for example, where parents consent to medical treatment that their child has refused but which is believed to be critical for their healthcare, or even life-saving. In these difficult cases, it is sometimes claimed that particular children or young people are not competent to make such important decisions. However, in practice, this justification may disguise the real rationale for intervention: that of care for that particular child's welfare. That is certainly not to say that children's wishes are unimportant – but that in some (exceptional) cases these may be trumped by concerns over welfare.
- 4.49 We argue then, that our threefold analysis of parental responsibilities is also applicable where children and young people fall into Case Three – but that the *balance* of those responsibilities will be exercised differently from Case Two. The parental role in helping their child to develop capacity begins to fall away, but has not yet become redundant, given that different decisions demand different levels of competence. Thus, encouraging children to make up their own minds with respect to very low risk activities (for example, contributing to interview-based research) might be regarded as practice for making later research decisions, where more might be at stake. Respect for their children as individuals who are able to make their own decisions will increasingly be the dominant feature of the parental role, but concerns about welfare will still be significant. In Case Three though, by contrast with the other cases, such concerns will primarily be expressed in the form of *advice and support*, rather than through exercising the role of substitute decision-maker. The exception may arise where parents have strong reasons to believe that participation could have serious implications for their child's welfare that are significant enough to outweigh other considerations. In the context of research, such exceptions are primarily likely to arise in connection with treatment that is only available in the context of a research study (where parents strongly believe that participation is essential for their child's welfare); or in connection with a research study that they believe poses too *high* a risk for their child to participate (and hence where they wish to veto involvement).

abuse or neglect": in other words the local authority retains protective powers with respect to competent children, despite their competence.

⁵²² As, for example, the UK Clinical Trials Regulations do, in defining 'minors' as under the age of 16, even though in many other areas of law in England and Wales parental powers *coexist* with those of children up to the age of 18.

4.50 As the above examples make clear, an important aspect of this analysis of parental powers and responsibilities lies in their *discretionary* nature. A key aspect of parenting rests in the gradual yielding of responsibility, accompanied by appropriate levels of support, from parent to child.⁵²³ Thus, for many decisions relating to research involvement, it is likely to be appropriate that children or young people will be the primary decision-makers, with the support of their parents. While we make the claim that parents continue to have a role with respect to their children's decision-making until they have full adult powers, an important aspect of that role is found in the *discretionary manner* in which it should be exercised. We return in Chapters 5 and 6 to consider how professionals should respond where they have concerns over how that discretion might be, or is being, exercised (see paragraphs 6.19–6.25). We also discuss how, depending on circumstances, parents too may need support in how they exercise their parenting role in this paradigm case just as much as in others (see paragraph 4.61).

⁵²³ See, for example, the discussion in Taylor R (2007) Reversing the retreat from Gillick? R (Axon) v. Secretary of State for Health *Child and Family Law Quarterly* **19**(1): 81-97, where it is argued that the Axon case demonstrates a growing respect for the rights and autonomy of children, with parental rights and authority diminishing or yielding to children as they mature.

Box 4.3: Examples of decision-making in case 3

"No, I think they say 16 is when you can sign the things in here but I still think it's good to have your parents there just as the extra person, because if you're on your own like making decisions and all this paper-work then you don't know what, you want to read all this stuff and just leave it to them to do and you don't know what you're... like sometimes when you have to sign something or and you're saying 'Should I sign this or not?' there's no one else to help you, it's kind of hard."⁵²⁴

"Mainly it was him more than me... He's almost 17 years old. That was his decision and ours, but we didn't tell him that. We let him decide."⁵²⁵

"I don't want to leave him out since he's 17. I try to give him the opportunity to make his own decision, but I will have the final say so of what's best for him, but I'll try to include him in it."⁵²⁶

"Personally if my parents told me I wasn't allowed to take part in the trial, I think that I would listen to them cos I would kind of trust their judgment on whether they think it is safe or not."⁵²⁷

"I don't think it's 18 and above or less than 18, if you are going to participate in the research right now you have to use your intelligence, if you consider the advantages and think it is going to help, it's you who will make the decision you don't have to quote the age or something."⁵²⁸

"If he can answer question, let him just answer. Sometimes they do things which the parents themselves get surprised, because they know how to do things [*other group participant: 'Nowadays!'*]. Now if at 13 years he goes to Mombasa, Malindi, and back, by himself, if you ask him silly questions, won't he surprise you with his answers?"⁵²⁹

"... my younger brother [aged 13 years] was involved in a pneumonia study and was given a diary to fill in for three days. Now when they came home they found me and him, I'm not his parent, the parents are not there, but the boy is big... he can explain everything. Now they involved me, if I can agree and I told them even he himself can agree because there's nothing there, it's just talking and filling. He himself said "I will do it". You see? He is a child, but can express himself."⁵³⁰

Additional factors influencing decision-making

4.51 Two further issues arise that fall outside the immediate parent-child relationship, but are still very important in influencing the decision that is eventually made in connection with children's or young people's participation in research. First, in coming to a decision

⁵²⁴ Coyne I, Amory A, Kiernan G, Gibson F and Breatnach F (2010) *Children with cancer: children, parents, and health professionals' perspectives on children's participation in shared decision making* (Dublin: Cancer Research Ireland), at page 101.

⁵²⁵ Olechnowicz JQ, Eder M, Simon C, Zyzanski S, and Kodish E (2002) Assent observed: children's involvement in leukemia treatment and research discussions *Pediatrics* **109**(5): 806-14, at page 811.

⁵²⁶ *Ibid.*

⁵²⁷ Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>; see also paragraph 2.19.

⁵²⁸ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

⁵²⁹ *Ibid.*

⁵³⁰ *Ibid.*

about whether it is ‘good’ for a child or young person to take part in a particular research procedure, the perceived value of research (including the question of to whom that value accrues) will be highly relevant. If parents perceive no, or very limited, value in the proposed research, they will have little reason for considering the trade-offs involved in participation. We return to this question of value below (see paragraphs 5.2 and 5.32).

- 4.52 Second, it is crucial to return to the point that there are many adults in the lives of children and young people who, in particular contexts and at particular times, have recognised responsibilities towards them (see paragraph 4.9). In the context of clinical research, the professionals with whom children, young people and their families come into contact clearly play a critical role in determining the involvement of children or young people in research. They may, for example, influence the decisions of parents and young people through the manner of their approach; they may decide *not* to approach a particular family regarding a research opportunity; or they may choose not to act on parental consent where a child is unwilling to participate. Where children and young people do proceed to take part in a particular study, then their experience of that study, and their attitudes to research more generally, will be affected by the interactions they and their parents have with the professionals concerned with that study. We turn to the responsibilities of this group of professionals in Chapter 6, after consideration in Chapter 5 of professional responsibility with respect to the prior questions of the development, design and review of research protocols that will ultimately be ‘offered’ to children and parents. Before we do so, however, we need first to examine one of the concepts most often cited in the context of professional responsibilities with respect to research with children: that of vulnerability.

Challenging vulnerability

“The term vulnerable can’t be used in isolation; we are always vulnerable to something specific, and the things that we are vulnerable to change over time.”⁵³¹

“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.”⁵³²

- 4.53 We note in Chapter 1 that much of the general approach to the regulation of clinical research involving children – from international ethical declarations, to national law – is underpinned by the idea that children, in contrast to ‘autonomous’ adults, are inherently vulnerable.⁵³³ This assumption has, in turn, influenced how the responsibilities of professionals involved in research (whether as researchers, clinicians, or those responsible for reviewing research) have been viewed. However, this straightforward association between childhood and vulnerability was strongly challenged throughout the Working Party’s consultative activities.

⁵³¹ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>, at page 8.

⁵³² Christian Medical Fellowship, responding to the Working Party’s call for evidence.

⁵³³ See, for example, World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, paragraph 19: “Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.”

- 4.54 In a factfinding meeting exploring the concept of vulnerability, it was argued that while a 'folk' or dictionary account of vulnerability as an indication that a person is 'at an increased risk of harm' may be relatively unproblematic, difficulties arise when trying to use the concept as a guide when making moral decisions.⁵³⁴ Use of the label of vulnerability for particular groups, such as children, or adults without capacity, or prisoners, inevitably fails to capture the diversity and richness of any group, and does not help identify particular members of that group who are, or are not, a subject of particular ethical concern. Similarly, a 'group approach' to vulnerability may lead to particular vulnerabilities being missed, because the person in question does not apparently belong to any of the identified groups.⁵³⁵ Even, however, where a person is appropriately identified as 'vulnerable', the use of this label does not necessarily provide an ethical steer to action, because the *reasons* for which they might be at increased risk of harm are not explained in any way by the label of vulnerability. Thus while, for example, the Declaration of Helsinki states that "some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm", it is silent on the (potentially very variable) *reasons* why particular individuals or groups might be at greater risk of being wronged or of incurring additional harm.⁵³⁶ On the other hand, it was suggested at the meeting that an awareness that particular groups, or people in particular circumstances, *may* be vulnerable can provide a useful alert: an indication that there is something of additional ethical concern at stake.
- 4.55 Children and young people participating in our stakeholder event similarly argued that, while some children in some circumstances could certainly be vulnerable, it was wrong to assume that children are *necessarily* so.⁵³⁷ Even young children can make decisions for themselves "if things are properly explained", and the point was made strongly that children living with particular conditions or disabilities (who are often seen as 'more vulnerable' than their contemporaries) do not want to be treated any differently from their friends.⁵³⁸ Concern was expressed that describing children as 'vulnerable' can simply 'stop the conversation' about whether children should participate in research; however, as in the discussion at the factfinding meeting, it was agreed that the label might still have value as a 'flag' to make sure that appropriate protections are in place.
- 4.56 The young people present at the stakeholder event also identified a number of ways in which they might feel more or less vulnerable in the context of research. "Being prepared" or "being empowered" were both cited as ways in which any sense of vulnerability might be lessened: and hence having information, or knowing how to go about obtaining information, was seen as an important factor in 'arming' children

⁵³⁴ Nuffield Council on Bioethics (2014) *Factfinding meeting: vulnerability* (London, 21 May: Nuffield Council on Bioethics). Note also the Oxford English Dictionary's definition of vulnerable as "exposed to the risk of being attacked or harmed, either physically or emotionally".

⁵³⁵ We note, in the very different context of childhood 'grooming', how the plight of teenage girls has been ignored because of the way they had been 'classified': in court, for example, they were described as prostitutes, rather than as abused children. See, for example, The Guardian (6 January 2015) *End use of outdated term 'child prostitution', says MP*, available at: <http://www.theguardian.com/society/2015/jan/06/child-prostitution-term-outdated-mp-ann-coffey>.

⁵³⁶ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, paragraph 19.

⁵³⁷ Nuffield Council on Bioethics (2014) *Note of stakeholder group meeting*, available at: <http://nuffieldbioethics.org/wp-content/uploads/Stakeholder-meeting-note.pdf>.

⁵³⁸ One participant described how teachers constantly tried to protect her, for example by suggesting that she did not participate in sports lessons - while she felt able to take part and make her own decisions about when to stop. The difficulties that arise when identifying particular subgroups of children as more vulnerable than others is explored in detail in Frankenberg R, Robinson I, and Delahooke A (2000) Countering essentialism in behavioural social science: the example of 'the vulnerable child' ethnographically examined *The Sociological Review* **48(4)**: 586-611.

against vulnerability. The support of parents was also described as an important factor. It was noted that they would know how their child handled difficult situations and, hence, would be best placed to help them; and also that it was reassuring for children to know that they and their parents had access to the same information.⁵³⁹ Teachers having access to information was similarly seen as a source of reassurance. In contrast, poor relationships with researchers, poor communication or “being put on the spot in front of strangers” could make young people feel more vulnerable, as could being given too *much* responsibility.

- 4.57 As these examples demonstrate, in many (though not all) cases, the factors that may potentially make children feel, or be, vulnerable in the context of clinical research do not arise *inevitably* because of the nature of childhood; and nor are they necessary features of research. Rather, they arise in the context of the developmental nature of childhood – experienced, for example, in a young child’s need for practical and emotional support in understanding what is proposed; or an older child’s anxiety about the impact of research participation on their school life. Once the relevance of this context is recognised, there will often be scope to modify aspects of the research in response. The extent, for example, to which children’s vulnerability may derive either from a lack of control over what is happening to them, or, conversely, from feeling that too much is being expected of them, is something that those responsible for research with children can largely control – both through the way they design the study itself, and in the way that they communicate with and support children and their families. (Such modification will not, of course, always be possible, a point to which we return in paragraph 4.60.)
- 4.58 The Working Party shares the concern, expressed by children, parents and professionals, that an unthinking use of the notion of vulnerability may be used as a ‘conversation-stopper’ with respect to children’s involvement in research. Indeed, there is a real risk that this apparently protective response to perceived or actual vulnerability may not only exclude children and young people from opportunities to participate in activities that are inherently worthwhile (see paragraphs 5.2 and 5.32), but could also harm the interests of many children in the future by preventing potentially valuable research from taking place. We further agree that an awareness that children may *potentially* be vulnerable in research may nonetheless provide a useful alert to those professionally concerned with research to ask themselves: ‘Does this research raise particular ethical challenges and what can I do about them?’ The real challenge for those professionals is thus the nature of the *response* they make to the alert, and their own sensitivity to the need to avoid taking advantage of a potentially unequal relationship.
- 4.59 At the beginning of this report, we set out our understanding of children as people who, from an early age, can take an active role in determining the direction of their lives, in the context of a shared life with others. We suggest now that **an appropriate response by professionals to concerns about children’s potential vulnerability in research is to ensure that they work in partnership with children, young people and parents throughout the whole endeavour of research.** Such a partnership approach will ensure that, whenever children and young people are invited to take part in research, the procedures to which they are being invited to consent have been developed with the input of others in a similar situation to themselves. Where it is not

⁵³⁹ Similar points were raised by students from a secondary school who took part in the Working Party’s Youth REC project, who emphasised how important it was for parents to have information so that they can meet their own responsibilities in caring for their child.

feasible to seek direct input from children in similar situations (that is, for some of the children and young people in Case One), then this engagement will be carried out on their behalf by parents; but, as we discussed earlier in this chapter, parents will also continue to play a role as their children develop through Case Two to Case Three. Such an approach implies a fundamental shift from seeking to protect children 'from' research, to protecting them through their own active engagement with how research with children and young people is designed and carried out.

- 4.60 Alongside this focus on a partnership with children, young people and parents in the design of studies, it is, however, crucial to recognise that it will not always be possible to achieve the desired end. Sometimes changes that might be needed to a research protocol to avoid putting children in a vulnerable position (for example, where the proposed procedure would be too distressing for a young child unable to understand what was happening), or over-burdening those who are already in a vulnerable situation (for example, because of the severity of their existing illness), cannot be achieved without compromising the ability of the research to produce meaningful results.⁵⁴⁰ In such cases, the proposed research cannot go ahead. Similarly, a proposal that has been developed with the input of children and families in the way described above, might still render particular children vulnerable (for example, in connection with the distress that some children feel in connection with hyperdermic needles). Again, in such cases, it would be inappropriate to recruit those particular children to the study.
- 4.61 In our consideration of the extent to which children may potentially be vulnerable in research, it is also important to be alert to the fact that **parents, too, may often need support in the context of their child's research involvement.** A necessary part of any parent's role in any context (not just that of research), is that of making decisions with and on behalf of their minor child. However, this day-to-day responsibility is inevitably more challenging to exercise if the decision to be taken involves potential burden or risk for their child, or arises in highly emotional and difficult situations (see paragraphs 2.6–2.11).⁵⁴¹ In some situations, such as in the immediate aftermath of a diagnosis of a life-threatening or life-changing illness, relatively few parents may be able to make decisions (or support their child in making a decision) without support themselves. This is an important recognition but, as with our analysis above with respect to children's potential vulnerabilities, it should not be seen as placing an automatic brake on certain kinds of research. Rather it acts as a prompt to consider how research studies may be developed and carried out, and how professionals can appropriately support parents in a way that does not make unreasonable demands on either parents or children.
- 4.62 In the following two chapters, we explore further what our analysis of vulnerability might mean for children, young people and their families: both in the development and design of research; and in the relationship between researchers and families when children and young people are invited to take part in a particular study.

⁵⁴⁰ See, for example, the justification for the use of "naturalistic experiments" regarding the effects of long-term cannabis use in Nordentoft M (2014) Adolescent cannabis use and adverse sequelae in adulthood *The Lancet Psychiatry* **1(4)**: 249-51, given the inevitable difficulties in carrying out a controlled study giving children cannabis and monitoring the effects.

⁵⁴¹ There is some (limited) evidence that compared to adult patients with cancer, parents of children with cancer struggle to absorb information about trials: see: Simon CM, Siminoff LA, Kodish ED, and Burant C (2004) Comparison of the informed consent process for randomized clinical trials in pediatric and adult oncology *Journal of Clinical Oncology* **22(13)**: 2708-17.

Chapter 5

Developing research proposals: professionals' responsibilities

Chapter 5 – Developing research proposals: professionals' responsibilities

Chapter 5 overview

This chapter considers the role of the many professionals involved in research, whose actions and attitudes have a powerful, if sometimes unseen, influence on the decisions that children and their parents are asked to make.

The role of professional virtues

- Professional virtues that lie at the heart of professional ethical practice in research with children and young people, and encourage a reflexive approach to practice, include trustworthiness (facilitating trust), openness, and courage. These virtues should be encouraged and nurtured.

Professional responsibilities in developing research

- Researchers should involve children, young people and parents in the development of their studies, for example through the young persons' advisory groups supported by clinical research networks. Such groups are not cheap to run, and their funding needs to be secured.

Professional responsibilities when reviewing research

- The fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a 'fair offer' to children, young people and their parents, where the value of the research and its likely risks, burdens, and benefits have been carefully weighed up.
- In order for research ethics committees to be well-placed to make finely balanced decisions as to whether the burdens and risks presented by a study protocol can ethically be justified, it is essential for them to have access to appropriate expertise: that of professionals with specialist knowledge of children's healthcare, and that of children and families.
- The National Research Ethics Service, in cooperation with relevant professional associations, should compile a list of experts from different areas of children's and young people's healthcare who are willing to be called on by RECs as advisors where necessary.

Drivers of research: prioritisation

- Those making decisions about which research avenues to pursue and which studies to fund should ensure that key stakeholders – including children, young people, parents and professionals – are appropriately involved.

Drivers of research: incentivisation

- In Europe, the Paediatric Regulation has made a big difference to research about medicines for children and young people. Issues still to be addressed, however, include the application of the rules on 'waivers', and more effective incentives to promote research on off-patent medicines that might be useful for children and young people.

Collaborative working

- There is a strong ethical imperative for researchers to work collaboratively with each other, and with key stakeholders such as condition-specific family support groups, to the maximum extent possible.

Introduction

- 5.1 In Chapter 4 we analysed why it is important to consider the ethical issues arising in research with children afresh, rather than – as has traditionally been the case – applying a general ‘adult’ model of research governance with additional protections. Aspects that we suggested are particularly important in this analysis include the developmental nature of childhood; and the specific responsibilities that parents (or others with parental responsibility) have in protecting their children’s interests, and in influencing the way their child develops into adulthood. Both these aspects of the parental role are underpinned by the regard owed to children as distinct individuals, regardless of their stage of development and maturity.
- 5.2 Based on this analysis we have argued that research that may not offer direct benefit to children or young people can, nevertheless, be compatible with their longer term interests. Where parents believe that taking part in a particular research study is compatible with their child’s interests, they may thus legitimately choose to consent to their child’s participation (see paragraphs 4.28 and 4.33). Clearly, however, whether or not research participation is compatible with children’s interests depends not only on the view taken by individual children/young people and their parents as to the value of contributing to that research, but also, crucially, on the aim and design of the research itself. We thus turn to the question of the role of the many professionals involved in research, whose actions and attitudes have a powerful, if sometimes unseen, influence on decisions that children and their parents are asked to make.

The role of professional virtues

- 5.3 Later in this chapter, we explore a number of examples of good practice in the *development* of protocols for research with children and young people; and in the systems which *scrutinise* these protocols. However, we first need to consider the broader issue of how, in practice, systems can be devised that encourage and promote ethical research with children, not just at the point of ethical review but throughout the whole trajectory of the research endeavour.
- 5.4 Any system, however well-intentioned, devised to encourage and promote ethical research may unwittingly lead either to unthinking adherence to a checklist of requirements, or may create such onerous hurdles that it acts, in practice, as a barrier to research. These problems become particularly acute in the case of research involving children because of the highly context-specific nature of childhood and family decision-making (see, for example, paragraphs 1.15 and 4.15). What may be perceived as an appropriate balancing of burden and benefit in one context may be quite inappropriate in another. Similar disparities arise in the diverse ways in which children and young people obtain degrees of decision-making control over their own lives. Thus it becomes particularly challenging to offer guidance that will be sufficiently context and culture-specific in multicentre and multinational research.⁵⁴² Yet, given that many of the conditions specific to childhood are relatively rare, such international cooperation is

⁵⁴² Needham AC, Kapadia MZ, and Offringa M (2015) Ethics review of pediatric multi-center drug trials *Pediatric Drugs* **17**(1): 23-30. See also: Ebrahim HB (2008) Situated ethics: possibilities for young children as research participants in the South African context *Early Child Development and Care* **180**(3): 289-98.

even more important in research with children and young people than in other forms of clinical research.

- 5.5 The challenges illustrated by the need for research that is both international in reach and yet sensitive to the context in which it takes place might be summed up in the question as to how *reflexive* ethical practice can best be promoted: that is, ethical practice that is not simply ‘enforced’ top-down by external requirements or bodies, but that is informed by experience and mutual learning; becomes an inherent part of daily practice; and is sensitive to difference in national and social contexts.⁵⁴³ This, in turn, brings us back to the particular context in which clinical research takes place: that of clinical practice. We are not concerned with consumer or contractual relationships between parties on an equal footing of knowledge and power. Rather we are concerned with the special professional relationships that exist between clinicians (or researchers with equivalent professional responsibilities) and the participants they recruit to take part in their studies – who may also be patients. The role that clinical research plays in both society and in clinical care, and the associated standing of researchers, means that they have certain responsibilities that are distinct from those in other professions.
- 5.6 Thus, rather than seeking to set ever more detailed regulatory requirements to ‘police’ ethical research practice with children and young people, we suggest that a more fruitful approach is to focus on the responsibilities that arise out of the professional role of the researcher, and in particular the **values** or **virtues** that inform how society as a whole expects those professionals to conduct their work. By seeking to describe the features of ethically-conducted research with children and young people, and the behaviours of those conducting such research, we can avoid the trap of attempting to (over)specify the procedures used to achieve them.
- 5.7 At the end of Chapter 1, we noted how an earlier Nuffield Council report concerned with novel neurotechnologies that intervene in the brain identified three ‘professional virtues’, or values, of inventiveness, humility and responsibility, and suggested that a proper balancing of these would provide a powerful steer to ethical research practice (paragraph 1.28). These three values capture important aspects of what is demanded of a clinical researcher in any field: the impetus to strive to innovate and improve healthcare, kept in check by a recognition of the uncertainties inherent in research, and exercised with due sense of the responsibility of inviting participants to take on any burdens and risks involved in a study. Our analysis in Chapters 1 and 4 of this report took a very similar approach, with its assertion of the essential value of research in improving children’s and young people’s health and healthcare, accompanied by a number of parental and professional responsibilities, including that of keeping the welfare of participants at the forefront of decision-making. We also identified further responsibilities arising out of the special developmental aspect of childhood: those of respect for individual children (regardless of capacity); and of supporting children and young people in developing their capacity for independent agency. Finally, we argued

⁵⁴³ See, for example, Alderson P, and Morrow V (2011) *The ethics of research with children and young people: a practical handbook* (London: SAGE Publications), who preface their introduction to practical guidance on social research with children with the comment at page 4: “There may not be a single correct or expert answer. Much depends on the context, the topics and methods of each study. This careful working towards the best or least harmful answer is part of ethical research, in a do-it-yourself and not simply a ready-made, off-the-peg approach.” See also: Bolton G (2014) *Reflective practice: writing and professional development (fourth edition)* (London: SAGE) and the discussion of reflexive governance in Laurie G (2011) Reflexive governance in biobanking: on the value of policy led approaches and the need to recognise the limits of law *Human Genetics* **130(3)**: 347-56; and Christensen P, and Prout A (2002) Working with ethical symmetry in social research with children *Childhood* **9(4)**: 477-97.

that a protective concern for children's potential vulnerability should, in many cases, be met through appropriate partnerships with children, young people and parents.

5.8 In the specific context of research with children and young people, we identify three particular virtues or professional characteristics that have emerged repeatedly throughout the development of this report and that, we suggest, lie at the heart of professional ethical practice:

- **trustworthiness;**
- **openness;** and
- **courage.**

5.9 **Trustworthiness** is an essential prerequisite for facilitating **trust**, which emerges as a central theme in all the relationships that feature in this report. Trusting relationships between families and researchers have been identified as a central factor when children and their parents make decisions about research participation (see paragraphs 2.25–2.29). Such relationships are maintained and supported by governance systems that are, and are perceived to be, trustworthy: the necessity of maintaining public and participant trust thus underpins the protective aspect of both scientific and ethical review. Trust between professionals is an essential feature of any form of collaborative working, whether within a small clinical team, or across multiple organisations and countries. Children and parents talk about trusting one another in shared decision-making (see, for example, Boxes 4.2 and 4.3), and a lack of such trust within families with respect to decisions about research participation is highly likely to lead to difficulties. Finally, any functioning system of governance, whether in terms of regulatory/scientific or ethical review, must be able to trust the researchers subject to that governance. However, too *much* trust may be problematic; as, for example, where existing clinical relationships between researchers and potential participants may risk skewing participation decisions. Similarly, trust may sometimes be misplaced; for example, where governance procedures do not deliver the scrutiny they are believed to offer.

5.10 **Openness** similarly characterises many of the positive aspects of clinical research practice that we have explored in this report. Open discussions between researchers and families with respect to the uncertainties inherent in research are essential if trusting relationships are to develop, and for families to feel confident about the decisions they make. Trust in the whole research process is strengthened by the open sharing of research findings; and potentially damaged by failing to communicate such valued information (see paragraph 3.27). As improvements in the treatment of leukaemia demonstrate (see Box 1.1), willingness to collaborate with and learn from other researchers has played a significant role in advancing knowledge about serious conditions: such collaboration is predicated on both openness and trust. Finally, as we noted earlier (see paragraph 5.4), the need for collaboration – both between sectors of the research community and across countries and continents – is particularly acute in research into conditions affecting children and young people.

5.11 **Courage** is cited less often than trustworthiness and openness as a significant professional characteristic, but can be critical in the context of research with children and young people, given the nervousness that such research may engender (see paragraph 3.45). Researchers need courage to undertake 'difficult' research, where the 'easy' option may be to divert their research interests into areas seen as less controversial. Research ethics committees (RECs) may, at times, similarly need to be

courageous when coming to decisions with respect to higher risk research protocols (see paragraphs 3.45 and 5.34). The proper involvement of children and young people in the research process, which involves at least a degree of transfer of power between adults and children, also involves courage.⁵⁴⁴ Having recognised the need at times for courage, however, it is also very important that it should not shade into foolhardiness: there always need to be checks and balances, and research and innovation cannot be encouraged at any cost.

- 5.12 We will return in Chapter 6 to discuss further how these virtues of trustworthiness, openness and courage characterise the direct relationships between researchers and the children and young people (and their parents) whom they seek to recruit into research studies. We now turn to the prior role of professionals in developing and scrutinising research protocols, and consider how both these professional virtues, and our analysis of vulnerability and the importance of partnership, might transpose into practical means to encourage high quality clinical research with children and young people.

Professional responsibilities in developing research

- 5.13 In Chapter 4, we suggested that research professionals should respond to concerns about children's potential 'vulnerability' in research by asking themselves: 'Does this research raise particular ethical challenges and what can I do about them?' (see paragraph 4.58). We further argued that these challenges can best be explored in light of children's and young people's *own* perceptions of the demands of the study. In the design and development of clinical research studies, the challenge for professionals is thus to ensure that they have worked in partnership with children, young people and their parents from the beginning (see Box 6.5).⁵⁴⁵ Genuine partnership will help to ensure that important aspects of the research question have been considered from the perspective of those whom the research aims to benefit and who are in a similar situation to potential participants; that researchers are aware of those aspects of study design that might be of concern to prospective participants; that, wherever possible, these concerns have been ameliorated; and that the information provided for potential participants is clear and age-appropriate. Such partnerships do, however, demand that researchers exercise all the professional virtues described above: in the development of open, trusting relationships with their partners; and in demonstrating the courage necessary to cede some degree of control with respect to the study design to children and young people.

- 5.14 We noted in Chapter 3 that there is an established network of young persons' advisory groups in the UK who are well-placed to take on aspects of this role (see paragraphs 3.37–3.39). Depending on the nature of the condition being researched, in some cases it will also be important for researchers to seek input from children, young people and parents with personal experience of living with a particular condition. Family support networks developed in connection with those conditions will often be able to facilitate

⁵⁴⁴ See also: Alderson P, and Morrow V (2011) *The ethics of research with children and young people: a practical handbook* (London: SAGE Publications), at page 109, who identify the courage needed (on both sides) in transferring power from adults to children when genuinely involving children in research.

⁵⁴⁵ The extent to which it will be culturally acceptable for children's voices to be heard in this way will inevitably vary. However, the Young Lives project demonstrated how the very process of being involved in research can change perceptions of children's roles, citing, for example, the reflection from a boy in India: "Till now no one has discussed like this with children. We feel happy for team members mingling with us. Earlier we never speak [up] before anybody. But now we are able to speak out in front of people like you without any fear". See: Morrow V (2009) *The ethics of social research with children and families, in Young Lives: practical experiences - working paper no. 53* (Oxford: Young Lives), at page 16. See also: Jabeen T (2009) 'But I've never been asked!' Research with children in Pakistan *Children's Geographies* 7(4): 405-19.

access to such input, especially in connection with long-term conditions (see also paragraphs 5.26–5.30). Organisations such as INVOLVE (funded by the NIHR to support public involvement in research)⁵⁴⁶ and the NIHR Research Design Service⁵⁴⁷ also have an important role to play in promoting and facilitating the involvement of children, young people and parents in the design of studies.⁵⁴⁸

- 5.15 **We strongly welcome the approach taken in the UK by the Clinical Research Network: Children, and by ScotCRN, in establishing and supporting young persons' advisory groups. We note and welcome how similar groups are being developed in other countries, and in specific areas of healthcare, such as mental health. We also recognise that such groups are not cheap to run, and that at present their costs tend to be borne out of public funding allocations for research which are already under considerable pressure.**
- 5.16 All stakeholders who use the services offered by these groups need to work together in order to ensure the groups have a secure funding base for the future, and, where necessary, are able to expand in order to respond to increasing requests from researchers. In particular, it seems evident that the commercial research sector should contribute towards their costs. Such contributions might, for example, be made through annual donations to a central fund, sufficient to support regular meetings by young persons' advisory groups and to cover the costs of other sources of condition-specific advice, such as specialist patient groups.⁵⁴⁹ Alternatively, a standard administration fee could be levied for each protocol considered by a group of young people. **Whatever the funding mechanism chosen, it is clearly critical that the independence of young persons' advisory groups should be maintained.** It is also important that there should be some degree of flexibility in how the available funding is used so that specialist charities, as well as young persons' groups, can be supported in the work they do in advising on research proposals.

Recommendation 1

We recommend that the Clinical Research Network: Children and the Scottish Children's Research Network should initiate discussions with their industry partners on ways in which industry could contribute to the costs of young persons' groups in the UK, without compromising their independence.

Recommendation 2

We recommend that all sponsors of clinical research develop systems to guarantee that their quality control of research proposals involving children and young people exposes those proposals to expert advice on good practice, and to the views of young people and

⁵⁴⁶ INVOLVE (2015) *Welcome to INVOLVE*, available at: <http://www.invo.org.uk/>. See, in particular, INVOLVE and PK Research Consultancy (2004) *A guide to actively involving young people in research: for researchers, research commissioners, and managers*, available at: <http://www.invo.org.uk/wp-content/uploads/documents/InvolvingYoungPeople2004.pdf>.

⁵⁴⁷ NIHR (2015) *Research Design Service*, available at: <http://www.rds.nihr.ac.uk/>.

⁵⁴⁸ For example, by collating and regularly updating the findings from methodological studies that systematically investigate the views and experiences of children, young people, and parents taking part in research, so that these findings and insights are made readily available to the wider clinical research community.

⁵⁴⁹ An approach on these lines was suggested by the Chief Medical Office for England at the GenerationR conference: Medicines for Children Research Network (2014) *GenerationR: young people improving research - 2013 meeting report*, available at: <http://viewer.zmags.co.uk/services/DownloadPDF?pubVersion=26&publicationID=62b8f2e9&selectedPages=all>, at page 13. For example, such contributions might be linked to companies' corporate social responsibility commitments.

parents.

Recommendation 3

We recommend that INVOLVE should collaborate with the National Institute for Health Research's Research Design Service and relevant experts at the Medicines and Healthcare Products Regulatory Agency to explore how the design and regulatory scrutiny of clinical trials can take more account of the experience of young people who have previously taken part in trials, and of their families.

Professional responsibilities when reviewing research

The role of the research ethics committee

- 5.17 Earlier in this report we discussed two distinct approaches that research ethics committees (RECs)⁵⁵⁰ or their equivalents might take when reviewing research proposals (see paragraph 3.45). These were characterised, on the one hand, as a 'protective' approach, focusing primarily on the potential burdens and risks to be borne by the research participants; and on the other as a 'facilitative' approach, that aims to ensure that potentially valuable research is able to proceed. REC members and chairs who took part in discussions with the Working Party strongly argued that a REC should have *both* these aims in mind when reviewing protocols. We agree. Consideration of the potential risks and burdens of the research *must* certainly play a central part in the ethical review of any research protocol. While it is important to recognise that children and parents will have diverse views on what constitutes a burden, or what risk they think acceptable to undertake (see paragraph 2.19), there are some risks or burdens that no children or young people should be asked to undertake, other than in the context of expected benefit for themselves. At the same time, the potential value of the research should not be overlooked, whether this may accrue in terms of the prospect of improved treatments or health services in the relatively near future, or in terms of developing the research skills of students and professionals at the start of their careers, hence facilitating the prospects of research in the future.
- 5.18 The question of what RECs should aim to do when reviewing research is, of course, one that arises in the context of all kinds of research, whatever the age of the participants. However, it is particularly important to emphasise this two-fold (protective/facilitative) responsibility in the context of research with children and young people because of the nervousness with which many REC members may approach the question of involving children (particularly younger children) as study participants. Elsewhere in this report we have discussed and challenged the commonly-held idea that children and young people are automatically vulnerable in research, and also the associated assumption that the governance of research involving children should be one in which additional protections are heaped on top of those thought to apply to adults (see paragraphs 4.53–4.62). These assumptions about children's vulnerability may lead to the sense that it is always 'safer' to prevent research going ahead because of concern about an aspect of the study, regardless of any parallel consideration of the

⁵⁵⁰ Note that while any research involving NHS patients within the UK will be reviewed by a REC, subject to oversight by the National Research Ethics Service (NRES), university RECs, such as those reviewing psychology or sociology research, may also be called upon to review research involving children and young people within the scope of this report.

active dangers to which all children, now and in the future, are exposed by the provision of care that is not soundly based on good evidence. At the same time, however much research may be needed, there is clearly an overriding requirement to ensure that the welfare of potential participants, whatever their age, is properly considered.

- 5.19 How is this balance to be achieved, in the particular context of clinical research with children and young people? First, in considering the important role that a REC should play in deciding whether the potential burdens and risks of a proposed protocol fall within an acceptable threshold, the very different *kinds* of harm that may be in question should not be forgotten. As we noted earlier (see paragraph 3.48), clinical research covers a very wide area of research activity. The associated risks of harm similarly vary both in kind (emotional, psychological or physical; temporary or permanent) and in likelihood and magnitude (from no risk of harm to high risk of substantial harm). In the context of medicines research, or research involving new interventional procedures, it may indeed be the case that proposed protocols involve high risks or burdens. However, many research protocols involving children scrutinised by RECs will not present such challenges.⁵⁵¹ Significantly, the particular risks and burdens inherent in different studies also arise in disparate contexts, in particular with respect to the relationship between that study and any illnesses from which potential participants may be suffering.
- 5.20 Thus, depending on the nature of the study, RECs are required to make very different kinds of judgments. In some cases, risks and burdens will arise in the context of research protocols relating to serious illnesses where ‘standard’ care options are inadequate: either because there are currently no such options, or because those that exist have very limited effectiveness or highly burdensome side effects, or both. In such cases, RECs will need to be satisfied both that risks and burdens have been minimised as far as possible, and that those that remain (however high) are outweighed by the prospective benefits for those participating. In the specific case of randomised controlled trials (RCTs), the REC will also need to be satisfied that there is genuine uncertainty within the clinical and scientific community with respect to the likely benefits and harms of the various ‘arms’ of the study. However, in cases where no direct benefit to the children or young people participating is in prospect, very different considerations as to the maximum amount of risk or burden permissible arise.
- 5.21 We summarised in Chapter 3 the current regulations with respect to such risks and burdens in research with children: in most jurisdictions these are permitted to be no more than minimal (see paragraphs 3.52–3.56). However, we also noted that children and young people are permitted, or even encouraged, to run risks in other areas of their daily life that far exceed any definition of ‘minimal’, such as those involved in playing contact sports, or in learning to drive (see paragraph 2.64). While in some cases these risks may be recognised and justified by the (direct or indirect) benefits they are perceived to bring, this cannot always be assumed, particularly where participation is compulsory as in some school-based activities. How are RECs to

⁵⁵¹ For example, NIHR Clinical Research Network: Children, responding to the Working Party’s call for evidence noted “the perception that paediatric research is very complex, high risk and fraught with practical difficulties. Whilst this may be true for some areas of research, it certainly isn’t necessarily the case that all paediatric research is ‘difficult’ or ‘dangerous’.” See also: Petrie KJ, Faasse K, Notman TA, and O’Carroll R (2013) How distressing is it to participate in medical research? A calibration study using an everyday events questionnaire *JRSM Short Reports* **4(10)**: 1-7.

respond to these conflicting societal messages as to what degree of risk is acceptable for what degree of (potential) gain?

- 5.22 We note that a number of expert organisations have, over the years, published indicative lists categorising the risks of particular procedures.⁵⁵² We also note that these judgments as to whether a particular procedure might present more than minimal risk are the subject of disagreement,⁵⁵³ and have, in some cases, changed over time.⁵⁵⁴ Moreover, we are aware of the ongoing debate as to the extent to which risks may legitimately be compared with those that participants may face in their own daily lives, given that some children may already be overburdened either by their illness, or by other factors in their lives (see paragraph 3.56). Rather than attempting to reproduce or revise any such lists of acceptable procedures, or comparator activities in daily life, we suggest that it is more appropriate to focus on the *expertise* that RECs, those tasked on a regular basis with making these judgments, are able to draw upon when approaching these questions.
- 5.23 **We conclude that, in order for RECs to be well placed to make these (sometimes very finely balanced) decisions as to whether, in a particular case, the burdens and risks presented by a study protocol can ethically be justified, it is essential for them to have access to appropriate expertise. We highlight two forms of such expertise: that of professionals with specialist knowledge of children's healthcare; and that of children and families.**
- 5.24 The importance of RECs having access to appropriate paediatric expertise (such as medical, nursing, psychological or psychiatric expertise, depending on the nature of the research) was a constant theme in evidence gathered by the Working Party. It was clear that there was genuine concern among some paediatric researchers that RECs may sometimes make decisions that particular protocols are unacceptable in ignorance of what is standard practice in paediatric and neonatal services. However, the Working Party was also made aware of some of the practical constraints on RECs of obtaining such expertise (see paragraph 3.44).

Recommendation 4

We recommend that, whenever research ethics committees consider protocols relating to research with children, they should always ensure that they have timely access to expert advice from the relevant area of children's and young people's healthcare. Such expertise may need to be obtained through an external adviser co-opted for the particular decision.

Recommendation 5

⁵⁵² 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; European Commission (2008) *Ethical considerations for clinical trials on medicinal products conducted with the paediatric population*, available at: ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf, Annex 4.

⁵⁵³ Freedman B, Fuks A, and Weijer C (1993) *In loco parentis*: minimal risk as an ethical threshold for research upon children *Hastings Center Report* **23(2)**: 13-9.

⁵⁵⁴ Arterial puncture, for example, was classified in 2000 by the RCPCH as 'high risk', while the European guidance in 2008 categorised it as 'minor increase over minimal risk'. X-rays were also classed in the 2008 European guidance as 'minor increase over minimal risk', but as 'negligible' or 'minimal' in guidance issued by Public Health England in 2011: Public Health England (2011) *Radiation risks from medical x-ray examinations as a function of the age and sex of the patient*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/340147/HPA-CRCE-028_for_website.pdf.

We recommend that the National Research Ethics Service, in cooperation with relevant Royal Colleges and other professional bodies, should establish a database of experts who are willing to act as REC advisors, from across the full range of potential clinical research areas involving children. The National Research Ethics Service might also consider ways in which researchers and research ethics committees might better communicate with each other with respect to any specialist areas of knowledge required to inform assessment of the protocol, for example through specific prompts in the online application form.

Recommendation 6

We further recommend that the National Research Ethics Service should keep under review the experiences of both research ethics committees and researchers with respect to the current system of 'flagging' committees as suitable for considering research with children and young people. If the evidence suggests any systematic difficulties with respect to the scrutiny of particularly complex or sensitive studies, the National Research Ethics Service should consider exploring alternative models, such as the creation of a limited number of expert research ethics committees, on the model, for example, of the Social Care Research Ethics Committee.

- 5.25 We were also struck by the difficulties that health professionals and others engaged in research sometimes appear to encounter in convincing their employers that serving as a REC member is time well-spent. Such difficulties demonstrate the extent to which research is not, as yet, seen as part of the 'core business' of the NHS. We note a number of ways in which such perceptions can be challenged. UK Chief Medical Officers, for example, have taken the step of writing directly to all NHS employers to encourage them to "look favourably on requests from doctors for absence to undertake national work of benefit to healthcare systems across the UK."⁵⁵⁵ Similarly, we note that those who undertake a number of public duties, including membership of health authorities and school governing boards, are guaranteed protected "time off work for public duties".⁵⁵⁶ Equivalent action should be taken to ensure that the professional time required for participation in this important domain of ethical review is similarly protected.

Recommendation 7

We recommend that the UK Departments of Health, NHS Employers, Universities UK and the Health Research Authority should jointly consider what steps they can take to protect the professional time needed for research ethics committees to work effectively.

Recommendation 8

We further recommend that Royal Colleges and professional bodies concerned with children's and young people's health should make their commitment to evidence-based care clear by reinforcing the professional responsibilities of their members to contribute

⁵⁵⁵ The Department of Health, Social Services and Public Safety (Northern Ireland), Welsh Assembly Government, The Scottish Government, Department of Health, and GMC (2012) *Letter re. requests for absence for work of national benefit*, available at: https://www.rcplondon.ac.uk/sites/default/files/letter_to_nhs_23_january_2012.pdf.

⁵⁵⁶ Gov.uk (2014) *Time off work for public duties*, available at: <https://www.gov.uk/time-off-work-public-duties>.

to the ethical review of research over their professional lifetime. For example, involvement of some form in a research ethics committee (including in an *ad hoc* advisory role) could be encouraged as part of continuing professional development schemes. A number of rotational posts for trainees working in different areas of children's and young people's healthcare could be linked with their local research ethics committees.

- 5.26 The equally critical input that can be obtained from parents, children and young people as to the acceptability of particular risks and burdens in the context of research should be set alongside the importance of access to specialist professional expertise. We have already alluded to the importance of such input in trial design (see paragraphs 5.13–5.15). Drawing on our conclusions that concerns about the 'vulnerability' of young participants should be countered by a partnership with children, young people and their parents (see paragraph 4.59), we suggest that RECs should draw strongly on such expertise, particularly when they are concerned about the potential impact of any of the procedures involved in the study protocol on children's day-to-day lives. The appropriate source of that input is likely to depend on the nature of the protocol: for example, where concerns arise as to whether it would be reasonable to ask children in general to undergo a particular number of blood tests over a particular timeframe, it would be appropriate to seek input from groups with a general interest in research, such as CRN: Children and ScotCRN young persons' advisory groups. Where the question relates to what a specific population of children or young people might feel (for example, those with a serious chronic condition), then that more specialised input is likely to be more appropriate.⁵⁵⁷ We return below (see paragraph 5.30) to the question of how RECs can ensure such input is obtained, without imposing undue bureaucratic burdens on their own functioning.
- 5.27 In describing the role of ethical review as both 'protective' and 'facilitative', we took the view that some harms *cannot* be justified, whatever the value of the information generated by the research. This claim derives, at least in part, from the very nature of clinical research: that it arises in, and is inextricably mixed up with, clinical practice, where relationships of trust between professionals and patients play a crucial role (see paragraph 5.9). The protective element of the REC's role thus enables assurance to be offered to those invited to take part in research that what they are being asked to do has been judged, independently, to be a reasonable request. It will then be for those (parents, children and young people) who receive that invitation to make their *own* decisions, as to whether (or not) it is one they wish to accept.
- 5.28 **We therefore take the view that the fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a 'fair offer' to children, young people and their parents, where the value of the research and its likely risks, burdens and benefits have been carefully weighed up.** This concept of research as a 'fair offer' emphasises that it remains the ultimate responsibility of those entrusted with research review to make independent judgments about acceptable levels of risk and burden, and how these may be balanced against any possible benefits. This assurance role is important not just with respect to the potential participants in the particular research study, but in order to promote wider

⁵⁵⁷ One such example cited to the Working Party was that of a proposed study of spinal muscular atrophy (SMA) involving a sham lumbar puncture in the control arm which caused the EMA's PDCO significant concerns. Comments on the protocol from families affected by SMA helped inform their decision: Treat-NMD (2013) *MHRA queries on a possible SMA trial*, available at: <http://www.treat-nmd.eu/sma/mhra-queries/>.

public confidence and trust in the whole endeavour of research, especially where public knowledge of research and research procedures is poor (see paragraphs 2.17–2.18).

- 5.29 In characterising the role of ethical review as that of assuring that research participation should constitute a fair offer, we thus challenge the view, expressed by some of our respondents, that the role of this review is simply to make sure that potential research participants have the right information to make a choice.⁵⁵⁸ The provision of high-quality, accurate and comprehensible information about a research protocol is an essential part of a ‘fair’ recruitment process, and we return to the professional responsibilities of researchers in this respect in Chapter 6 (see paragraphs 6.8–6.14 and 6.18). However, if RECs were to focus *only* on the quality of information available, this would effectively put the entire burden of responsibility on the parents, children and young people invited to take part in research, with no assurance offered as to the reasonableness of what was involved. Such an approach would, by implication, characterise the relationship between professionals and patients as one of ‘buyer beware’, rather than one of professional concern and trust.⁵⁵⁹
- 5.30 We suggest that RECs should routinely expect researchers to have involved children, young people and parents, as appropriate, in the design of their studies (see Box 6.5). RECs will then be able to draw on the reported opinions of children, young people and parents in order to assure themselves whether the study design is appropriate; whether any risks and burdens have been minimised and justified; and whether information materials are comprehensible to their target audience. If this is not possible or necessary in a particular case (for example, because of the urgency of the research, insurmountable cost reasons for locally funded researchers in low-income settings, or because relevant guidance from children, young people and parents is already available), this should be justified to the REC.

Recommendation 9

We recommend that research ethics committees should routinely require researchers to have involved children, young people and parents, as appropriate, in the design of their studies. Researchers who have not sought input in this way should be required to justify to the research ethics committee why this was not appropriate in their case, and be able to demonstrate an appropriate knowledge of relevant literature and guidance.

- 5.31 We note that, the more difficult or burdensome the study (for example, where it involves significant risks associated with new treatments), the more important it becomes for children, young people and parents to be involved in the study design, in order to offer assurance both to researchers and REC members that what is being asked of potential participants constitutes a fair offer. We note, and welcome, that the quality criteria for membership set by Enpr-EMA (the European umbrella group for children’s clinical research networks) include requirements relating to public

⁵⁵⁸ Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁵⁵⁹ We recognise that, for some, the language of a fair ‘offer’ itself implies a consumer or transactional relationship. We suggest, however, that the concept of an ‘offer’ is not limited to such a relationship, and is applicable also in this (professional and trust-based) context. Indeed, by ensuring that any ‘offer’ made to potential participants is ‘fair’, RECs precisely aim to counteract any potential inequalities in the relationship based on asymmetries of knowledge and power.

involvement, as well as scientific and clinical expertise, recognising the core role that such involvement should play in the design and conduct of good research.⁵⁶⁰

- 5.32 Ensuring that invitations to participate in research constitute a fair offer is not, however, simply a matter of the judgment of acceptable risks and burdens, accompanied by an assurance of the quality of information materials on which potential participants will base their decisions. There is also the question of the *value* of the proposed research and, in particular, whether the protocol will answer, or at least contribute to, the research question it purports to address (which may legitimately, in the case of student projects, include the development of research skills that may benefit children's healthcare in future). If the research is unlikely to meet its professed aim (whatever form that may take) it is hard to see how the invitation to take part in research can be said to be a fair offer to potential participants.⁵⁶¹
- 5.33 This brings in the wider debate on the extent to which ethical review should also encompass scientific questions.⁵⁶² In the same way that we suggested that RECs should take into account whether children and parents have had appropriate input at the design stage of a study protocol, we suggest here that the duty of the REC with respect to the scientific validity of the study protocol must be to *ensure* that these questions have been adequately addressed by others. This may be achieved, for example, through appropriate liaison with those concerned with regulatory or peer review. RECs will often not be in a position to make judgments themselves on questions of whether, for example, a study is adequately powered to produce meaningful results. It is, however, their role to be confident that these issues have been properly considered by those with appropriate expertise. This issue arises in connection with the review of *all* research, regardless of the age of the participants; and there is nothing to justify a REC taking a more active approach with respect to scientific validity in research with children than it would deem appropriate for research with adults.
- 5.34 In focussing on the role of the REC in ensuring that research involving children constitutes a fair offer to children and parents, it is also important to recognise a REC's second and equally important function: its facilitative role, which arises in recognition of the essential social good of well-designed and ethically-conducted research. **It is not an ethically neutral act to say 'no' to a research proposal that might potentially lead to better outcomes for children's and young people's healthcare.** Being *over-*protective may be as damaging as being insufficiently protective.⁵⁶³ The fundamental aim of ethical review must be the active encouragement of research that has the potential to improve children's healthcare, while ensuring risks are kept to a minimum acceptable level. Recognising that saying 'no' to research is not ethically neutral adds additional weight to the recommendations set out in paragraphs 5.24 and 5.30, in

⁵⁶⁰ European Medicines Agency (2014) *European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA)*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp&mid=W00b01ac05801df74a.

⁵⁶¹ See, for example, Chalmers I (2014) The development of fair tests of treatments *The Lancet* **383(9930)**: 1713-4.

⁵⁶² Nuffield Council on Bioethics (2014) *Factfinding meeting: the role of ethical review* (London, 6 February: Nuffield Council on Bioethics).

⁵⁶³ See, for example, the discussion of the tendency towards 'innate conservatism' in: Denegri S (24 April 2014) *Blog: do we really need the Medical Innovation 'Saatchi' Bill? I'm unconvinced.*, available at: <http://simondenegri.com/2014/04/24/do-we-really-need-the-medical-innovations-saatchi-bill-im-unconvinced/>. See also the argument that the medical community must be more willing to take risks: Boston Business Journal (31 October 2014) *Pediatric summit explores growing issue of risk vs. benefits of rare disease drugs*, available at: <http://www.bizjournals.com/boston/blog/bioflash/2014/10/pediatric-summit-explores-growing-issue-of-risk-vs.html?page=all>.

respect to the expertise that must be available to the REC when making a decision, or recommending modifications, to a study involving children.

Ethical review in practice

5.35 Having explored the fundamental role of ethical review, along with some of the practical ways in which RECs might be assisted in carrying out this role, we now turn to the question of how the professional virtues identified at the start of this chapter (see paragraphs 5.3–5.12) might inform the ethical review process itself. We suggest, first, that the way in which the REC itself conducts its business should be in accordance with these virtues; and, second, that these virtues should be at the heart of what is expected of researchers whose protocols are under scrutiny. Features of ethical review processes, and ethical research practices, that demonstrate these virtues could include:

- Open and constructive communication between researchers and RECs, based on a shared understanding that any invitation to take part in research must constitute a 'fair offer' in which children, young people, and their parents can reasonably place their trust.
- Openness with respect to communicating the outcomes of research, whether positive or negative, both to participants and to the wider public.
- Recognition by RECs of the role of professional judgment by the researcher, and the need at times to allow for professional discretion in the field: for example, through requirements describing guiding values and outcomes, rather than highly specified procedures from which no deviation is permitted (see paragraphs 6.10–6.14).
- Recognition by researchers of the role of RECs in scrutinising their capacity to exercise that discretion.

5.36 We note and welcome a number of practical ways in which these features are currently encouraged in UK and European contexts. Enpr-EMA, for example, is currently working to identify and share examples of good practice by RECs in their review of research involving children and young people (see paragraph 3.61). Within the UK, NRES encourages all applicants to NRES RECs to offer feedback about their experiences of ethical review, providing the opportunity for constructive communication between researchers and RECs.⁵⁶⁴ On the specific issue of communicating the outcomes of research, the HRA has issued draft guidance for researchers, stating that research participants should be "routinely informed" about how to access study findings once the research is over.⁵⁶⁵ Other practical ways in which these aims might be furthered in the current UK context include:

- Routine audit of REC decisions by NRES to identify the impact (whether positive or negative) of amendments to research protocols involving children and young people requested by RECs as part of their positive opinions, in order to identify and share good practice;

⁵⁶⁴ Dr Simon Woods, HRA National Research Ethics Advisors' Panel member, personal communication, 14 November 2014.

⁵⁶⁵ Health Research Authority (2014) *Information for participants at the end of a study: draft guidance for researchers*, available at: <http://www.hra.nhs.uk/about-the-hra/consultations-calls/closed-consultations/guidance-participant-information-end-study-active/>, at page 1.

- Researchers, as a routine part of their study proposal, to outline how they plan to communicate the outcomes of their research, both directly to the children and young people taking part; and also more widely, for example, through their institution's website.

5.37 Finally, it is very important to note how these virtues may also be highly relevant with respect to the requirements that RECs may set with respect to the recruitment of children and young people, such as those relating to consent processes. We return to this aspect of the REC role in Chapter 6, alongside our consideration of the direct responsibilities of researchers in this respect.

Drivers of research

Research prioritisation

5.38 We noted earlier in this report the challenges inherent in determining what forms of research with children should be regarded as having higher priority than others (see paragraph 3.10). While the *burden* of any particular condition (incorporating both the severity of the condition and how common it is) is clearly highly significant in considering priorities for research, this cannot be the only factor to be taken into account; such an approach would overlook, for example, the impact of rare diseases on children and their families. Other considerations that must also be taken into account include the practical scientific question of which research directions are most promising at the time funding decisions need to be made; and the unpredictable nature of research, with the prospect of findings in one field having unexpected influence in another. Similarly, there is no simple way of judging the relative importance of research relating to prevention, treatment or care: all have important, and different, roles to play in improving the lives of children living with particular conditions now, and in the future.

5.39 Moreover, it is necessary to be alert to the very different sources of funding available for research into childhood conditions and their associated constraints. Research funding that derives from charitable trusts or fundraising, for example, will often, by its nature, be directed to particular ends; and research funded by private companies will inevitably take the likely commercial viability of any end product into consideration. Public funding available for research, by contrast, is potentially more flexible in its deployment, although still subject to the pressures of public and Parliamentary scrutiny.

5.40 **Given the complexity of these judgments on priorities, made more complex still by the myriad of potential funding sources, we conclude that our primary ethical concern with respect to prioritisation should relate to the *process* by which such decisions are reached. Drawing on our emphasis on the importance of partnerships between research professionals and potential research participants (see paragraph 4.59), we suggest that the key challenge for those responsible for making decisions about which studies to fund must be to ensure that key stakeholders, including children, young people, parents and professionals, are appropriately involved in those funding decisions.** The model of the James Lind Alliance's (JLA) 'priority setting partnerships' provides an excellent example of how this is already being achieved in some areas, such as in the care of premature babies, and teenage cancer (see paragraph 3.6). The consensus approach used by the JLA recognises the very wide range of interests at stake, and ensures that all voices are heard, without privileging any one perspective. Such collaborative approaches also act to promote transparency and trust in the priority-setting process, as well as avoiding unnecessary and wasteful duplications of research effort.

- 5.41 **We similarly endorse and encourage ongoing work by Enpr-EMA (the European ‘network of research networks’), exploring how European children’s research networks can contribute to the priority-setting debate, and how they can facilitate the involvement of children, young people and parents in those discussions (see paragraph 3.9). More, however, needs to be done to encourage debate at national and regional level about priorities across the range of childhood conditions. We encourage health departments (within the UK and beyond) to take the lead in initiating debate on the most pressing priorities in child health research in their own countries, and in ensuring that children, young people and parents, as well as relevant professional experts, are appropriately involved in those discussions.**
- 5.42 The European Medicines Agency’s (EMA) Paediatric Committee (PDCO) also has an important role to play in this process of prioritisation, through its ongoing work to develop inventories of ‘paediatric needs’ for medicines research across a range of therapeutic areas (see paragraph 3.8). **We note, and support, PDCO’s general commitment to involving children and young people in its activities, and, in particular, proposals made in 2013 that such involvement should include input into the definition of significant therapeutic needs. We strongly encourage PDCO to continue to take these plans forward.** Such a commitment again highlights the importance of active young persons’ groups within national, and pan-European, clinical research networks (see paragraph 5.15) which provide a practical mechanism for such involvement.

Incentivising medicines research with children and young people

- 5.43 It is clear from the European Commission’s 2013 report (see paragraph 3.16) that the 2006 Paediatric Regulation, combined with the incentives included within the Orphan Medicines Regulation, has started to make a welcome difference to the amount of information available to prescribers on the effect of medicines on children. Within Europe, medicines research with children is now part of the mainstream: research sponsors must routinely develop paediatric investigation plans (PIPs) unless a waiver has been granted; medicines targeting new indications (causes or symptoms of disease) in children are beginning to become available; the quality of children’s clinical trials is improving; and there is more innovative thinking in the development of medicines for children. However, as we identified in Chapter 3, a number of issues remain: in particular relating to the use of class waivers with respect to research that might still be of benefit to children; the ineffectiveness of the incentives that sought to encourage research with children on older off-patent medicines; and the question of how best to incentivise research in conditions that only, or primarily, affect children (see paragraphs 3.18–3.22).
- 5.44 **We welcome the significant benefits that the 2006 Paediatric Regulation has brought about within Europe, in increasing the focus on medicines research with children. We recognise, in particular, the very positive and proactive approach EMA and PDCO have taken to their regulatory role, using it not only simply to police the system established by the Regulation, but also actively to promote effective, collaborative, research with children and young people through a variety of practical means (see paragraph 3.25).⁵⁶⁶ We strongly encourage the**

⁵⁶⁶ For example through the development of ‘model PIPs’ for conditions under-represented in research: see: European Medicines Agency (2012) *5-year report to the European Commission: general report on the experience acquired as a result*

EMA and PDCO to build on these successes, using the opportunity of the forthcoming ten-year review of the Regulation with respect to any identified need for legislative change. In particular, at paragraphs 5.45–5.49, we highlight the following areas where more must be done.

Class waivers

5.45 It is clear to us that the class waiver system is not working as originally intended, and that some research that could benefit children is not taking place. We noted earlier in this report, in the context of ethical review, that it is not an ethically neutral act to say ‘no’ to a research proposal that might potentially lead to better outcomes for children’s healthcare (see paragraph 5.34). The same ethical imperative arises in the context of regulatory permissions or requirements. We strongly urge PDCO to complete its review of the class waiver system as a matter of urgency and, in the future, to ensure that where the mechanism of action of a medicine is potentially relevant for children and young people, research with children and young people to explore that potential goes ahead. Pending the completion of that review, we note that there is nothing to *prevent* sponsors of research from choosing to put forward a PIP even where they would be entitled to receive a waiver, and indeed that some sponsors have done so (see paragraph 3.22). We urge sponsors to consider this option, and PDCO to raise awareness of it.

Recommendation 10

We recommend that European Medicines Agency’s Paediatric Committee should complete its review of the class waiver system as a matter of urgency and ensure that where the mechanism of action of a medicine is potentially relevant for children and young people, research with children and young people goes ahead.

Recommendation 11

We recommend that where research sponsors are eligible for a waiver under the current class waiver system, they consider the evidence on the possible relevance of the mechanism of action of their product for *other* conditions occurring in children and young people. Wherever appropriate, they should undertake research with these age groups on a voluntary basis.

Incentives for older off-patent medicines

5.46 It is clear to us that more needs to be done to incentivise or promote research on the use of off-patent medicines used to treat children and young people, including the development of age-appropriate formulations. A number of approaches were cited to us which we feel merit further consideration, particularly in light of the forthcoming review of the 2006 Regulation, and the prospect offered of legislative amendment. If industry is thought to be the best source of such research, then a different approach would need to be taken to incentivisation. One possible model might be that of ‘transferable market exclusivity’, where the successful completion of a PIP with respect to an off-patent medicine would allow the value of the incentive to be transferred to a

different product.⁵⁶⁷ Any such incentive would need to be carefully targeted to ensure it was limited to cases where there was a clear need for the research; this could, for example, be achieved by linking it to the EMA's inventory of priority needs, or by giving PDCO the discretion to accept or reject the proposal on the basis of need. Other suggestions put to us included the use of imaginative tax breaks, if necessary on a country-by-country basis.⁵⁶⁸

Recommendation 12

We recommend that the European Medicines Agency should give serious consideration to innovative approaches to incentivisation for research with children on the use of off-patent medicines, as part of its preparation for the ten-year review of the 2006 Regulation.

Collaborative working

- 5.47 Industry, however, is not the only possible source of research activity with respect to off-patent medicines in children; academic researchers and patient groups are also potentially well-placed to initiate work in this field, collaborating as appropriate with industry, or seeking additional support from the EMA, to ensure that regulatory requirements are met (see paragraph 3.18). The potential value of collaborative working as a response to the difficulties encountered with the paediatric use marketing authorisation (PUMA) serves to highlight the much more general need for cooperation within children's research. **While the realities of different academic, professional and commercial interests across the research sector cannot simply be ignored, we suggest that there is a strong ethical imperative for researchers working in the field of clinical research with children and young people to work collaboratively with each other, and with key stakeholders such as condition-specific family support groups, to the maximum extent possible.**
- 5.48 This imperative is particularly strong with respect to research into rare conditions of childhood, where the cohort of potential research participants is relatively small, and where a failure to collaborate may lead either to underpowered studies, or to children and young people being recruited into successive studies with associated burdens on themselves and their families.⁵⁶⁹ We welcome initiatives such as those facilitated by the EMA to encourage multi-arm trials to compare multiple new medicines against standard treatments (see paragraph 3.25), and the development of collaborations between industry, academia, regulators and patient groups such as the Innoative

⁵⁶⁷ Nuffield Council on Bioethics (2013) *Factfinding meeting: setting the research agenda* (London, 9 September: Nuffield Council on Bioethics). For an overview of this, and other innovative methods of incentivisation, see: Global Health Technologies Coalition (2009) *Current and proposed incentive mechanisms: GHTC incentives & innovative financing working group*, available at: http://www.ghtcoalition.org/files/GHTC_Incentive_Mechanisms_List.pdf. See also: Creating Hope Act, section 908 of the FDA Safety and Innovation Act 2012, 21 U.S.C Sec 360ff, which provides market incentives for the development of drugs for rare paediatric diseases by introducing priority review vouchers: Kids v Cancer (2012) *Rare pediatric disease priority review voucher incentive program: section 908 of the FDA Safety and Innovation Act, based on the Creating Hope Act*, available at: <http://www.kidsvcancer.org/thecreatinghopeact/section-908-final-text/>.

⁵⁶⁸ See, for example, the R&D tax credits outlined in the GHT Coalition document above, and the creative industry tax reliefs introduced for the UK film industry: HM Revenue & Customs (2014) *Corporation tax: creative industry tax reliefs*, available at: <http://www.hmrc.gov.uk/ct/forms-rates/claims/creative-industries.htm>.

⁵⁶⁹ See, for example, Stoneham SJ, Hale JP, Rodriguez-Galindo C *et al.* (2014) Adolescents and young adults with a "rare" cancer: getting past semantics to optimal care for patients with germ cell tumors *The Oncologist* **19(7)**: 689-92: "We contend that it is time to move beyond trial eligibility that is defined only by which clinical trial organization can "lay claim" to the patient", at page 690.

Medicines Initiative.⁵⁷⁰ We further welcome the increasing focus on transparency in the sharing of research data, noting that research with children and young people led the way in this area of European regulation (see paragraphs 3.13 and 3.24).

5.49 Finally, we note that questions of collaboration and cooperation arise not only in response to concerns about protecting financial or professional interests, but also in connection with organisational boundaries. Adolescents with cancer, for example, are far less likely than younger children to be recruited into studies, but may also be automatically excluded from adult trials, regardless of whether they would meet the clinical criteria for the study.⁵⁷¹ We note that recent examples of good practice in overcoming these hurdles, both in the form of international collaboration and data-sharing, as cited above, and through the creation of the necessary physical infrastructure in the form of treatment centres for ‘adolescents and young adults’ (defined as 15-24 year olds), have been initiated by voluntary sector organisations such as the UK’s Teenage Cancer Trust and Teen Cancer America.⁵⁷² Examples such as these again highlight the crucial role played by voluntary sector groups, and the close links they maintain with children, young people and parents living with these conditions.

⁵⁷⁰ Innovative Medicines Initiative (2014) *Homepage*, available at: <http://www.imi.europa.eu/>. See also the UK’s Innovative Medicine Review, launched in November 2014, which will examine how more collaborative work between companies and regulatory and evaluation bodies can ensure that innovative products can be assessed more quickly, and how charities and patient groups can play a greater role: Department of Health, Department for Business, Innovation & Skills, (20 November 2014) *Major investment in life sciences*, available at: <https://www.gov.uk/government/news/major-investment-in-life-sciences>; and the launch of the Alliance for Children’s Therapeutics: Seattle Children’s Research Institute and Kineta Launch the Alliance for Children’s Therapeutics (11 June 2014) *First-of-its-kind pediatric research and funding collaboration to speed development of medications for autoimmune diseases*, available at: <http://www.seattlechildrens.org/press-releases/2014/first-of-its-kind-pediatric-research-and-funding-collaboration-to-speed-development-of-medications-for-autoimmune-diseases/>.

⁵⁷¹ Stoneham SJ, Hale JP, Rodriguez-Galindo C *et al.* (2014) Adolescents and young adults with a “rare” cancer: getting past semantics to optimal care for patients with germ cell tumors *The Oncologist* **19(7)**: 689-92.

⁵⁷² *Ibid.*

Chapter 6

Taking part in research:
professionals'
responsibilities

Chapter 6 – Taking part in research: professionals' responsibilities

Chapter 6 overview

Responsibilities of researchers

Researchers who invite children and young people to take part in research should:

- treat children and young people as individuals of value in themselves;
- support parents in their attempts to help their children develop in their ability to make autonomous choices;
- act in accordance with children's and young people's immediate and longer term welfare; and
- act in accordance with the professional virtues outlined in Chapter 5: trustworthiness, openness and courage.

Communication

- Professionals responsible for recruiting children and young people to take part in a study must ensure that the invitation (which the REC has deemed a 'fair offer') is extended in a fair manner. Good communication is essential, both in terms of the clarity and accessibility of the information materials provided (whatever the format), and, critically, in terms of the quality of face-to-face communication.

Making decisions: consent and assent

- Where children and young people have sufficient maturity and understanding to make their own decision about research participation, but are not yet treated as fully 'adult' by the law of their country (Case Three), consent should, wherever possible, be sought from both the children or young people concerned, and from their parents.
- Where children and young people are not yet able to make their own decision (Case Two), there is an ethical imperative to involve them in the decision as much as possible. Requirements to seek assent from children invited to take part in research should be understood as requirements to involve children, as much as they wish and are able, in decisions about participation. In devising assent processes, researchers should be concerned primarily with how best to develop trusting relationships with children and communicate information appropriately throughout the research.

Responding to disagreement

- In most cases, if there are disagreements within families about participation, then it is best if this particular child or young person does not take part. Professionals should respect parents' views with respect to their child's participation in decisions about research, but parental preferences cannot cancel out professionals' own responsibilities. While parental consent renders their child's participation in research legally permissible, it does *not* make it mandatory. This leaves an important area for professional discretion and judgment.

Responsibilities in the absence of parents

- Children and young people who lack parental support should not automatically be excluded from the opportunity to participate in research. In such cases, the role of the REC in scrutinising the risks, burdens and benefits of research will take on added importance, as will local stakeholder involvement. Where it can be foreseen at the planning stage that children without parental support are likely to be eligible to participate, additional protections, such as an independent advocate able to witness the recruitment process, could be considered.

Introduction

- 6.1 In Chapter 5, we considered how our characterisation of children and young people, and the responsibilities of their parents towards them, might help us to understand the role of professionals responsible for those aspects of clinical research that are often invisible to research participants and the general public: the prioritisation, design and review of research studies. We now turn to consider those professional responsibilities in connection with professionals' *direct* interactions with children, young people and their families: those that arise when children and young people are invited to take part in research, and indeed those that arise throughout and after the study itself. We use the terms 'researchers' or 'professionals' very broadly, to include all those staff members who interact directly with children and young people at any point during the research, while recognising that the specific responsibilities may differ depending on a professional's role. Looking at the issue from the perspective of children, young people and their families, the question is therefore what they should feel able to expect both of an ethical recruitment process and of ongoing participation in an ethically-conducted study. In other words, what might a 'fair offer' to participate in worthwhile research look like to the children, young people and families to whom the 'offer' is made?
- 6.2 We begin with the premise that the ethical considerations identified in Chapter 4 which underpin how parents make decisions with or on behalf of their children may also apply to researchers who have direct interactions with children and young people in the context of clinical research. Clearly researchers do not take on a parental role, but at particular points in time they occupy a professional role with respect to particular children or young people which, as an adult-child relationship, brings with it associated responsibilities.⁵⁷³ Together with these direct responsibilities to children and young people, we suggest that researchers also owe responsibilities to parents, reflecting the fact that parental responsibilities to their minor children continue to run in tandem with temporary responsibilities borne by other adults. The manner in which these two sets of responsibilities interact will shift as children mature, just as the nature of parental responsibilities evolves through the paradigm cases (see paragraph 4.35). Finally, as professionals, researchers also have obligations to maintain particular standards of professional conduct.
- 6.3 Researchers' responsibilities might therefore be characterised as obligations to:
- treat children and young people as individuals of value in themselves (a direct obligation to children and young people, that arises independently of family dynamics).
 - support parents in their attempts to help their children develop in their ability to make autonomous choices (hence an indirect obligation to children and young people, exercised through obligations to their parents);
 - act in accordance with children's and young people's immediate and longer term welfare (for example minimising any distress arising in connection with research involvement, only proceeding if confident that participation in research is compatible

⁵⁷³ See, for example, the argument that, in the context of a child's healthcare, paediatricians and parents are 'co-fiduciaries' of children who are patients: McCullough LB (2009) Contributions of ethical theory to pediatric ethics pediatricians and parents as co-fiduciaries of pediatric patients, in *Pediatric Bioethics*, Miller G (Editor) (New York: Cambridge University Press). Similar responsibilities arise for other adults who have a time-limited, but nevertheless responsible, relationship with children, such as doctors, teachers, and those providing childcare.

- with their interests, and being sensitive to the importance of maintaining family harmony with respect to research participation); and
- act in accordance with the professional virtues outlined in Chapter 5: trustworthiness, openness and courage.

We discuss further below how these responsibilities might be exercised in practice, first with respect to researchers' direct obligations to children and young people, and second in the context of researchers' interactions with parents and their children together. We then look at the particular challenges that may arise where children and young people do not have parents to support them, whether on a temporary or permanent basis.

Responsibilities to children and young people

"I think that they really shouldn't think of all the participants as a whole group of people but more as individuals because everyone has different lives and it could affect them in different ways."⁵⁷⁴

Involvement in research decisions

- 6.4 We start with the first requirement: that of treating children and young people as distinct individuals, of value in themselves, and the implication this has for the ways researchers engage with them when considering research participation. While this requirement clearly applies to *all* children and young people, regardless of their age and stage of development, we suggest that the ensuing responsibilities for researchers in the way they interact with children and young people are distinct for each of the cases we describe in Chapter 4 (see paragraph 4.5). Where children fall into Case One (such as babies, or children experiencing temporary incapacity, who are unable to contribute their own view with respect to research involvement), researchers' responsibility to respect them as individuals overlaps almost entirely with their responsibility to consider their immediate and longer-term welfare. The primary focus of researchers, along with parents, will be on whether or not the research procedures involved will be a cause of distress, or potential harm, for this particular child (as indicated, for example, by his or her responses). Where children and young people fall into Cases Two or Three, however, responsibilities for researchers arise that are quite distinct from, and additional to, these welfare concerns. We consider first children and young people in Case Three: those who are intellectually and emotionally able to make their own decision about research involvement.

Children and young people in Case Three

- 6.5 Children and young people fall within Case Three where they are capable of understanding what is involved in taking part in a particular piece of research and of deciding for themselves whether or not to take part, but are not as yet given full decision-making power under national legislation (see paragraphs 4.42–4.50).⁵⁷⁵ **We take the view that, where children and young people have this level of**

⁵⁷⁴ Participant in the Youth REC film. See: Spencer G, Boddy J, and Rees R (2014) *"What we think about what adults think": children and young people's perspectives on ethics review of clinical research with children* (London: Nuffield Council on Bioethics).

⁵⁷⁵ In England and Wales, this would apply to children and young people under 18 for most research, given general coexistence of parental powers with children's powers, but under 16 in the specific context of clinical trials, since minors there are specifically defined as under 16.

understanding, professionals have an ethical obligation actively to seek their consent, not their 'assent', regardless of any additional requirements of national legislation. At the same time, parents continue to have a legitimate interest in their children's decisions until they are formally recognised as an adult within their national jurisdiction. We therefore suggest that, wherever possible, professionals should seek consent both from the children and young people concerned, and from their parents. Such an approach is respectful of children and young people, and of the continuing role of their parents, and provides a practical focus for encouraging a genuinely shared decision.⁵⁷⁶ A focus on shared family decision-making is particularly helpful in this context as it obviates the need for fine judgments to be made as to whether or not a particular child or young person really does have the capacity to make a particular decision.

Recommendation 13

We recommend that, where children and young people have sufficient maturity and understanding, but are not yet treated as fully 'adult' by the law of their country, professionals should, wherever possible, seek consent from both the children or young people concerned, and from their parents.

- 6.6 As we discuss in more detail below, it is crucial that the *process* of seeking consent from children and young people and their parents should not be confused with the *manner* in which that consent is documented. For children and young people and their parents to provide meaningful consent (or equally, for them to decide to refuse the invitation to participate), they must have access to high quality information, opportunities to discuss the project with professionals able to answer their questions, and assurance that their decision will not affect the provision of standard care (see paragraphs 6.17–6.18 and 6.28). The consent, once given, should be recorded in a way that is culturally appropriate. In a UK context, this is likely to involve both the young person and parents signing the consent form; but other methods of documenting the consent process, such as audio or video recordings, or a note by the researcher, should be equally acceptable, particularly where these methods have been chosen as a result of local community engagement in the development of the study.⁵⁷⁷ A signature on a consent form is only a means of *recording* a decision; it is the decision itself, and the (ongoing) process that enables that decision, that is the ethically significant part of the 'consent'.⁵⁷⁸

⁵⁷⁶ See, for example, Hart RI, Foster HE, McDonagh JE *et al.* (2015) Young people's decisions about biologic therapies: who influences them and how? *Rheumatology*: Published online first (5 February 2015) for an account of how young people in their early 20s continue to play considerable value on parental support, particularly from their mothers. See also: Morrow V, and Richards M (1996) *Young people's transition to adulthood* (York: Joseph Rowntree Foundation), which notes that "there is no sharp distinction between childhood and adulthood: it is a complex mixture of continuing dependency on parents stretching into the twenties and beyond".

⁵⁷⁷ See, for example, The University of Nottingham (2015) *REACH: Rojiroti Evaluation Assessing Children's Health - pilot project*, available at: <http://www.nottingham.ac.uk/reach/pilot-project.aspx>. See also: Shenk K and Williamson J (2005) *Ethical approaches to gathering information from children and adolescents in international settings: guidelines and resources* (Washington, DC: Population Council) for further discussion of the importance of community engagement.

⁵⁷⁸ See, for example, the discussion in Harston GWJ, Sheehan M, and Kennedy J (2014) Emergency medicine research: rites, rituals and consent *Emergency Medicine Journal* **31**(2): 90-1.

Box 6.1: Case study: taking a shared approach to consent

Lucy is a 15 year old who is asked if she would like to participate in a study of her relapsing nephrotic syndrome, a chronic condition where the kidneys become inflamed and lose protein. The study will look at a short course of daily prednisolone (an anti-inflammatory medicine) in response to upper respiratory tract infection. Two weeks before her regular outpatient appointment, Lucy's usual doctor posts an information sheet for both Lucy and her parents. The information sheet describes the study and explains its aims. At the appointment, her doctor asks Lucy and her mother if they have read the information sheets and would like to talk further about the study. When they say yes, the research nurse for the study is asked to join them.

The doctor and research nurse ask Lucy if she would like to speak to them on her own about the study, which she agrees to. During this time, they discuss what the study involves and that Lucy will have to have a pregnancy test before taking part in the study. Her mother is then asked to join them again and they talk through the different treatment arms in the study, and the hospital visits involved. The team check that both Lucy and her mother understand what they have been told. They ask Lucy's mother if she has any extra questions she wants to ask. The team then give Lucy and her mother time together to discuss the decision, which they had also previously discussed in the car on the way to the appointment. They jointly decide to proceed, and so both Lucy and her mother sign the consent form for the study.⁵⁷⁹

- 6.7 There will, of course, always be cases where a shared decision-making model will not work: because of the nature of the research; because of disagreement within the family; or in cases where children and young people do not have the kind of family support envisaged above. We return to the latter two cases below (see paragraphs 6.19–6.27 and 6.31–6.41). **Where the nature of the research is such that parental involvement is believed to be inappropriate, or might undermine the research objective or even threaten a young person's well-being, we take the view that it may be ethically acceptable to approach children and young people in Case Three without parental knowledge or involvement. However, such approaches should be subject to specific review by a REC.** It would thus be open for a REC to approve a proposal that children and young people in Case Three be invited to participate in research where there was good reason to believe that parental involvement in the decision would compromise the accuracy of the information received. This might, for example, include research exploring young people's drug use or sexual activity.⁵⁸⁰ In coming to such a decision, the REC would take into account both the likely value of the research (for example, with respect to informing health service provision within the area), and the sensitivity of planned recruitment processes. Depending on the circumstances, such an approach to research might need, or benefit from, wider community engagement at the design and development stage: openness towards the wider community at this early stage will do much to promote trust in the

⁵⁷⁹ With thanks to Helen Sammons, Working Party member.

⁵⁸⁰ See, for example, Kenyan guidelines on HIV testing in clinical treatment and applicable to research, where young people "engaged in behaviour that puts them at risk" may be treated as mature minors and hence able to give consent without parental involvement: Republic of Kenya Ministry of Health (2006) *Guidelines for HIV testing in clinical settings: 3rd edition*, available at: http://www.who.int/hiv/topics/vct/KENYA_HIV_Guidelines_2006.pdf.

value of the proposed study, and in the robustness of the scrutiny to which it will be subject.⁵⁸¹

Children and young people in Case Two: what do we really mean by ‘assent’?

- 6.8 We have characterised Case Two as applying to children and young people who are able to form views and express wishes about research involvement, but without the capacity to make an independent decision. We have also suggested that quite young children, in some cases from the ages of two or three, may be able to understand that they are being asked to do something to help other people, rather than for their own benefit (see paragraph 4.6). We argue that as soon as children have the ability, even at this most basic level, to express views and wishes about the research, researchers have an obligation to *involve* them in a way that is appropriate to their understanding and development. This involvement must also be compatible with respect for the parenting approaches of particular parents (see paragraph 6.16). For young children, this might involve talking directly to children – *after* discussing the proposal with their parents – to describe what the research involves, using pictures or other means to explain what might happen, and responding appropriately to their reactions (see box 6.2). For older children, it might be more appropriate to discuss the possibility of research involvement with children and their parents together, again with appropriate information materials to support understanding.

⁵⁸¹ For a helpful discussion of this approach in Nigeria, see: 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).

Box 6.2: Case study: involving young children in vaccine trials**Thoughts from a paediatric research nurse.⁵⁸²**

“For a vaccine research study, we prepare age-appropriate information, including sticker charts, and bring age-appropriate toys. Though these are used as a means of distraction and as a reward system, they also help to guide children through the process using what is familiar to them.

An experienced paediatric health professional can easily assess the parent-child relationship, and children’s and parents’ past experiences of medical interventions, and medical conditions, in a short time. It is important to be aware of these factors and to allow both parties chance to talk about them.

We ask parents what they have told their child and what they feel their child has taken on board. We also ask parents what they think will help their child. We introduce ourselves to children and establish their understanding of our visit. We may use pictures on the adapted information sheets for this purpose. Generally, it is not children’s lack of comprehension of the process and the rationale behind the basic purpose of the study that causes difficulties, but rather the health professional’s inability to communicate this. Children’s own experience can help with this and parents are essential in helping their child to remember. For example: ‘Some children get very poorly – have you been poorly? We need to check new medicines to see if they stop children getting poorly – do you remember having medicine?’

When undertaking invasive procedures, the process should be explained, again with parents’ assistance, in recalling past experiences, such as ‘watching Mummy having her blood test’. It is essential that it is acknowledged that it may hurt, and that if it does we can stop (anaesthetic cream is used for blood tests). It is important that those undertaking the study acknowledge children’s non-verbal communication, and adapt to ensure that children have a sense of control in this situation. This means asking children things like where they want to sit, and what they would like to play with. An experienced health professional is adept at doing so.

For follow-on visits, if children don’t want to continue, they need to be allowed to voice this and withdraw. Researchers and parents need to let this happen. Often it is fear of pain, and when you talk to them, they say that as long as it doesn’t hurt they would like to help. There is a genuine sense of this. I have worked with children in these circumstances. We agree that if it hurts, we’ll stop. I have been hugged afterwards by a child who was so pleased they had done it, both for themselves and their parents. A three year old when asked by a parent why they had let me do the blood test said, “because I trusted her”. Another three year old said I could have one attempt at a blood test. Having not got blood, I stopped. The parents wanted another attempt, but the boy said: “She will not do it again because we agreed,” and he was right. Parents sometimes need to be reminded of their child’s informed decisions, and to feel assured that they have not ‘wasted our time’, which is often the overriding concern. The experienced paediatric professional is the advocate for this agreement with each child. This may be the first established relationship with a non-familiar adult, and it is empowering.

In a hospital setting, when pre-school children have experience of both invasive and non-invasive therapies needed to ensure they stay healthy, and have an established understanding of procedures and their conditions, they are far more informed when approached for a study than a child who doesn’t have this experience. These children are even better equipped to voice logical and rational arguments regarding taking part or not taking part. Again they have a right for this to be respected.”

⁵⁸² With thanks to Liz Davis, Working Party member.

- 6.9 The term 'assent' is often used to describe these interactions with children who do not, as yet, have the capacity to make independent decisions about research participation. As we saw in Chapter 2, however, the various guidelines that refer to assent paint a highly confusing picture. At one extreme, assent is presented as encompassing a three year old's "emergent capacity to agree", while at the other, it is limited to the "knowing agreement" of children fully able to understand what is involved but prevented by domestic law from providing researchers with a legally effective consent (see Box 2.3 on pages 60-1). Moreover, the focus in some guidelines on obtaining assent in writing seems to confuse assent with the process of obtaining legally-effective consent that will enable the research to proceed. A requirement for written assent also risks focusing researchers' and parents' attention primarily on the *act* of obtaining a signature, and away from the ethically-significant *process* of involving children and young people that should be an essential prerequisite to such an act.
- 6.10 We thus suggest that much greater clarity with respect to the assent of children and young people to take part in research would be obtained by distinguishing clearly between the process of involving children in participation decisions, and any act by which this is documented.⁵⁸³ Researchers' direct responsibilities to children, arising out of respect for them as distinct individuals, make it an ethical imperative that children who have any ability to engage with the question of research participation are appropriately involved in that decision (see paragraphs 6.23-6.24, and Box 6.5). Indeed, failure to take this responsibility seriously constitutes a breach of trust between researchers and the children they are seeking to recruit. *How* the process of involving children is then documented is very much a secondary concern.

Recommendation 14

We recommend that requirements in guidance and regulation to 'seek' or 'obtain' assent from children who are being invited to take part in research should be understood as requirements to involve children, as much as they wish and are able, in the decision about participation. In devising assent processes, researchers should primarily be concerned with how best to develop trusting relationships with children and communicate information appropriately throughout the research.

- 6.11 The ways in which this involvement may be achieved will clearly vary significantly, depending on the nature of the research, the participants, and the context in which the research takes place. Information material appropriate to the children and young people's level of understanding, and to the cultural environment in which the research is taking place, is important; but even more important is the emphasis to be placed on sensitive and skilled communication. Researchers seeking ethical approval of their studies with children and young people should be able to demonstrate that all those who will be interacting directly with children and families as part of the proposed research have the necessary communication skills. Researchers and other staff involved in research who do not routinely work with children should have access to relevant training *before* the research begins.

⁵⁸³ 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; Sibley A, Sheehan M, and Pollard AJ (2012) Assent is not consent *Journal of Medical Ethics* **38**(1): 3; Wilkinson D (2012) Dissent about assent in paediatric research *Journal of Medical Ethics* **38**(1): 2.

- 6.12 **The fact that children have been appropriately involved in the participation decision should be recorded for future reference. However, this record must not be perceived as the main point of the process.** Assent forms constitute one possible form of documentation: they may act as a prompt for the researcher, and some children may see an invitation to sign a form as recognition of their value as an individual. They are not, however, the only (or necessarily the best) way of recording children's involvement. Alternative forms of documentation might include inviting children and young people to co-sign the consent form with their parents, or for parents to note on the consent form that their child has been involved in the decision. Increasingly, though, it may become more appropriate to use interactive online technologies, both as a means of sharing information about the research and recording children's involvement.⁵⁸⁴ The record of the way in which children have been involved in the decision must also, crucially, be culturally appropriate. In some contexts, signing a form may be perceived as threatening, rather than empowering. In such cases, alternative methods of documenting both assent and consent, such as voice or video records, drawing pictures, or making a note in children's health records, should be employed.⁵⁸⁵
- 6.13 This focus on the way in which children and young people in Case Two are properly involved in research participation decisions highlights again the important part played by the professional virtues of trustworthiness, openness and courage (see paragraphs 5.8–5.11). Research professionals need to build a trusting relationship with the children and young people whom they are inviting to participate in their studies, and with their parents; they need to be open with them, explaining clearly what the research will involve and the choices available to them; and they need to have the courage to cede control appropriately to children taking part, as described in Box 6.2 above.
- 6.14 These virtues are similarly important in the way REC members review research proposals involving children and young people. We recommended above that, when devising assent processes, researchers should primarily be concerned with how best to develop trusting relationships with children, and communicate information appropriately throughout the research (see Recommendation 14). Similarly, the focus of REC scrutiny should be on the appropriateness of the processes that the researchers intend to use to involve children and young people in decision-making, the information resources they will use in these processes, and the communication skills of those who will be directly responsible for interacting with potential participants. This flexible approach to the engagement of children and young people in research decisions has been described as a form of “personalized assent” that depends on trust in “the moral responsibility and integrity of the researcher.”⁵⁸⁶ Trusting researchers with flexible approaches to assent takes courage on the part of those responsible for REC scrutiny. As we note at paragraph 5.35, recognition by researchers of the responsibility held by

⁵⁸⁴ For a discussion of how digital technologies such as laptops, smartphones, and tablet devices can be used to offer support for conveying information about research, and to facilitate children's and young people's decision-making in the context of research, see: Parsons S, and Abbott C (2013) *Digital technologies for supporting the informed consent of children and young people in research: the potential for transforming current research ethics practice*, available at: http://responsible-innovation.org.uk/torrii/sites/default/files/Parsons%20%26%20Abbott%20Digital%20technologies%20for%20informed%20consent%20FINAL_0.pdf.

⁵⁸⁵ See, for example, the techniques used by the Young Lives research teams in Peru, Vietnam, Ethiopia and India: Morrow V (2009) *The ethics of social research with children and families, in Young Lives: practical experiences - working paper no. 53* (Oxford: Young Lives). See also the 2013 policy change in India, which requires that “in all clinical trials, in addition to the requirement of obtaining written informed consent, audio-visual recording of the informed consent process... is required to be done while adhering to the principles of confidentiality”: Central Drugs Standard Control Organization (India) (2013) *Order: 19 November*, available at: <http://cdsco.nic.in/writereaddata/Office%20Order%20dated%2019.11.2013.pdf>.

⁵⁸⁶ Giesbertz NA, Bredenoord AL, and van Delden JJ (2014) Clarifying assent in pediatric research *European Journal of Human Genetics* **22**(2): 266-9.

RECs for scrutinising their capacity to exercise such discretion is an essential part of the process.

- 6.15 We recognise that the approach to consent and assent advocated in this chapter represents a significant shift in current practice, in emphasising how context-specific and child-specific these processes need to be. Such an approach imposes additional challenges both for the researchers and for those responsible for the scrutiny of research proposals. Practical guidance on realising these aims in practice is urgently needed.

Recommendation 15

We recommend that research funders encourage or commission good quality research proposals exploring how the approaches to consent and assent put forward in this report might best operate in practice. Such research would provide a secure foundation for future good practice guidelines, tools and resources that are sensitive to a range of contexts.

Responsibilities to children and parents together

- 6.16 Having explored professionals’ *direct* responsibilities to children and young people in the context of research, we now turn to the responsibilities that arise out of the recognition that children should always be seen in the context of their families: that is, professionals’ responsibilities to children and parents together.⁵⁸⁷ Approaches to parenting are many and diverse, even within apparently homogenous communities. An exploration of how children with chronic illnesses and their parents individually understood consent processes in the context of a US-based paediatric trial, for example, identified four distinct parental approaches to their child’s decision making, characterised as exclusionary, informative, collaborative, and delegated approaches.⁵⁸⁸ Researchers will need to be sensitive to these differences, while still remaining alert to the responsibilities they owe directly to children and young people themselves.

Extending the fair offer: communication

- 6.17 We have argued that partnerships between professionals, children, young people, and their parents in the development of research will minimise the risk of children and young people being placed in a vulnerable position through research participation. We have further suggested that the role of RECs is to ensure that any invitation to children or young people to take part in research is a ‘fair offer’ that they can trust. Professionals subsequently responsible for *extending* that offer to children, young people and their parents have a critical part to play in maintaining that partnership, and ensuring that an invitation to take part in research is genuinely ‘fair’.
- 6.18 Good communication is an essential element of this process – both in terms of the clarity and accessibility of the information provided (whatever the format), and,

⁵⁸⁷ See, for example, the discussion of the “dynamic triad with multiple relationships formed between the researcher, the youth, and the youth’s parent(s) or guardian(s) in Trussell DE (2008) Unique ethical complexities and empowering youth in the research process *Journal of Park and Recreation Administration* 26(2): 163-76, at page 167.

⁵⁸⁸ Snethen JA, Broome ME, Knafel K, Deatrick JA, and Angst DB (2006) Family patterns of decision-making in pediatric clinical trials *Research in Nursing & Health* 29(3): 223-32.

critically, in terms of the quality of face-to-face communication (see Box 6.5). In addition to what has been noted above with respect to age-appropriate information for children and young people themselves, it is crucial that their parents feel well-informed about what the study involves, and that information about burdens, risks and benefits is presented as openly and clearly as possible. As part of that process, professionals need to be alert to wider environmental influences on children, young people and their parents; for example, with respect to a 'pro-science' climate that could exacerbate risks of therapeutic misconception (see paragraph 1.17). Particular challenges in communication arise where researchers are also providing direct care to children or young people (see paragraph 6.28).

Facilitating shared decision making

- 6.19 The language of 'partnership' highlights the importance of the tripartite relationship between professionals, parents, and children and young people. It also raises the issue of how professionals should respond to the diverse approaches that parents may take with respect to involving their children in decision-making. We suggest that the starting point for professionals should always be one of *respect* for parents' role in determining how, and at what speed, their child develops towards being an independent decision-maker. As we suggested in Chapter 1, children and young people do not function in isolation, but rather in the context of their particular family and social environment. When approaching children and young people about the prospect of research participation, professionals must be sensitive to the variable forms of family dynamic that may be in play. However, this respect for individual parental approaches must run alongside and, where necessary, be constrained by professionals' own direct responsibilities to children and young people: to respect them as individuals and to have regard for their welfare. **Thus, while professionals should respect parents' views with respect to their child's participation in decisions about research, parental preferences cannot act to cancel out professionals' own responsibilities. While parental consent renders their child's participation in research legally permissible, it does not make it mandatory, thus leaving an important area for professional discretion and judgment.**
- 6.20 The need for such discretion could arise in a number of circumstances, including where parents wish to exclude their child altogether from a decision (for example, out of a desire to protect them from knowledge of their diagnosis), or where parents wish their child to take part in research, but he or she disagrees. In the first case, if parents remain adamant that their child cannot be part of the decision at all, even though they are clearly able to form and express their own preferences, professionals may take the view that it is not possible to include them in the study, unless there are strong welfare reasons for inclusion that trump all other considerations.⁵⁸⁹ In cases like these, however, researchers have a strong professional obligation to endeavour first to encourage and support parents in enabling their children's voices to be heard.⁵⁹⁰
- 6.21 Such cases, however, should be distinguished from those that arise where children or young people are in Case One because of a temporary inability to engage at all: for example, because of severe pain, distress, or emotional confusion at the point at which

⁵⁸⁹ See, for example, Spriggs M, and Gillam L (2013) Deception of children in research *Journal of Medical Ethics* **41(2)**: 179-82.

⁵⁹⁰ Such situations may arise, for example, as a result of perceptions of appropriate gender roles: in some cases, girls and young women may need particular support from researchers to enable their voices to be heard: see Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

the decision must be made. Such circumstances may arise, for example, where decisions about research protocols are closely interwoven with treatment decisions and need to be made urgently at the time of diagnosis (such as with the diagnosis of some cancers, as described in paragraph 1.9 and Box 6.3 below), or where children are unconscious and questions of research relating to emergency care arise. In such cases, where even sharing brief information with a child may not be possible, it may be appropriate for professionals to act solely on parental consent at this point of initial recruitment.⁵⁹¹ However, professionals' direct responsibilities to respect children or young people as individuals underpin a duty to ensure that children and young people are *subsequently* engaged in explanations about the research, including any choices about their involvement, as soon as they are able to be so.

- 6.22 As we noted above, children's assent and engagement in decision-making about research is a process, not a one-off event. Children and young people who are unable to engage at the start of the process must be encouraged and enabled to do so as soon as they are able. Similar issues may arise in longitudinal research where children are recruited as babies, but continue taking part in the study as they grow older, at which point it becomes essential to involve them appropriately in ongoing decision-making. This process of engagement is important not only because of the respect it confers on young research participants, but also because it provides the opportunity for them to understand the contribution they are making, an issue that young people were repeatedly keen to stress to the Working Party. It is important to avoid the illusion of choice where none really exists; however, a child who is part of a trial because it is inextricably linked to treatment considered essential for their welfare can still be afforded a sense of agency by giving them with an understanding of the contribution they are making.

⁵⁹¹ Health Research Authority (2015) *Principles of consent: emergency research (England and Wales) - children / young people in other emergency research*, available at: <http://www.hra-decisiontools.org.uk/consent/principles-emergency-EnglandandWales.html>.

Box 6.3: Case study: young children with cancer

Parents from the Paediatric Oncology Reference Team (PORT)⁵⁹² highlight the situation of young children who are seriously ill with a life-threatening cancer, such as leukaemia or a brain tumour, where all focus may be on starting treatment as quickly as possible. That treatment may, however, potentially include research elements such as randomisation to different treatment options. In such cases, decisions about these research elements may need to be made, at least on an initial basis, immediately after diagnosis. If children are emotionally and physically unable to deal with any information about the study at that particular point, requiring them to read or listen to an information sheet describing the research aspects of the protocol may neither promote their welfare, nor be respectful of them as individuals. It may also be a distraction from helping them to understand that they have a serious illness that requires treatment. In some families, there may be an understandable desire not to share the full gravity of the situation with children, and to keep information sharing to a minimum, particularly in the early days of what could be a long treatment process.

Where children have no genuine choice about whether or not to take part in research (because it is so closely interwoven with their treatment, and parents / professionals believe that treatment within this particular research context is best for their welfare) it is disingenuous to imply that they have a free choice about participation or withdrawal. This is in contrast to non-interventional studies going *alongside* treatment, such as research about their experiences of cancer care, where choices about participation, and the possibility of future withdrawal, should genuinely exist.

In cases like these, children are likely to move over time from Case One to Case Two as they respond to initial treatment. They will then be able to absorb appropriately communicated information about the research aspects of their treatment protocols, and to express their views on these.

PORT are currently working on patient information sheet templates that are concise, use simple language, and clearly explain the trial questions, as opposed to standard treatment (for example explaining the relevant side-effects of the trial medicines as opposed to medicines used in standard treatment). It is PORT's hope that parents' improved understanding of the trial will allow them to better engage with their child regarding trial questions, as this becomes appropriate.

- 6.23 Where disagreement about research participation arises *within* families, professionals have a responsibility to engage both with parents, and with children and young people, with the aim of negotiating an acceptable solution that is respectful of all parties. As we discussed in Chapter 4, young children's wishes cannot always be determinative, particularly where researchers and parents reasonably believe that they might obtain significant benefit from participation (see paragraph 4.11), and it may well be appropriate to persuade them. Parents who have sought to convince their child that participating in research to benefit others is a 'good thing to do' might legitimately feel that if, for example, the researcher simply accepts their child's 'no' at a point of minor discomfort, their own parenting role has been undermined. However, professionals' own responsibilities towards children, and in particular the importance of their creating a trusting relationship with them (see Box 6.2 above) place strict limitations on how far they should proceed in the absence of consensus.

⁵⁹² Paediatric Oncology Reference Team (PORT) (2015) *Homepage*, available at: <https://sites.google.com/site/ukportgroup/home>.

- 6.24 **Where children (even young children with limited understanding of what is proposed) explicitly and consistently dissent, there will generally be both ethical and practical reasons why it would be right for professionals to accept that dissent, despite parental willingness to proceed. The more children are able to understand what is involved in a research proposal, the greater the justification needed to act against their clearly expressed wishes. The multiple factors in play in such cases, however, make simple 'yes' or 'no' answers as to how professionals should approach these difficult decisions impossible to offer. Rather, they reinforce the fundamental importance of reflexive professional practice, directed towards creating and sustaining open trusting relationships with children, young people, and their parents.**
- 6.25 **Similar issues may arise where children or young people in Case Three wish to participate in a research study, but their parents do not agree. In such cases, professionals have an important role in seeking to inform and encourage parents. However, if these attempts prove unsuccessful, then in most cases participation in research should not go ahead.** Even in countries where the law recognises coexisting powers of children/young people and their parents to consent (hence providing for a legally effective consent from a minor), professionals must take into account the position of children and young people within their families, and cannot simply ignore the realities of family hierarchies and the consequences for those involved of overriding them.⁵⁹³ We have discussed the specific situation where research may be permissible with children and young people in Case Three *without* parental involvement (see paragraph 6.7) and we discuss below cases where parents are temporarily or permanently absent (see paragraphs 6.31–6.41). However, where parents have been involved in the process of their child being invited to take part in research, and have consistently taken the view that their child should *not* take part, then strong justification would be required to warrant participation on the basis of children's or young people's consent alone.
- 6.26 In the very different circumstances of babies and very young children in Case One, clearly parents' decisions about whether or not they should participate in research will be determinative. However, depending on the context in which the possibility of research involvement arises, such as during neonatal care, parents may be particularly in need of sensitive support from professionals (see paragraph 4.61).

⁵⁹³ See, for example, Hart R, and Lansdown G (2002) Changing world opens door to children *CRIN News* 16: 9-11 who discuss "the damaging impact of creating a struggle of values at home" in the context of failures of communication, cited in Alderson P, and Morrow V (2011) *The ethics of research with children and young people: a practical handbook* (London: SAGE Publications), pp107-8. Note, similarly, the emphasis placed by both young people and adults in the Working Party's consultation in Kilifi, Kenya on the importance of family discussions and willingness on the part of both young people and parents to listen to, and learn from, each other: Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

Box 6.4: Case study: support for parents

“Where the clinicians offering a trial took a leisurely approach, parents could feel that they too could take time to reflect.

‘They said I could take as much time as I wanted... [within] a certain time as [the baby] did need something to be done. They didn’t rush me into a decision. [The doctor] said “I’ll leave [the form] with you... I’ll leave you to talk and you come down to me when you’re ready.” So there was no pressure on the doctor’s part. He was really good... sitting talking to us for a good half hour, forty-five minutes explaining everything.’”

*‘Tessa’ describing her experience of being invited to enrol her baby in a randomised control trial shortly after birth.*⁵⁹⁴

6.27 Parents of children of any age may, of course, disagree with each other with respect to whether or not it is appropriate for their child to participate in research. In such cases, it will again be the professional responsibility of researchers to seek to negotiate a solution that will be acceptable both to the children and to the adults concerned.⁵⁹⁵ While, depending on the jurisdiction, the law may only require consent from one parent to permit research to go ahead, there is an important difference between one parent being silent or absent, and active disagreement between parents. As in cases where disagreement arises between children and their parents, irreconcilable disagreement between parents may in practice mean that children or young people cannot be included in the study. Slightly different issues arise where one parent is absent, and the other is uncertain of their authority to consent.⁵⁹⁶ In such cases, if national legislation permits one parent to authorise participation, professionals will need to exercise their discretion in determining whether or not to seek that consent, taking into account the reality of family dynamics and power relationships. In areas where this issue is known to arise repeatedly (for example, where many fathers live and work away from their families), proactive community consultation could help create wider community acceptance of consent by one parent only.

Particular challenges for professional judgment

Clinicians and researchers: professionals’ dual roles

6.28 Questions of professional judgment may become particularly acute in circumstances where professionals have dual roles, both as researchers, and as clinicians providing care to children and young people who might potentially participate in their studies. In such cases, professionals must ensure that their own, legitimate, interests in the success of their research are not permitted to compromise the interests of children and young people under their care.⁵⁹⁷ On the one hand, they must be alert to how families

⁵⁹⁴ Snowdon C, Elbourne D, and Garcia J (2006) “It was a snap decision”: parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials *Social Science & Medicine* **62**(9): 2279-90, pp2285-6.

⁵⁹⁵ Similar issues may arise where children live between two or more households, or there are disputed guardianship arrangements: see, for example, Abebe T (2009) Multiple methods, complex dilemmas: negotiating socio-ethical spaces in participatory research with disadvantaged children *Children’s Geographies* **7**(4): 451-65, at page 456.

⁵⁹⁶ This may often be the mother. See, for example, Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>, pp17-8.

⁵⁹⁷ de Vries M, Houtlosser M, Wit J *et al.* (2011) Ethical issues at the interface of clinical care and research practice in pediatric oncology: a narrative review of parents’ and physicians’ experiences *BMC Medical Ethics* **12**(1): 18. See also: Caldwell PHY, Dans L, de Vries MC *et al.* (2012) Standard 1: consent and recruitment *Pediatrics* **129** (supplement 3): S118-S23 who

may be influenced by existing trusting clinical relationships and may find it hard to say 'no' (see paragraph 2.27). On the other hand, concerns about undue influence may prompt professionals in such circumstances to be so non-directive that children, young people and parents can feel abandoned in their decision-making (see paragraph 2.26). Professional judgment is required to strike the right balance, ensuring that potential participants and their parents understand what is involved in the study (and their clinician's own involvement in it), and are clear that their decision about research participation will not affect their care in any way. Families may also welcome the possibility of discussing the proposed research with another professional who is not directly involved in caring for their child. Similar concerns may arise in the context of longitudinal research, both because of children's developing ability for engagement over the research period (see also paragraph 6.22), and because the sense of obligation engendered by long-term involvement in a study may make it harder for both parents and children to say 'no' at any given point.⁵⁹⁸

Recommendation 16

We recommend that, where a protocol indicates that children and young people may be recruited by a health professional responsible for their care, research ethics committees should explore with researchers the justification for this approach. Where such recruitment procedures are appropriate, research ethics committees may wish to assure themselves that there are support arrangements in place, such as access to another member of the research team to whom families can turn for additional information if they wish.

Innovative treatment outside research

- 6.29 As we noted in Chapter 1, innovative or experimental treatments may occasionally be provided outside the context of research (see paragraph 1.6). Such use is permitted by the Declaration of Helsinki within the professional discretion of clinicians,⁵⁹⁹ but is controversial because of the potential lack of scrutiny and associated safeguards that are required for research. A necessary corollary of the licence to exercise such discretion is found in the expected virtues or characteristics of professional practice. As we discuss above (see paragraphs 5.5–5.12), in the specific context of research with children, we suggest that the virtues of trustworthiness, openness and courage are particularly important.
- 6.30 We take the view that, wherever possible, novel therapies of any kind should be subject to properly evaluated research. Where, exceptionally, novel treatment outside the context of research is appropriate (for example, in some cases of "compassionate

argue, at S121, that this is a key issue in cases where research is seen as an integral part of good care (i.e., in oncology), rather than as an extra activity.

⁵⁹⁸ Williams G (2012) Children as means and ends in large-scale medical research *Bioethics* 26(8): 422-30.

⁵⁹⁹ World Medical Association (2013) *WMA Declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/index.html>, paragraph 37: "In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available."

use⁶⁰⁰), it should be regarded as a professional obligation of the health professional concerned to ensure that information about treatment outcomes and the clinical course of the patient's condition is collected and made publicly available; for example, through a registry or publication. Such a commitment to openness is necessary both to maintain trust, and to ensure that any significant information (for example, relating to adverse effects) is available to other clinicians with patients in similar situations.

Recommendation 17

We recommend that the Royal College of Paediatrics and Child Health takes the lead with other Royal Colleges and relevant professional bodies in exploring how best to ensure that information as to the outcomes of 'innovative' or 'experimental' treatment given to children or young people outside the context of research is properly documented and made available to others concerned.

Responsibilities in the absence of parents

Temporary absence of parents

- 6.31 The temporary absence of parents who would usually expect to be involved in decisions affecting their child may arise either in the form of actual physical absence, or as 'situational incapacity', where parents are present but too shocked or distressed to make a decision. In such cases, the responsibilities of professionals towards children and young people summarised at the start of this chapter (see paragraph 6.3) take on an added importance, as they will be exercising these responsibilities alone rather than in support of the parental decision-making role.
- 6.32 If it is reasonable for research decisions to be delayed until a parent is present and able to make a decision, clearly there is no justification for proceeding in their absence. However, there will inevitably be some health-related situations where the question of enrolling a child or young person in research without the support of their parent will arise. These may include research linked with the emergency care of children and young people.⁶⁰¹ Distinct issues may also arise in the temporary absence of parents of young people in Case Three who have the capacity to consent for themselves but where, ordinarily, joint consent would be sought from the young person and their parent (see paragraph 6.5 and Recommendation 13).
- 6.33 In the case of emergency research in the absence of a parent able to make a decision, the role of the REC in scrutinising the risks, burdens and benefits of the research will become even more important. We argued in Chapter 5 that the primary responsibility of a REC was to decide whether a research protocol would represent a 'fair offer' to children, young people and parents (see paragraph 5.28). In circumstances where, at least initially, parents will have no role, there is an added burden on RECs to be confident that the proposal is fair. Such confidence on the part of RECs is likely to be

⁶⁰⁰ See the discussion in Brierley J, and Larcher V (2009) Compassionate and innovative treatments in children: a proposal for an ethical framework *Archives of Disease in Childhood* **94**(9): 651-4.

⁶⁰¹ Health Research Authority (2015) *Principles of consent: emergency research (England and Wales) - children / young people in other emergency research*, available at: <http://www.hra-decisiontools.org.uk/consent/principles-emergency-EnglandandWales.html>. See also: Davies H, Shakur H, Padkin A *et al.* (2014) Guide to the design and review of emergency research when it is proposed that consent and consultation be waived *Emergency Medicine Journal*: Published online first (31 July 2014); Schreiner MS, Feltman D, Wiswell T *et al.* (2014) When is waiver of consent appropriate in a neonatal clinical trial? *Pediatrics*: Published online first (6 October 2014).

boosted by the active involvement in the design process of children, young people and parents – for example, those who have in the past had some experience of emergency research (see Box 6.5). Trust in the research proposal and its objectives may also be enhanced through local public engagement when the study is being developed, mirroring our approach to research with young people in Case Three where parents have been explicitly excluded because of the nature of issues addressed (see paragraph 6.7).

- 6.34 The question then arises as to the scope for children or young people to be involved in participation decisions. In many cases of emergency research, children or young people, regardless of their age or maturity, will be in Case One because they are unconscious, or severely incapacitated by pain or emotional distress. In such cases, no engagement will be possible at the time the initial decision is taken. Where, however, children and young people are in Case Two and able to contribute their view, then all means (appropriate to the urgency of the situation) should be used to encourage them to do so. Unless there are very strong welfare reasons to the contrary, any hesitancy on the part of children and young people to participate should be respected. If children and young people are in Case Three then their decision to consent or refuse should similarly be respected. Depending on the nature of the research, it may also be appropriate for a third party – such as a nurse not directly involved in the research – to witness the discussion between the researcher and potential participant.⁶⁰² Where a parent is present, but too shocked or distressed to take a decision, they should be encouraged to be as involved in the discussions as they can be, but not forced into a decision-making role.⁶⁰³
- 6.35 Where a study involving emergency research in the absence of parental consent is approved by a REC, it will be critical to inform and involve parents as soon as possible after the research begins. While sometimes described as ‘deferred’ or ‘retrospective’ consent by parents, this is misleading as, by definition, parents are not in a position at that point to refuse. Rather, **the process should be understood, first, as the provision of information about what has happened, and then as an invitation to consent for future procedures (where appropriate) and for the use of any data gathered as a result of the earlier procedures.** Similarly, where children and young people were in Case One when the research began because they were unconscious or in too much pain or distress, they should be invited to engage in discussion and participate in future decision-making as soon as they have recovered sufficiently to do so.

Non-emergency research

- 6.36 For children or young people in Case Three, the absence of a parent raises different issues from those in Cases One and Two (see paragraph 6.32). By definition, they are thought to have the capacity to make decisions for themselves, even though their parents may still also retain the *authority* to make those same decisions. Thus, for

⁶⁰² This model is being developed, for example, for emergency research with adults in the John Radcliffe hospital in Oxford, where over 50 professionals, such as nurses and radiographers, have come forward to be trained: Mark Sheehan, personal communication, 16 April 2015.

⁶⁰³ See, for example, the approach used in the FEAST trial in Africa where parents were invited to ‘assent’ rather than ‘consent’ because of the emergency circumstances in which the research arose: Molyneux S, Njue M, Boga M *et al.* (2013) ‘The words will pass with the blowing wind’: staff and parent views of the deferred consent process, with prior assent, used in an emergency fluids trial in two African hospitals *PLoS ONE* **8(2)**: e54894.

children or young people in Case Three, clinical research that may be permitted in the absence of parents might relate not only to emergency research (where a decision cannot be delayed) but also to non-emergency circumstances where parents are not present, such as where young people seek medical care on their own. As we suggest in the context of research with young people that might be directly undermined by parental involvement (see paragraph 6.7), RECs will need to consider whether it is reasonable, in the circumstances, for researchers to seek a shared decision or accept a young person's consent alone.

Permanent absence of parents

- 6.37 Some children may simply not have parents, or other adults with a parental role, to support them at all. This situation may arise more often in low income countries, where a high number of children may be orphaned, living in child-headed households, on the periphery of wider family groups without the regular support of a meaningful 'parent-child' relationship, or on the streets. However, permanent absence of parents may also occur in high income countries, where teenagers live away from their immediate family because of relationship breakdowns, or where parental responsibility is exercised through institutional means (for example, where a local authority has parental responsibility for a child in care). Where children live in foster care, for example, foster parents do not have parental responsibility, and may only exercise responsibilities that have been explicitly delegated to them.⁶⁰⁴ In practice, children and young people in these situations tend to be excluded from research, regardless of their own wishes with respect to participation. Where particular treatments are only available in the context of research (which may arise in high as well as low income countries: see paragraph 1.11), then children and young people not living with their parents are similarly excluded from treatment that might potentially be of benefit to them.
- 6.38 In the UK context, although the difficulties involved in seeking consent where parental responsibility is held at institutional level should not be underestimated, there will still always be *someone* who has the authority to give consent for 'looked-after' children and young people⁶⁰⁵ to take part in research. The Medicines for Children Research Network (now 'CRN: Children') has published an account of how, with persistence, a looked-after child who was eligible to take part in a study concerned with impaired sleep in children with neuro-developmental disorders was finally able to participate after six months of negotiation by a study nurse with the local authority social services department, and the active support of her foster mother.⁶⁰⁶ The success achieved by researchers in this case demonstrates the crucial role played by individual research professionals in facilitating access to research; and also the importance of developing good working relationships with local social service departments, and raising their awareness of the potential value of such research participation.
- 6.39 While in the UK context consent from a person (or institution) with parental authority will always be necessary for children and young people in Case One or Case Two,

⁶⁰⁴ See, for example, guidance by the Fostering Network on this issue, which cites how young people in foster care often miss out on day-to-day activities such as sleepovers or school trips, because the authority to agree has not been delegated to their foster parents, and obtaining permission from the local authority is too cumbersome or slow: The Fostering Network (2015) *Parental responsibility and delegated authority*, available at: https://www.fostering.net/all-about-fostering/foster-carers/looking-after-child/delegated-authority#.VL0_d9KsW5K. For an account of the particular difficulties, see also: Hopkins P (2008) Ethical issues in research with unaccompanied asylum-seeking children *Children's Geographies* 6(1): 37-48.

⁶⁰⁵ Children and young people in the care of a local authority.

⁶⁰⁶ Medicines for Children Research Network (2010) *Widening participation for all children*, available at: <http://www.cm.nihr.ac.uk/wp-content/uploads/neurological/Widening%20participation%20for%20children-AUG2010.pdf>.

somewhat different issues arise in the context of children and young people in Case Three. As we noted earlier in this chapter, for some forms of research it may be appropriate for RECs to agree for consent to be sought from young people in Case Three alone, without the knowledge or involvement of their parents (see paragraphs 6.7 and 6.36). Where research has been approved in this way, clearly looked-after young people in Case Three could similarly participate without the need to seek local authority permission. In other cases, particularly where researchers have reason to believe that those eligible for their study may include looked-after young people, and the burden and risk of the research is low, RECs could be asked to consider whether exceptions to the need for parental consent could be agreed (see Box 6.5).

Recommendation 18

We recommend that the UK children's research networks (Clinical Research Network: Children and the Scottish Children's Research Network) work with the Children and Family Court Advisory and Support Service (Cafcass) to develop good practice guidance for social services departments and researchers to facilitate the opportunities for looked-after children and young people to participate in research.

- 6.40 In low income settings, it may sometimes be the case that there is no one at all who is able to give or withhold consent on behalf of children without parents: children may be orphans, living with older siblings or being cared for by a number of adults with little emotional attachment.⁶⁰⁷ In such circumstances, the ethical challenges for involving children and young people in Case One or Case Two in research bear similarities to those arising in emergency research (see paragraphs 6.33–6.34). Where professionals have reason to believe that participation in research includes the prospect of direct benefit for children and young people, then there may be good welfare reasons why they should attempt to facilitate their access to research that has been judged to be both of value and a 'fair offer'. Judgments like these, however, require confidence and reflexivity on the part of both the researchers responsible for the study, and the REC members responsible for scrutinising it. Local stakeholder involvement will play an important point in helping RECs to determine whether research in these circumstances would indeed constitute a fair offer for these children and young people.⁶⁰⁸ The challenges faced by professionals in these circumstances highlight the critical importance both of researchers' access to training in ethical considerations and of capacity building for RECs. Where it can be foreseen at the planning stage that children without parental support are likely to be eligible to participate, additional protections, such as an independent advocate able to witness the recruitment process, could be considered (see paragraph 6.34). Ensuring that Case Two children in these

⁶⁰⁷ See, for example, Kruger M, Ndebele P and Horn L (2014) *Research ethics in Africa: a resource for research ethics committees* (Stellenbosch, South Africa: SUN MeDIA), at page 96. See also an account of the work of Maureen Kelley who highlights how orphans and vulnerable children may have multiple caregivers, and notes how the consequent lack of continuity, and frequent lack of emotional attachment between child and caregiver, can undermine the meaningfulness of surrogate decision-making: Cheah PY (1 October 2014) *Blog: consent and assent in paediatric research - panel discussion at the World Congress of Bioethics, June 2014, Mexico City*, available at: <http://www.ethox.ox.ac.uk/ethox-blog/consent-and-assent-in-paediatric-research-panel-discussion-at-the-world-congress-of-bioethics-june-2014-mexico-city>. Parents may also be simply inaccessible, for example because they are working away from home. See: Clacherty G, and Donald D (2007) Child participation in research: reflections on ethical challenges in the southern African context *African Journal of AIDS Research* **6(2)**: 147-56.

⁶⁰⁸ See, for example, Bwakura-Dangarembizi M, Musesengwa R, Nathoo K *et al.* (2012) Ethical and legal constraints to children's participation in research in Zimbabwe: experiences from the multicenter pediatric HIV ARROW trial *BMC Medical Ethics* **13(1)**: 17.

circumstances are appropriately involved in the decision about taking part in research poses further significant challenges to researchers.

- 6.41 Finally, we consider the question of young people in Case Three: those who are still considered 'minors' in their own jurisdiction but have the ability and maturity to make their own decision about participation in research. In the absence of any adults who are able to give a legally effective consent, we again suggest that young people's own consent, or decision not to participate, should be determinative, as in the situation of the temporary absence of parents described above (see paragraphs 6.34 and 6.36). In making a judgment as to whether children or young people have this degree of maturity, researchers may legitimately take into account the degree of control and responsibility that an individual child or young person is used to exercising in other areas of their life.⁶⁰⁹ However, in so doing it is critical to take into account whether they really are able to take on this responsibility without finding it an undue burden.⁶¹⁰ The role of professional discretion is therefore crucial in ensuring that children and young people are not inappropriately excluded from worthwhile research, while avoiding burdening an already over-burdened child.

⁶⁰⁹ Vakaoti P (2009) Researching street-frequenting young people in Suva: ethical considerations and their impacts *Children's Geographies* **7**(4): 435-50; Cheah PY, and Parker M (2015) Research consent from young people in resource-poor settings *Archives of Disease in Childhood* **100**(5): 438-40.

⁶¹⁰ Cheah PY (1 October 2014) *Blog: consent and assent in paediatric research - panel discussion at the World Congress of Bioethics, June 2014, Mexico City*, available at: <http://www.ethox.ox.ac.uk/ethox-blog/consent-and-assent-in-paediatric-research-panel-discussion-at-the-world-congress-of-bioethics-june-2014-mexico-city>.

Box 6.5: Points to consider when carrying out clinical research with children and young people

- Have you involved children, young people and parents in the development of your study?
 - In the design of the study itself? (e.g. the number of appointments or interventions required)
 - In the development of easy-to-understand information about the study?
- Does your study represent a fair offer to prospective participants? Are you confident that the value of the study, and its likely risks, burdens and benefits, have been carefully weighed up from the perspective of potential participants? Have children, young people and parents been involved in identifying possible benefits, risks and burdens?
- Is expertise in a particular area of children's healthcare important in order for the REC to understand the approach taken in this study? Has this been communicated to the REC, so that it is well placed to obtain advice if necessary?
- Are you able to demonstrate how you will communicate, and discuss, information about the study appropriately and sensitively with potential participants and their parents, so that they are able to make free and informed choices about whether to take part? Does everyone in your team who will be interacting with children, young people and parents have the necessary communication skills?
- Good assent practice is about the *process* of involving children and young people meaningfully in decisions about research. Are the particular methods you have chosen for involving children and young people in decisions about taking part the most appropriate ones?
- Children and young people who have the capacity and maturity to make their own decision about your study should be invited to give consent (not assent), even if the law additionally requires parental consent. Does your consent process and documentation allow for this?
- Decisions about research participation should, wherever possible, represent a shared decision between parents and children/young people. How will you encourage shared decision-making?
- Is the subject matter of your research such that it may be appropriate or necessary to recruit children and young people *without* the involvement of their parents? If so, can you justify the approach you have chosen?
- What arrangements have you made to support children and young people who do not have a parent, or another adult exercising a parental role, so that they are not excluded from your study?
- Will clinicians be responsible for recruiting children and young people, for whom they are providing care, to take part in research? If so, is this the most appropriate approach? Have you considered alternative approaches?
- Does the information provided for children, young people and parents explain how and when they can find out about the outcomes of the research? Will those outcomes also be explained in accessible language?

Chapter 7

Concluding thoughts

Chapter 7 – Concluding thoughts

Striking the right balance: conceptual recommendations

- 7.1 The terms of reference for this inquiry required the Working Party to consider the extent to which current systems for regulating clinical research with children and young people achieved the right balance between three important considerations:
- the scientific and clinical benefits that research may bring;
 - the role of children and young people themselves in research decisions; and
 - the proper protection of those taking part in studies.

In considering this question, we were struck repeatedly by the overriding importance of the second of these considerations: the role to be played by children, young people, and their families. However, it also became clear that this role was not limited simply to decisions relating to children's and young people's *own* potential participation in research, but rather was critical across the whole research agenda, including in the prioritisation, design, and scrutiny of studies.

The potential value of clinical research

- 7.2 From early on in our considerations, it became clear that the starting point for our analysis should be the claim that “scientifically valid and ethically robust research, addressing questions of importance to the health of children and young people, should be seen as intrinsically good, and as a natural and necessary part of a healthcare system” (paragraph 1.19). Such a claim, however, demands considerable elucidation: what *are* the features of “ethically robust” research, and what systems are required to ensure that they are in place? In the language of our terms of reference, how is the proper balance between the benefits of research, the involvement of children and young people, and the protection of research participants to be assured?

Understanding children, young people and parents as partners

- 7.3 We concluded that a critical feature of ethically robust research lies in the recognition of children, young people, and their parents as genuine partners in the research endeavour. In the context of their own family and social environment, children and young people have the potential from an early age to play an active role both in determining their own lives and in engaging with others, as part of their social world. Clinical research must thus always be *with* children and young people, not *on* them: children and young people are not mere passive subjects but rather active participants in a joint enterprise of research. So, instead of trying to second-guess what aspects of a particular health condition are of most concern to children and young people living with it, or what elements of a proposed study protocol might be unacceptably burdensome or distressing for them, researchers should ensure that the experiences and opinions of children, young people, and parents inform the development of their studies from the beginning. Such an approach casts a whole different light on how we understand the notion of the ‘vulnerability’ of children and young people in research, and how the potential for such vulnerability can be minimised through open and honest partnerships.

Professional responsibilities within that partnership

- 7.4 Recognising children, young people and parents as partners in research that may affect their lives and healthcare should not, however, shift responsibility away from professionals. As we saw in Chapter 2, decisions about research participation are often taken at times of great emotional stress for families; even where this is not the case, the knowledge and professional status of researchers may still result in children and families feeling at a disadvantage, or unable to make a free choice about participation. These potential inequalities emphasise both the importance both of the professional virtues that inform researchers' practice (trustworthiness, openness and courage), and the role of providing assurance played by those responsible for the ethical scrutiny of proposed studies. The 'proper protection' of research participants remains the responsibility of professionals, albeit informed by the knowledge and experience of those most likely to be affected by the research.

Sensitivity to context

- 7.5 An important thread of the Working Party's analysis throughout this report has been awareness of the *diversity* of childhood experience. This diversity is significant both in the heterogeneity of those understood as 'children' (from newborn babies to young people on the brink of adulthood), and in cultural understandings of how childhood is perceived: what is expected of, or regarded as acceptable for, children and young people at different stages of their development. In coming to our conclusions and recommendations, we have sought to be sensitive to this diversity, both in our identification of three paradigm cases of childhood in which distinct ethical questions about children's involvement arise, and in the extent to which our analysis and recommendations may resonate beyond the UK.
- 7.6 Our practical recommendations (notably those in Chapters 5 and 6) relating to specific aspects of research governance have been targeted primarily towards a UK audience, on the basis that they have in the main been informed by the knowledge and experiences of families and professionals within the UK. However, as we discussed in our Introduction, we were also alert to the fact that clinical research with children and young people is often international in its scope. Moreover, international guidelines and declarations (while not necessarily binding unless implemented in national legislation) play an important role in shaping understandings worldwide of what should be considered 'ethical' in research with children and young people.
- 7.7 In addition to our practical recommendations, we also made a number of *conceptual* recommendations throughout this report that we believe will help to ensure that the right balance is struck between the sometimes competing considerations summarised in paragraph 7.1. We suggest that these conceptual recommendations, if implemented flexibly and with regard to local context, should be of relevance to all those concerned with research with children and young people, both in the UK and beyond. We draw them together in Box 7.1.

Box 7.1: Conceptual conclusions and recommendations

Position of children and young people

- Children and young people should be seen as people who, in the context of their own family and social environment, have the potential, from an early age, to play an active role in determining their own lives and in engaging with others (paragraph 1.25).
- Three paradigm cases identify situations in which children's or young people's potential for input into a decision about research raises distinct ethical questions:

Case One: children who are not able at this time to contribute their own view as to whether they should take part in research, such as babies and very young children, or children who are temporarily unable to contribute because they are so unwell or are unconscious.

Case Two: children who are able to form views and express wishes, but who are not yet able to make their own independent decisions about research.

Case Three: children and young people who potentially have the capacity and maturity to make their own decisions about taking part in a particular research study, but who are still considered minors in their domestic legal system (paragraph 4.5).

Role of parents

- Ethical considerations that parents should take into account when making decisions with or on behalf of their children include:

Respect for children as individuals, regardless of their age or capacity, expressed, for example, through consideration of children's wishes and respect for their bodily integrity, although children's wishes may not always be determinative.

Recognition of children's developing capacity for autonomous agency, and the supportive or educational role of parents in helping their child develop and 'practise' decision-making skills and confidence.

Concern for children's immediate and longer-term welfare. Longer-term welfare is concerned with children's and young people's future 'good' including, but not limited to, what is 'best' for them in terms of their physical health or personal interests. Parents also have a responsibility to seek to influence the values that their child acquires as they grow up, and to shape the adult they become (paragraph 4.10).

Understanding welfare

- An understanding of children's longer-term welfare should encompass the possibility of contributing to wider social goods. This could take the form of participation in properly regulated clinical research in order to contribute to the knowledge base necessary to improve healthcare for all children in the future (paragraph 4.28).
- The language of 'best interests' is often used to capture this general concern for children's welfare, but is misleading in the context of research, as research-related procedures are not, primarily, carried out for the personal benefit of participants. Parental consent to research should therefore be based on their confidence that participation in the proposed research is *compatible* with their child's immediate and longer term interests (paragraph 4.33).
- There is a morally significant difference, which may potentially justify differential treatment, between 'competent children' and adults. Children, however intellectually capable, do not have full adult powers – and hence also do not have full adult responsibilities. Parents are there, both ethically and legally, to share that responsibility until the agreed threshold of adulthood is reached (paragraph 4.47).

Challenging vulnerability

- Concerns about the potential vulnerability of children and young people in research should be treated as an alert, and not as an automatic brake on research: a prompt to researchers to ask themselves ‘Does this research raise particular ethical challenges and what can I do about them?’ (paragraph 4.58).
- An appropriate response by professionals to concerns about children’s potential vulnerability in research is to ensure that they work in partnership with children, young people, and parents throughout the whole research endeavour. Such a partnership approach will ensure that, whenever children and young people are invited to take part in research, the procedures to which they are being invited to consent have been developed with the input of others in a similar situation to themselves (paragraph 4.59).

Professional virtues

- Professional virtues that lie at the heart of professional ethical practice in research with children and young people, and encourage a reflexive approach to practice, include trustworthiness (facilitating trust), openness, and courage. These should be encouraged and nurtured (paragraph 5.8).

Role of ethical scrutiny

- In order for research ethics committees to be well-placed to make finely balanced decisions as to whether the burdens and risks presented by a particular study protocol can ethically be justified, it is essential for them to have access to appropriate expertise: that of professionals with specialist knowledge of children’s healthcare, and that of children and families (paragraph 5.23).
- The fundamental role of ethical review is to ensure that an invitation to participate in research would constitute a ‘fair offer’ to children, young people and their parents, where the value of the research and its likely risks, burdens and benefits have been carefully weighed up (paragraph 5.28).

Making decisions about taking part in research

- Where children and young people have sufficient maturity and understanding to make their own decision but are not yet treated as fully ‘adult’ by the law of their country (Case Three), consent should, wherever possible, be sought from the children and young people concerned, and from their parents (paragraph 6.5).
- Where children and young people are not yet able to make their own decision (Case Two), there is an ethical imperative to *involve* them in the decision as much as possible. Requirements to ‘seek’ or ‘obtain’ assent from children who are being invited to take part in research should be understood as a requirement to involve children (as much as they wish and are able) in the decision about participation. This involvement should be recorded in some way, but it is the *process* of involvement that is ethically significant (paragraphs 4.11 and 6.10).

Prioritisation of research

- Our primary ethical concern with respect to prioritisation decisions relates to the *process* by which such choices are made. The key challenge for those responsible for making decisions about which research to pursue and which studies to fund is to ensure that key stakeholders, including children, young people, parents and professionals, are appropriately involved in those decisions (paragraph 5.40).

Making research part of everyday life

- 7.8 The aim of our analysis in this report, summarised in the conceptual conclusions and recommendations in Box 7.1, has been to clarify some of the key ethical concerns that arise in the context of clinical research with children and young people. In so doing, we have sought to remove potential barriers to research that may arise because of misplaced anxieties about what constitutes ethically acceptable practice. However, the barriers to research practice, as we outline in the background chapters of our report (see, for example, paragraphs 2.17–2.18 and 3.62–3.64) are not limited to concerns about ethical acceptability.
- 7.9 In order to reach the point where clinical research is genuinely seen as a core ‘everyday’ part of health service provision, commitment to evidence-based care will be required on the part of *all* those able to influence how care is delivered: including health professionals, health managers, and those responsible for health policy. It will also require substantial commitment on the part of policy-makers to increase knowledge of research among the general public. For children, young people, and parents to feel confident in taking part in research, they need to be able to trust that what they are being asked to do constitutes a fair offer. The task of researchers will be made much easier if the children and young people they are seeking to recruit, along with their parents, already have *some* understanding of the need for clinical research to improve healthcare, and of the many safeguards in place to ensure that what they are being invited to do is fair and worthwhile. Similarly, those who have had the opportunity to find out more about research are much more likely to take up the kinds of opportunities to influence the wider research agenda that we have advocated in this report. In the context of the UK, we suggest that the All Party Parliamentary Group on Medical Research, which has been active and engaged in the question of clinical research with children, would be well placed to initiate work on how best to achieve these aims.

Recommendation 19

We recommend that the All Party Parliamentary Group on Medical Research should take the lead in exploring ways of increasing general public awareness of clinical research in general, and of the benefits of such research for children’s and young people’s health and healthcare.

- 7.10 During our inquiry we heard many suggestions as to how this awareness might be increased. These included inclusion in school curricula, podcasts on hospital websites, ‘ambassador’ work undertaken by young people already involved in clinical research networks, open days by research centres, wider publicity of research opportunities, and greater knowledge and enthusiasm on the part of health professionals. We are aware of some positive initiatives along these lines, including the ‘It’s ok to ask’ campaign by the National Institute for Health Research (NIHR), encouraging patients and carers of all ages to ask their doctors about research.⁶¹¹ We thus conclude our report by highlighting the central importance of further work exploring the most effective methods of increasing knowledge and awareness, and the means of implementing them. For research to become part of the ‘core business’ of the NHS and other health services, it

⁶¹¹ National Institute for Health Research (1 May 2013) *It’s ok to ask - the NIHR’s new patient empowerment campaign*, available at: <http://www.ct-toolkit.ac.uk/news/its-ok-to-ask-the-nihrs-new-patient-empowerment-campaign>.

is important that we see an increasingly positive attitude towards research among potential participants and health professionals, together with confidence in the ethical robustness of that research.

Appendices

Appendix 1: Progress in leukaemia research

This Appendix summarises developments in the field of leukaemia research in recent decades, and provides the basis from which Box 1.1 was drawn.

Example of progress through research: the case of leukaemia

The development of treatment for children who have leukaemia has been lauded as a success story for clinical research.⁶¹² The most recent statistics (2001-5) for the ten-year survival rates of children (0-14 years) in Great Britain who have leukaemia are at 81 per cent, compared with 27 per cent for 1971-5 (the oldest figures published by Cancer Research UK).⁶¹³

Current survival rates have emerged out of several decades of clinical research into leukaemia in children and young people. During the 1940s and 50s, at a period where research for leukaemia took place predominantly in the US,⁶¹⁴ leukaemia was treated with single agent chemotherapy which was only effective temporarily and produced very severe side effects. Nearly all children who developed the illness died,⁶¹⁵ and enthusiasm for research was further hindered by the distrust generated by fraudulent claims in the early 1940s for the effectiveness of chemotherapy.⁶¹⁶ By 1948, however, the first reports of remission, albeit for a short period of time, were made by researchers who used drugs to reduce the amount of folic acid in their patients' bodies.⁶¹⁷ However, although this early 'experimentation' using folic acid antagonists resulted in improvement for some children with leukaemia, it was at terrible cost in side effects that led to strong resistance from junior doctors caring for the children on oncology wards.⁶¹⁸

Progress was made in the 1950s for the treatment of children with childhood acute lymphoblastic leukaemia (ALL) through the creation of the first cooperative group for ALL in the US, as patient numbers in single hospitals were insufficient for clinical cancer trials.⁶¹⁹ While the UK Medical Research Council proposed multi-centre trials for leukaemia around the same time, these did not include children as a specific focus.⁶²⁰ Indeed, the recruitment of children under the age of 14 was identified as a particular anxiety: difficulties were

⁶¹² See, for example, Leukaemia and Lymphoma Research (2014) *Milestones in the treatment of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/childhood-cancer-awareness-month/milestones-treatment-childhood-leukaemia>.

⁶¹³ See: Cancer Research UK (2014) *Childhood cancer survival statistics*, available at: <http://www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer/survival/childhood-cancer-survival-statistics>, figure 3.5.

⁶¹⁴ Barnes E (2005) Caring and curing: paediatric cancer services since 1960 *European Journal of Cancer Care* **14**(4): 373-80.

⁶¹⁵ For a timeline of developments in treating children with leukaemia, see: Leukaemia and Lymphoma Research (2014) *A history of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/full-page/history>. At this time, children were usually offered single drugs such as methotrexate or 6-mercaptopurine.

⁶¹⁶ Bud RF (1978) Strategy in American cancer research after World War II: a case study *Social Studies of Science* **8**(4): 425-59.

⁶¹⁷ Farber S, Diamond LK, Mercer RD, Sylvester RF, and Wolff JA (1948) Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin) *New England Journal of Medicine* **238**(23): 787-93. Folic acid has been found to stimulate the metabolism of DNA; anti-folates in the form of methotrexate are still used to treat acute lymphoblastic leukaemia. See also: Leukaemia and Lymphoma Research (2014) *A history of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/full-page/history>.

⁶¹⁸ See: Wishart A (2006) *One in three: a son's journey into the history of science and cancer* (London: Profile Books).

⁶¹⁹ Keating P, and Cambrosio A (2007) Cancer clinical trials: the emergence and development of a new style of practice *Bulletin of the History of Medicine* **81**(1): 197-223, at page 199.

⁶²⁰ Moscucci O, Herring R, and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20**(1): 23-52, at page 31.

envisaged ensuring the cooperation of parents and nursing staff due to the need for bone marrow aspirations.⁶²¹

The 1960s brought about the use of chemotherapy using multiple elements, which improved survival rates significantly.⁶²² Much of this progress was again made by researchers in the United States,⁶²³ although a children's leukaemia trial began at Great Ormond Street Hospital in May 1960.⁶²⁴ The 1960s also saw the 'story' of children with leukaemia being openly discussed for the first time in the UK's national media.⁶²⁵

The 1970s and 80s brought further progress with the introduction of bone marrow transplants,⁶²⁶ and brain and spinal column radiation (craniospinal radiation).⁶²⁷ The early 1970s also saw the ten-year survival rate rise from 27 per cent in the first half of the decade, to 39 per cent in 1976-80.⁶²⁸ However, a researcher working in the 1970s has observed that "at that time, in the early trials, we didn't have all the support we have now, so that getting patients who were very myelosuppressed and very immunosuppressed, was quite dangerous and there had been a tendency to ease off and given patients time to recover. We now know that's a big mistake."⁶²⁹ During the mid-1970s, national trials for ALL in the UK (UKALL trials), were introduced, which were open for every child diagnosed with ALL to participate in. The 1970s also saw US training fellowships for paediatric oncology advertised in the UK press, and some researchers who were successful in their applications later returned to the UK with experience of managing multi-centre trials incorporating chemotherapy.⁶³⁰

By the beginning of the 1980s, 80 per cent of all UK children with a diagnosis of ALL were being recruited into UKALL trials.⁶³¹ Despite this, the UK was seen to 'lag behind' the US in terms of progress with its research into childhood leukaemia, so researchers took the step of following a US protocol (CCSG 162 1A) exactly, so that they might learn how approaches to research differed. The team found that when they undertook the protocol in a UK-setting, children who took part died from infections such as pneumocystis during remission because the UK lacked the intensive support infrastructures available in US centres.⁶³² By 1980, septrin, an antibiotic, was administered as a way of preventing pneumocystis among children

⁶²¹ These concerns were raised in 1959 by the Working Party for the Evaluation of Different Methods for Therapy: see Moscucci O, Herring R, and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20(1)**: 23-52, at page 34.

⁶²² Leukaemia and Lymphoma Research (2014) *Milestones in the treatment of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/childhood-cancer-awareness-month/milestones-treatment-childhood-leukaemia>.

⁶²³ See, for example, Rivera GK, Pinkel D, Simone JV, Hancock ML, and Crist WM (1993) Treatment of acute lymphoblastic leukemia - 30 years' experience at St. Jude Children's Research Hospital *New England Journal of Medicine* **329(18)**: 1289-95.

⁶²⁴ See: Moscucci O, Herring R, and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20(1)**: 23-52, at page 34.

⁶²⁵ Barnes E (2008) Cancer coverage: the public face of childhood leukaemia in 1960s Britain *Endeavour* **32(1)**: 10-5.

⁶²⁶ The first successful bone marrow transplant performed in 1968 on a child with severe combined immunodeficiency syndrome. See: Gatti R, Meuwissen H, Allen H, Hong R, and Good R (1968) Immunological reconstitution of sex-linked lymphopenic immunological deficiency *The Lancet* **292(7583)**: 1366-9.

⁶²⁷ See, for example, Willoughby M (1976) Treatment of overt meningeal leukaemia in children: results of second MRC meningeal leukaemia trial *British Medical Journal* **1(6014)**: 864-7.

⁶²⁸ Cancer Research UK (2014) *Childhood cancer survival statistics*, available at: <http://www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer/survival/childhood-cancer-survival-statistics>, figure 3.5.

⁶²⁹ Interview with Professor Tim Eden, cited in Moscucci O, Herring R, and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20(1)**: 23-52, at page 41.

⁶³⁰ Barnes E (2005) Caring and curing: paediatric cancer services since 1960 *European Journal of Cancer Care* **14(4)**: 373-80, pp374-5.

⁶³¹ Leukaemia and Lymphoma Research (2014) *A history of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/full-page/history>.

⁶³² Moscucci O, Herring R, and Berridge V (2009) Networking health research in Britain: the post-war childhood leukaemia trials *Twentieth Century British History* **20(1)**: 23-52, at page 44.

with ALL, and by the late 80s, ten-year survival rates for children with leukaemia reached 63 per cent.

In the 1990s, studies examined environmental factors that may cause leukaemia in children.⁶³³ Researchers also identified the difference between ALL (a distinct disease in children) and acute myeloid leukaemia or AML (a very similar disease in adults and children).⁶³⁴ Developments such as these are marked by a rise in the ten-year survival rate of 70 per cent in the early 1990s, and 76 per cent in the late 1990s.⁶³⁵ Research continues into new chemotherapy drugs, resistance to chemotherapy, and stem cell transplants.⁶³⁶

⁶³³ For a review of studies that have investigated these environmental factors, see: Belson M, Kingsley B, and Holmes A (2007) Risk factors for acute leukemia in children: a review *Environmental Health Perspectives* **115**(1): 138-45, at 139-42.

⁶³⁴ Mentioned in Leukaemia and Lymphoma Research (2014) *A history of childhood leukaemia*, available at: <http://leukaemialymphomaresearch.org.uk/full-page/history>.

⁶³⁵ Cancer Research UK (2014) *Childhood cancer survival statistics*, available at: <http://www.cancerresearchuk.org/cancer-info/cancerstats/childhoodcancer/survival/childhood-cancer-survival-statistics/>.

⁶³⁶ See: Cancer Research UK (2013) *Acute lymphoblastic leukaemia research*, available at: <http://www.cancerresearchuk.org/about-cancer/type/all/treatment/whats-new-in-acute-lymphoblastic-leukaemia-research>.

Appendix 2: Method of working

Background

The Nuffield Council on Bioethics established the Working Party on *Children and clinical research: ethical issues* on 13 June 2013. The Working Party subsequently met eight times between June 2013 and November 2014.

In order to inform its deliberations, in August 2013, the Working Party launched an initial call for evidence and two online surveys via the Survey Monkey website; one for young people, and the other for their parents. In total, 51 individuals and organisations contributed to the call for evidence, and 117 young people and 72 parents responded to the online surveys. Although some responses to the initial call for evidence were from individuals based in low and middle income countries, the Working Party made additional efforts to encourage further responses from this group. We therefore worked with representatives of the Global Health Reviewers' Network (GHRN - part of the Global Health Network),⁶³⁷ and the KEMRI Wellcome Trust Research Programme (based in Kilifi, Kenya)⁶³⁸ to produce modified versions of the original call for evidence. These were distributed among both networks' contacts, and we subsequently received eight responses to the GHRN document, and ten to the KEMRI document.

Between September 2013 and December 2014, the Working Party also held a series of factfinding meetings, which addressed distinct questions and issues that arose throughout the project. It also carried out two literature reviews: one focusing on research evidence relating to how children, young people, and their parents experience taking part in clinical research; and the other on the development of clinical research in the context of childhood leukaemia. We were also able to draw on information provided in a review of international literature in the context of research with children and young people.⁶³⁹ In October 2014, 15 external reviewers, encompassing a wide range of experiences and perspectives, were invited to comment on a draft version of the report, which was subsequently reviewed in light of the comments received.

We are very grateful to all of these contributors for the generosity with which they gave their time: for their enthusiasm; and also for their expertise.

Call for evidence

The call for evidence took two forms: the first was a 14-question consultation document 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), and the KEMRI Wellcome Trust Research Unit in Kilifi, Kenya. The second

⁶³⁷ Global Health Reviewers (2014) *Homepage*, available at: <https://globalhealthreviewers.tghn.org/>.

⁶³⁸ KEMRI Wellcome Trust Research Programme (2014) *Homepage*, available at: <http://www.kemri-wellcome.org/>.

⁶³⁹ Southern Cross University and University of Otago (2012) *International literature review: ethical issues in undertaking research with children and young people* (Lismore and Dunedin: Southern Cross University and University of Otago).

part of the consultation was comprised of two surveys (one aimed at parents, and one at young people) posted to the online questionnaire site 'Survey Monkey' (see Appendix 3).⁶⁴⁰

Stakeholder Group

At its first meeting, the Working Party decided to establish a Stakeholder Group of young people and parents. Some of these young people had direct experience of research participation, whereas others had none. The members of this group met twice, and also commented by email; for example, on materials developed for our schools workshops.

17 July 2013: first stakeholder meeting

The main aim of the first meeting of the Stakeholder Group was to give participants the opportunity to help shape the project from the start. In particular, participants were urged to give their opinions as to the main ethical challenges arising out of clinical research with children and young people. The input of the stakeholder group allowed the Working Party to take their suggestions into consideration *before* it drafted its call for evidence and associated surveys.

- **Kerree Ahern**, hospital and healthcare professional, with personal experience of paediatric research as a parent of two children
- **Alison Dixon**, personal experience of paediatric research as a parent
- **Robert Dixon**, maths teacher, with personal experience of paediatric research as a participant
- **Katie Donald**, member of the RCPCH Youth Advisory Panel, with an interest in paediatric research
- **Phillippa Farrant**, trustee of the Muscular Dystrophy Campaign; chair of the Duchenne Family Support Group; personal experience and interest in paediatric research as a parent
- **Thines Ganeshamoorthy**, member of the RCPCH Youth Advisory Panel, with personal experience of/interest in paediatric research
- **Helen Hickey**, trials manager, Institute of Translational Medicine, University of Liverpool
- **Bharti Mevani**, children and young people's participation and advocacy manager, RCPCH
- **Ravi Mistry**, medical student; member of the RCPCH Youth Advisory Panel, with an interest in paediatric research
- **Liz Philpots**, head of research, Association of Medical Research Charities
- **Zoe Picton-Howell**, personal experience and interest in paediatric research as a parent; solicitor and tutor medical law and ethics at Edinburgh University Medical School; lay member of the RCPCH Child Health Review Expert Committee on Epilepsy
- **Farrak Pradhan**, patient insights advocacy coordinator, RCPCH
- **Becky Purvis**, head of policy, Association of Medical Research Charities
- **Mohini Samani**, member of the RCPCH Youth Advisory Panel, with an interest in paediatric research
- **Ruth Sanders**, research delivery project manager, Health Experiences Research Group, University of Oxford; personal experience of paediatric research as a parent
- **Adam Swift**, professor of political theory, Centre for Ethics, Law and Public Affairs, University of Warwick

⁶⁴⁰ Further information on the call for evidence is available at Appendix 3.

30 April 2014: second stakeholder group meeting

The second meeting of the Stakeholder Group focused on obtaining feedback on the Working Party's initial thoughts about its report. As well as those who attended the first Stakeholder Group meeting, other individuals also contributed:

- **Adit Bassi**, Young Persons' Advisory Group, Liverpool
- **Kate Dewhirst**, Young Persons' Advisory Group, East Midlands
- **Jeevan Gosal**, Young Persons' Advisory Group, East Midlands
- **Mark Howells**, Clinical Research Network: East Midlands
- **Freya Lynch**, Young Persons' Advisory Group, Great Ormond Street Hospital
- **Olivia Ibbotson**, Young Persons' Advisory Group, East Midlands
- **Fathima Manaal**, Young Persons' Advisory Group, Liverpool
- **Jennifer Preston**, consumer liaison manager, NIHR Clinical Research Network: Children
- **Erin Walker**, joint lead for patient and public involvement and engagement in research, Great Ormond Street Hospital / University College London Biomedical Research Centre
- **Kirsty Widdowson**, consumer liaison officer, Clinical Research Network: East Midlands

Factfinding meetings

A series of factfinding meetings were held with people with personal and/or professional interest in issues in children, young people and clinical research. A total of nine meetings were held, mainly involving discussion sessions lasting between one and a half and two and a half hours.

9 September 2013 (am): making research decisions – who decides and how?

The main aim of this meeting was to consider how decisions about children's involvement in research should be made.

- **Paul Baines**, paediatric intensive care consultant, Alder Hey Children's Hospital; PhD researcher for a project on 'Making medicine decisions of children: a philosophical approach'
- **Phil Bates**, lecturer in family and child law, Open University School of Law
- **Myra Bluebond-Langner**, chair of paediatric palliative care, UCL Institute of Child Health, and Great Ormond Street Hospital
- **Jo Bridgeman**, professor of healthcare law and feminist ethics, University of Sussex
- **Anthony Douglas**, chief executive, Cafcass
- **Virginia Morrow**, senior research officer, Young Lives project, University of Oxford
- **Claire Snowdon**, qualitative researcher, Department of Medical Statistics, London School of Hygiene and Tropical Medicine; lead researcher, BRACELET (Bereavement and Randomised Controlled Trials) study
- **Simon Woods**, senior lecturer and co-director, Policy, Ethics and Life Sciences (PEALS) Research Centre, Newcastle University

9 September 2013 (pm): setting the research agenda

This meeting sought to explore how the paediatric research agenda is set, and what role (if any) children, young people, and parents may play. It also sought to assess the effectiveness of recent regulation in promoting paediatric research.

- **Alasdair Breckenridge**, chair of the Emerging Science and Bioethics Advisory Committee (ESBAC); former chair of the MHRA
- **Simon Denegri**, chair of INVOLVE and national director for public participation and engagement in research, NIHR
- **Julia Dunne**, group manager, Special Populations, MHRA
- **Catherine Elliott**, director, Clinical Research Interests, MRC
- **Elin Haf Davies**, scientific administrator, paediatrics, European Medicines Agency; research officer, School of Healthcare Sciences, Bangor University
- **Pauline McCormack**, research associate, Policy, Ethics and Life Sciences (PEALS) Research Centre, Newcastle University
- **Vivienne McDonald**, director, Integrated Site Strategies and Patient Strategies, Quintiles
- **Jenny Preston**, consumer liaison manager, Children Research Network: Children
- **Marita Pohlschmidt**, director of research, Muscular Dystrophy Campaign
- **Penny Ward**, pharmaceutical physician, Faculty of Pharmaceutical Medicine

11 October 2013: the role of clinicians and researchers

The key aim of this meeting was to consider the role of clinicians and scientists in responding to the key ethical challenges that arise when undertaking or reviewing research in children.

- **Ananta Dave**, consultant and adolescent psychiatrist, Dudley & Walsall Mental Health Partnership NHS Trust
- **Margaret Fletcher**, professor of clinical nursing, University of the West of England
- **Robert Hemmings**, statistics unit manager, MHRA; chair of the EMA's Scientific Advisory Committee
- **Daniel Morgenstern**, consultant in paediatric oncology, Great Ormond Street Hospital
- **Moira Mugglestone**, director, National Collaborating Centre for Women's and Children's Health
- **Angelika Siapkara**, unit manager, paediatrics, Vigilance Risk Management of Medicines (VRMM) Division, MHRA

6 February 2014: the role of ethical review

This meeting considered the process of the ethical review of paediatric research.

- **Hugh Davies**, research ethics advisor, Health Research Authority
- **Glenys Hunt**, chair of the Liverpool East Research Ethics Committee
- **Gareth Tudor-Williams**, reader in paediatric infectious diseases, Imperial College London; consultant physician, Imperial College Healthcare NHS Trust
- **Mark Turner**, associate director – international affairs, CRN: Children
- **Simon Walton**, chair, South East Coast, Brighton and Sussex Research Ethics Committee; consultant anaesthetist
- **Penny Ward**, pharmaceutical physician, Faculty of Pharmaceutical Medicine

21 May 2014: vulnerability

The focus of this meeting was a general discussion exploring what is meant when we talk of 'vulnerability, and the extent to which it is a helpful term when thinking about how to protect children appropriately in research contexts.

- **Lucy Frith**, senior lecturer in Bioethics and Social Science, University of Liverpool
- **Anne Rathbone**, PhD candidate, University of Brighton, focusing on participatory research methods on resilience development with young adults with learning difficulties

- **Katherine Wade**, PhD candidate, University College Cork; thesis entitled 'medical research with neonates: a children's rights approach'
- **Anthony Wrigley**, senior lecturer in ethics, Centre for Professional Ethics, Keele University

19 June 2014: drivers of research

Follow-up from the meeting on 9 February 2014, with Julia Dunne, formerly of the MHRA, Bobbie Farsides and Katharine Wright.

4 November 2014: risk

Meeting with Ariella Binik, Biomedical Research Centre postdoctoral fellow at the Ethox Centre (University of Oxford) to discuss the question of how risk might be approached in the context of children, young people, and clinical research. Mark Sheehan, Bobbie Farsides, Katharine Wright, and Kate Harvey also attended the meeting.

December 2014: research in the context of cancer treatment

Meetings to discuss clinical research in the context of children and young people with cancer: with Christopher Copland (Consumer Representative, National Cancer Research Institute) on 8 December; and Danielle Horton Taylor and Neil Ranasinghe (members of the Paediatric Oncology Reference Team) on 18 December.

School-based activities

In order to obtain views from children and young people who did not necessarily have direct experience of clinical research, the Working Party also undertook two school-based projects: the Youth REC project (see Appendix 4), and the 'Chocolate trial' activity with primary school students (see Appendix 3).

School and community consultation in Kilifi, Kenya

With the support of our Working Party members based in Kenya, we were able to draw on the views of school children and community representatives in Kilifi, Kenya (see Appendix 3).

Literature review

The Working Party undertook two literature reviews of existing research relevant to its work.

The first was undertaken by Working Party member Robin Gill, and focused on the development of clinical research in the context of childhood leukaemia. A summary of this review is available at Box 1.1 of this report.

The second literature review was carried out by Kate Harvey, a member of the Nuffield Council's secretariat. This review collated research literature (primarily, but not exclusively, UK-based) that addressed the question of how young people, as well as their parents, report the experience of participating in clinical research.

External review

A draft version of the report was circulated in October 2014 to 15 external reviewers with personal and / or professional expertise in the issues arising out of involving children and young people in clinical research. The reviewers were:

- **Priscilla Alderson**, professor emerita of childhood studies, Institute of Education, University of London
- **Deborah Bowman**, professor of bioethics, clinical ethics and medical law, St. George's, University of London
- **Jo Bridgeman**, professor of healthcare law and feminist ethics, University of Sussex
- **Simon Denegri**, chair of INVOLVE, and national director for public participation and engagement in research, NIHR
- **Phillippa Farrant**, chair of Duchenne Family Support Group
- **Faith Gibson**, clinical professor of children's and young people's cancer care, Great Ormond Street Hospital
- **Allison James**, director of the Centre for the Study of Childhood and Youth, University of Sheffield
- **Virginia Morrow**, senior research officer, Young Lives Project, University of Oxford
- **Agnes Saint Raymond**, head of Programme Design Board, European Medicines Agency
- **Abha Saxena**, coordinator, Global Health Ethics, World Health Organization
- **Alan Smyth**, professor of child health, University of Nottingham
- **Mark Turner**, consultant neonatologist, University of Liverpool
- **David Walker**, professor of paediatric oncology, University of Nottingham
- **Natasha Wilcock**, student, Varndean College, Brighton
- **Simon Woods**, co-director, PEALS, Newcastle University

Appendix 3: Wider consultation for the report

Call for evidence

The Working Party's initial call for evidence (including indicative questions – see list of questions below – but also inviting respondents to raise any other issues within the remit of the terms of reference) was launched on 7 August 2013 and remained open until 31 October 2013. Fifty-one responses to the call for evidence were received (of which 25 came from individuals and 26 from organisations). Respondents included people with a personal interest (for example, parents of a child who had participated in clinical research, as well as the young person themselves), a professional interest (for example, as a result of their work in clinical research, for a charity or a support group, or for a governmental or non-governmental organisation), those with academic interests, individuals with legal/regulatory interests, as well as those with a general interest in the issues raised. Summaries of responses to our call for evidence, and each of the two Survey Monkey questionnaires, are available on the Council's website.⁶⁴¹

Following the launch of the call for evidence, the Working Party identified the need to obtain further input of researchers and participants from outside the UK: particularly in low and middle income countries. We therefore liaised with The Global Health Reviewers' community (part of the Global Health Network),⁶⁴² so that a modified version of the call for evidence could be distributed among its members.⁶⁴³ The versions of the call for evidence that were issued as part of the global call for evidence are available at below. They elicited eight responses, and also comments via the GHRN blog.

In addition, Working Party members Vicki Marsh and Sassy Molyneux adapted and circulated a further version of the call for evidence to contacts identified via their networks at the KEMRI Wellcome Trust unit in Kilifi, Kenya, eliciting ten responses.⁶⁴⁴

All responses were circulated to Working Party members and discussed at subsequent meetings. They were very important in shaping our deliberations, and the Working Party would like to express its gratitude to all those who responded. We would also like to thank those who facilitated the distribution of the call for evidence, including Susi Bull, Liam Boggs, Vicki Marsh, and Sassy Molyneux.

⁶⁴¹ Nuffield Council on Bioethics (2015) *Children and clinical research: ethical issues - summary of consultation responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>; Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of young people's responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>; Nuffield Council on Bioethics (2015) *Survey Monkey questionnaire: analysis of parents' responses*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

⁶⁴² Global Health Reviewers (2014) *Homepage*, available at: <https://globalhealthreviewers.tghn.org/>.

⁶⁴³ 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/>.

⁶⁴⁴ A report of these consultative activities was also produced. See: Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme). For further information, see: Nuffield Council on Bioethics (2015) *Children and clinical research: evidence gathering activities*, available at: <http://nuffieldbioethics.org/project/children-research/evidence-gathering-activities/>.

Call for evidence: questions

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

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.

Call for evidence: questions issued via KEMRI networks

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 participants? 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 individuals 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?

Call for evidence: questions issued via Global Health Reviewers' Network

1. What do you consider to be 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?
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?
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?
8. Any other comments?

List of respondents to the call for evidence

Individuals

Anonymous (4)

Dr Ayesha Ahmad

Dr Janice Allister

Dr Anna Basu, Newcastle upon Tyne Hospital NHS Foundation Trust

Basil Bekdash

Professor Jo Bridgeman

Iain Chalmers, Coordinator, James Lind Initiative

Professor Jane C. Davies

Dr Karen Devries

Anne Elmer

Rhiân Evans

Professor Caroline H.D. Fall

Professor Saul N. Faust, Director, Southampton NIHR Wellcome Trust Clinical Research Facility, University of Southampton

Professor Faith Gibson

Richard Hain

Dr Daniel E. Lumsden

Professor Kathryn Maitland

Nigel Monaghan

Wim Pinxten, Hasselt University, Belgium

Melody Redman

Professor Andrew Tomkins, Institute for Global Health, UCL, London

Hector Velarde MD, Mexico

Organisations

Academic Paediatricians' Forum of Leicester University and Leicester Hospitals

Academy of Medical Sciences
 The Association of Medical Research Charities (AMRC)
 AstraZeneca
 British Heart Foundation
 British Medical Association
 The British Society of Paediatric Dentistry
 Children and Young People Oral Health Research Group, School of Clinical Dentistry,
 University of Sheffield
 Christian Medical Fellowship
 Ethical Medicines Industry Group
 Great Ormond Street Hospital for Children NHS Foundation Trust; UCL Institute of Child
 Health
 Health Ethics and Law, University of Southampton (HEAL UoS)
 Health Research Authority
 Instituto Nacional de Salud del Niño del Peru; Instituto de Investigación Nutricional del Peru;
 Hospital Nacional Edgardo Rebagliatti Martins; US Naval Medical Research Unit No.
 6, NAMRU-6
 Mary MacLeod OBE, Chair, Great Ormond Street Hospital Clinical Ethics Committee
 NIHR Clinical Research Network: Children
 Oxford Vaccine Group
 Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI)
 Paediatric Oncology Reference Team (PORT)
 Felicity Shenton, Development Manager, Investing in Children
 Teenage Cancer Trust
 Together for Short Lives and Association for Paediatric Palliative Medicine Joint Research
 Group
 University of Cambridge Department of Paediatrics
 University College London and the European Network for Cancer Research in Children and
 Adolescents
 U.S. Presidential Committee for the Study of Bioethical Issues
 The Wellcome Trust

Respondents who submitted published material

The Working Party also received submissions of published material from six individuals:

Dr Kristien Hens, Katholieke Universiteit Leuven
 Dr Kathy Liddell
 Professor Kathryn Maitland
 Professor Barbara A. Noah
 Professor D. K. Theo Raynor, University of Leeds
 Professor Peter Smith, London School of Hygiene and Tropical Medicine

List of respondents to the KEMRI document

Anonymous (2)
 Dr Muhammed Afolabi, Clinical Scientist, Medical Research Council Unit, the Gambia
 Dr Roma Chilengi, Scientific Director, Centre for Infectious Disease Research, Zambia and
 Adjunct Assistant Professor, University of North Carolina at Chapel Hill, USA
 Mr Fred Kanyoke, Institutional Ethics Committee Administrator, Kintampo Health Research
 Centre, Kintampo, Ghana
 Dr Margaret Phiri Kasaro, Clinical Scientist, Research Department, Centre for Infectious
 Disease Research, Zambia

Mr Kingsley Kayan, Quality Assurance (QA) Manager, Kintampo Health Research Centre, Kintampo, Ghana

Dr Malick Ndaiye, Research Clinician, MRC Laboratories, the Gambia

Dr Molline Timbwa, Research Clinician in severe acute malnutrition studies involving children, KEMRI Wellcome Trust Research Programme, Kilifi, Kenya

List of respondents to the GHRN document

Anonymous (4)

María del Carmen Díaz, Master en Bioética, Facultad de Ciencias Médicas de la Universidad Nacional de Rosario, Argentina

Fasela Emmanuel, NIMR, Lagos, Nigeria

Eleonora Espinoza MD, MSc Denis Padgett MD, MSc, Comité de Ética de Investigación Biomedica, Facultad de Ciencias Medicas, Universidad Nacional Autonoma de Honduras, Tegucigalpa Honduras

Morenike O. Folayan, Obafemi Awolowo University and the New HIV Vaccine and Microbicide Advocacy Society

Survey Monkey questionnaires

The Working Party published also two online surveys, using the website 'Survey Monkey' with the aim of asking a more limited number of questions, hence encouraging a wide range of responses from parents and young people who either have direct experience, or general interest, in the issues raised by the involvement of children and young people in clinical research. We received 72 responses to the parents' Survey Monkey questionnaire, and 117 responses to the questionnaire for young people. The questions posed by both of these surveys are available below.

Survey Monkey questionnaire for young people

1. If someone said they wanted you to be involved in clinical research, what do you think that would mean?
2. Who do you think should decide whether you take part in clinical research? (Please tick one option.)
 - You
 - Your parent(s) or guardian(s)
 - Your doctor
 - Your parents/guardians AND your doctor
 - You AND your parents/guardians
 - You AND your parents/guardians AND your doctor
 - Other (state who)
3. What do you think should happen if you want to take part in research but your parents or guardians disagree?
4. What do you think should happen if you don't want to take part in research, but your parents or guardians think you should?
5. Please state how you feel about taking part in these types of research (options: strongly agree; agree; neutral; disagree; don't know/doesn't apply)
 - Answering questions about my health
 - Having regular blood tests
 - Having regular tests such as MRI scans (which produce pictures of the inside of your body)
 - Trying out new medicines or medical techniques to see if they work (for example, where a medicine has been used in adults before, but not in children)
 - Talking to someone about my feelings, for example if I feel sad or worried
6. What would be your concerns or worries about taking part in research?
7. What could be done to make you feel more comfortable about taking part in clinical research, and less worried?
8. What might encourage you to take part in clinical research? (Tick as many as you like)
 - Knowing about local research opportunities
 - Feeling appreciated (e.g. thank you letter)
 - Finding out what happened after the research (e.g. whether it led to any changes in children's medical treatment in the future)
 - Making it easy to take part (e.g. close to home or through school/college)
 - Money or vouchers as a reward for taking part
 - Other (please specify)
9. If you were told that the research probably wouldn't help you but might help other children in the future, would you still take part? (Please explain.)

Survey Monkey questionnaire for parents

1. What do you understand by the term 'clinical research'?
2. What would be your main concerns about enrolling your child/children into a clinical research study, and why?
3. What could be done to help alleviate any of your concerns about enrolling your child into a clinical research study?
4. Do you think you would gain anything from enrolling your child in a clinical research study? If so, what?
5. Would you allow your child to be involved in making decisions about participating in a clinical research study, and why?
6. If you would not allow your child to be involved in making decisions about participating in a clinical research study, would this change if your child was older?
7. Who should make the final decision regarding your child's involvement in a clinical research study? (Please say why.)
 - Parent(s)
 - Child
 - Parents *and* child
 - Clinician
 - Clinician *and* parents
 - Clinician, parents *and* child
 - Other (please state who)
8. How comfortable would you feel about taking your child out of a clinical research study? (For example, if you thought it was being detrimental to their health, or if the arrangements became very inconvenient?)
9. Would you be willing to involve your child in a clinical research study if you knew that it would not improve your child's condition directly, but might improve treatment options for other children suffering with the same condition? (Please say why)
 - Yes
 - No
 - Maybe
10. What might encourage you/your child to participate in a clinical research study? (Tick any that apply)
 - More information about research opportunities
 - Appreciation (e.g. thank you letters)
 - Information about the outcome of the research (e.g. articles published in medical journals/changes in medical practice)
 - Participation made easier (e.g. convenient location; easy travel)
 - Small financial reward (e.g. £5 token)
 - Larger financial reward (e.g. £50 token or cash)

KEMRI consultation activity

Between January and March 2014, Irene Jao, Nancy Mwangome, Alun Davies, Sassy Molyneux, and Vicki Marsh from the KEMRI Wellcome Trust Research Programme undertook a consultation exercise with community representatives and secondary school students in Kilifi, Kenya.

The consultation activity involved small discussions with four groups of KEMRI's community representatives, and four groups of secondary school students from KEMRI's Schools Engagement Programme (SEP). In total, 33 community representatives and 24 students participated in the activity. All eight group discussions were held in community-based venues in Kilifi, and were facilitated by social scientists from KEMRI. Discussions lasted about one

hour, and were held in Swahili, a Mijikenda language or a mixture of Swahili and English. A report of the consultation activity summarises the groups' discussions, and sets out discussion guides and questions that were put to participants.⁶⁴⁵

We would like to thank the facilitators and participants who took the time to take part in this consultation activity, and Kevin Marsh for supporting this engagement in Kilifi.

Chocolate trial: activity with primary school students

In November 2013, Katharine Wright and Kate Harvey visited Bishop Gilpin Church of England Primary School in Wimbledon to talk to 60 children aged between eight and nine about clinical research.⁶⁴⁶

Part of this activity involved a 'chocolate trial', where the students were given the option of being allocated a particular flavour of chocolate randomly, if they chose to take part in the research. After the chocolate trial had been concluded, students were then asked to think about clinical research more generally, and were invited to write their thoughts about a mock study on paper tablecloths. Comments made by the students appear in this report, and both images and comments have since been used to create the cover of this report.

We would like to thank the students who took part for their enthusiasm, and their teachers and parents for facilitating our visit.

⁶⁴⁵ Jao I, Mwangome N, Davies A, Molyneux CS and Marsh V (2014) *Nuffield Council on Bioethics Working Party on ethical issues for research involving children: report on consultations with community representatives and secondary school students in Kilifi, Kenya* (Kilifi, Kenya: KEMRI Wellcome Trust Research Programme).

⁶⁴⁶ For a detailed account of this activity, see: Nuffield Council on Bioethics (25 November 2013) *Blog: what do you mean - ask children?!*, available at: <http://blog.nuffieldbioethics.org/?p=907>.

Appendix 4: ‘Youth REC’ films

Background

In addition to contributions from children and young people who responded to our Survey Monkey questionnaire (most, if not all, of whom were likely to have a prior interest in or experience of clinical research), the Working Party also identified a need to obtain views from children and young people without direct experience of clinical research. Subsequently, we worked with Janet Boddy (University of Sussex), Rebecca Rees (Institute of Education, University of London), and Grace Spencer (University of Nottingham)⁶⁴⁷ to undertake a film project which enabled young people to take on the role of an ethics committee. We also sought the views of our stakeholder group (see Appendix 2) when developing materials for this project. Two films created as a result of this project have proved to be valuable resources for the Working Party during its deliberations, and we would like to thank all those involved with their creation.

Adult REC film

A mock research protocol was developed by the Working Party and the three researchers, in collaboration with Somnath Mukhopadhyay (Chair of Paediatrics, Brighton and Sussex Medical School). The mock protocol focused on a novel way of identifying the most appropriate treatment for childhood asthma, given children’s variable responses to two standard medications. This protocol was first discussed by members of an ‘Adult’ REC (assembled solely for the purposes of the project). The Adult REC was comprised of Becky Godfrey, Elin Haf Davies, Dez Holmes, Isla-Kate Morris, and Simon Walton; the REC was chaired by Bobbie Farsides.

In order to capture the discussions of the Adult REC, the Working Party engaged Vivianne Howard, a documentary filmmaker, to create a film of the REC’s discussions. This film explores the aims and methods of the study, and includes interviews with Professor Mukhopadhyay (who adopts the role of principal investigator), a seven-year-old girl with asthma and her family, as well as the discussions of the Adult REC on the merits of the protocol and its associated ethics application, consent forms, and information sheets.⁶⁴⁸

Youth REC film

Following the production of the first film, the second stage of the project began. This involved asking children and young people at three different schools in the Brighton area (at three age groups: 10-11 (junior); 11-14 (secondary); 16-18 (sixth form)) to explore the same mock protocol as that which was discussed by the Adult REC. The participants’ discussions at these workshops were facilitated by Grace Spencer, and filmed by Vivianne Howard. Content recorded at each of these workshops was then edited to form a second film, which focuses

⁶⁴⁷ The three researchers with whom we worked subsequently produced a report of the project: Spencer G, Boddy J, and Rees R (2014) *“What we think about what adults think”: children and young people’s perspectives on ethics review of clinical research with children* (London: Nuffield Council on Bioethics).

⁶⁴⁸ Nuffield Council on Bioethics (2014) *Processes, papers and professors: how clinical research in young people gets approved*, available at: <https://www.youtube.com/watch?v=VaiZ58uiwdU>.

on the discussions of the young people at each school, and their thoughts on the protocol and its additional materials.⁶⁴⁹

Future use

The Youth REC project was launched formally at an event at the Brighton and Sussex Medical School on 25 March 2014, and each film is now available on YouTube.⁶⁵⁰ In addition, some of the students involved in the second film have produced a blog on their experience of the workshops, and their thoughts on clinical research.⁶⁵¹ The films and associated written materials have also since been presented at other schools, colleges, and universities, and form part of the Nuffield Council's educational resources.⁶⁵²

⁶⁴⁹ Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>.

⁶⁵⁰ Nuffield Council on Bioethics (2014) *Processes, papers and professors: how clinical research in young people gets approved*, available at: <https://www.youtube.com/watch?v=VaiZ58uiwdU>; Nuffield Council on Bioethics (2014) *Be a part of it: what young people think of clinical research*, available at: <http://www.youtube.com/watch?v=e2k6eA0dn9Q>.

⁶⁵¹ Nuffield Council on Bioethics (9 April 2014) *Blog: involving children in research - 'what we think about what adults think'* available at: <http://nuffieldbioethics.org/blog/2014/involving-children-in-research-what-we-think-about/>.

⁶⁵² Nuffield Council on Bioethics (2014) *Materials on clinical research ethics*, available at: <http://nuffieldbioethics.org/education/materials-resources-educators/materials-clinical-research-ethics/>.

Appendix 5: Young people's resources arising from this report

Background

The Working Party felt that it was very important to make the findings of this report accessible to children and young people themselves, and to involve them in any further resources we developed. This arose from our recognition of the importance of involving children and young people in designing research and research resources earlier in this report.

Advice from CRN: Children's Young Persons' Advisory Groups

Having identified the need to present the key themes of the report in a format that children and young people would find both accessible and engaging, members of the Nuffield Council's secretariat visited the Liverpool Young Persons' Advisory Group (YPAG) on 29 November 2014 to ask for their advice in establishing how this might best be done. The group suggested that we should convey the messages of our report to younger audiences through an animated film and a magazine-style short version of this report. It was suggested that the film animation should be aimed at children aged ten and over, and the magazine aimed at young people over the age of 14.

Magazine version

Following our visit to Liverpool, we drafted a shorter version of this report, and then sought further input from young people, so that we could ensure that the tone, language, and content made sense to younger readers, without being patronising to older children and young people. Young persons' groups in London (the Great Ormond Street Hospital YPAG), Liverpool, Aberdeen (ScotCRN YPAG), and Connecticut (the KIDS initiative) discussed the draft and gave detailed feedback both on the language used and design ideas. At a return visit to the Liverpool YPAG in February 2015, five-minute interviews were carried out with seven members of the group, which were then used as audio clips embedded in the electronic version of magazine itself. The final version of this magazine is available on the Council's website.⁶⁵³

We are very grateful to the members of the Liverpool YPAG, GOSH YPAG, ScotCRN YPAG, and the KIDS initiative in Connecticut for all their input, and for the facilitation assistance we received from Jennifer Preston, Erin Walker, Pamela Dicks, Nick Federico, and Charles Thompson. We would also like to thank the individual feedback we received from Isabella Farsides, Robin Blair, Kathryn Dally, and Mark Taylor.

⁶⁵³ Nuffield Council on Bioethics (2015) *Children and clinical research*, available at: <http://nuffieldbioethics.org/project/children-research/>. See also: Nuffield Council on Bioethics (2015) *Children and clinical research: animation and interviews*, available at: <http://nuffieldbioethics.org/project/children-research/animation-interviews/> to hear audio clips recorded from interviews with Liverpool YPAG members.

Animation

In February 2015, we met with five animation companies with the aim of developing a short film that addressed some of the key conclusions made in this report, but with a narrative thread that appealed to young people. We chose to work with a documentary production company called Mosaic.⁶⁵⁴ With Mosaic, we identified key points we wanted the film to address, and formed a series of questions which we then put to a group of 14 young people at a two-hour workshop in London in March 2015. This group of young people (aged between ten and 18) were drawn from the Nuffield Council's school contacts (for example, schools where Council members or staff had previously given presentations on the Council's work), and so were not 'experts' in clinical research.

The workshop was divided into two parts. In the first part, the young people were asked to address a series of questions on issues relating to clinical research that are covered in this report. In the second half of the workshop, the group was asked to explore the images that came to mind when particular situations were put to them. Both of these sets of questions and scenarios are shown in the boxes below.

Questions raised and visual scenarios posed to animation workshop participants

1. When you hear the term 'health research', what does it bring to mind?
2. Why do you think research happens?
3. Who do you think carries out health research?
4. Why do they need to do research with children?
5. What might make you want to take part in research?
6. What might worry you about taking part in research?
7. What might worry your parents about you taking part in research?
8. Do you think anything could be done to reduce worries that you or your parents might have?
9. Who do you think should make decisions about young people taking part in research?
10. What do you imagine being involved in research to be like? What do you think happens?
11. When you think of a typical 'researcher' what do you imagine them being like?
12. What do you think the perfect research experience would be like?
13. What, if anything, do you think should happen after the medical research you have been involved in is over?
14. How could young people be encouraged to take part in research?

⁶⁵⁴ Mosaic Films (2015) *About us*, available at: <http://mosaicfilms.com/about-mosaic-films/>.

Visual scenarios presented to animation workshop participants

1. You have been asked if you would like to take part in medical research for a new treatment which could help lots of people. The research is quite intense and will take up a lot of your free time. How do you feel? Positive / Negative? Why? Explain using visual similes / metaphors and comparisons.
2. You go to a meeting with the researcher who is organising the trial for some more information. She goes into minute scientific detail which you find really difficult to understand. How does it make you feel?
3. You ask the researcher to explain more simply to you and your parents. She does – and you begin to understand what the research involves. How do you feel?
4. The researcher checks both your and your parents' understanding, and asks if you have any more questions to ask. She says that you would be able to back out of the research at any point – even after it has started. She then tells you that you should take some time to consider whether it is right for you and, just before you leave, gives you some leaflets with a bit more information on the research. How do you feel the meeting with the researcher went? Do you feel differently about the research from the way you did before the meeting?
5. You are discussing with your parents about whether you will do it. They really think you should do it and are trying hard to persuade you but you're still not sure – they aren't listening to your reasons. How does it feel?
6. The next day your parents apologise and say they would like to hear your opinions – that your thoughts are the ones that matter most. How does it feel?
7. You decided to do it and are now three weeks into the research. You have done a lot of tests and haven't had any time to do the things you usually enjoy – like meeting your friends. How do you feel?
8. You explain your problem to the researcher and she agrees that they should tailor the times that the research takes place so it suits you better. You draw up a new schedule together. How do you feel?
9. The research is finished. It is a year later and you get a letter from the researcher explaining that the trial you took place in has led to a successful new treatment that will help thousands of other people. How do you feel?

Following this workshop, Mosaic worked with members of the Council's secretariat to produce a script for the animation. This script was also sent to those who participated at the animation workshop, to get further feedback, and to ensure that the 'voice' of the central character accurately represented that of a young person.

The final animation conveys some of the key themes of the report from the perspective of Mia – a character who goes through some of the questions and issues that might be raised when a young person is invited to take part in clinical research. The voice of Mia was provided by Evie Rothwell, who attended the animation workshop. The animation, which is

now available on the Council's website,⁶⁵⁵ will be used in the Council's engagement work in the future, and will be made available to charities and stakeholders who are directly concerned with involving and including children and young people in clinical research.

We would like to thank Robin Blair, Oliver Dean, Sainath Eleti, Jessica Freeman, Hannah Garnett, Zach Hartman, Rhiannon Meller, Victoria Morgan, Ellis Richardson, Alexander Roberts, Evie Rothwell, Zachary Santoro, Natasha Wilcock, and Tanya Wooley for their participation at the animation workshop. We would also like to thank their teachers for facilitating our contact with them: particularly Cathy Brook from Southend High School for Boys, John Luton from Varndean College in Brighton, Claire McShane from St. Teresa's School in Effingham, and Rebecca Ward from Graveney School in Tooting. We would also like to thank Adam Wishart, for his advice on producing the animation, and Laurie Harris, Lillian Fu, Andy Glynne, and Molly Bond from Mosaic Films.

⁶⁵⁵ Nuffield Council on Bioethics (2015) *Health research: making the right decision for me*, available at: <http://nuffieldbioethics.org/project/children-research/>.

Appendix 6: The Working Party

Bobbie Farsides (Chair) is Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School. She has been researching and teaching in the field of bioethics for over twenty years, and her research focuses on the experience of health care professionals and scientists operating in ethically contested fields of biomedicine. Bobbie also has a strong commitment to public policy work and serves on a number of committees including the Emerging Science and Bioethics Advisory Committee and the UK Donation Ethics Committee. Research ethics has been a constant interest throughout her career including practically-focused work in the developing world context.

Joe Brierley is a Consultant in Paediatric and Neonatal Intensive Care at Great Ormond Street Hospital, where he is the lead clinician for end of life issues, and also for ethics and law research. He chairs the Bloomsbury Local Research Ethics Committee, is Vice Chair of Great Ormond Street's Clinical Ethics Committee, and is a member of the Ethics and Law Advisory Committee of the Royal College of Paediatrics and Child Health. He also teaches and publishes on paediatric research ethics. His family, which includes a daughter with complex health issues, have participated in both quantitative and qualitative research studies.

Imelda Coyne is Professor of Children's Nursing at Trinity College Dublin, Ireland. Her research examines family-centred care practices, and children and young people's participation in healthcare decision-making. Projects include: interventions for shared decision-making; adolescents' transition to adult health services; quality of healthcare provision for children and families; and child and adolescent experiences of mental health services. She is a member of the Research Development Advisory Group and the Thematic Policy Group (called 'Children's voices will be heard') at the Department for Children and Youth Affairs (DCYA), Ireland.

Elizabeth Davis is a Paediatric Nurse currently working as a Paediatric Immunology Nurse Specialist, and also as a Children's Network Nurse for the Oxford Academic Health Science Children's Clinical Network. From 2008 to 2014 she worked as a Paediatric Research Nurse at The Oxford Vaccine Group, working with children and young people of all ages. Previously she worked with the school health nurses, in the acute setting at the John Radcliffe hospital, mainly in the Paediatric Intensive Care Unit, and on the Adolescent Unit. She also teaches yoga in schools, and at CHIVA (Children with HIV association) summer camp as a means of building self esteem and quietening the mind.

Sara Fovargue is Reader in Law at Lancaster University specialising in health care law and ethics. Her research largely centres around the legal and ethical issues raised by biotechnology and reproduction, and she is particularly interested in xenotransplantation. Themes within her work include autonomy, risk, regulation, and the relationship between law and ethics. Her research explores legal and ethical aspects of clinical research, regulation and risk, and she is interested in decision making processes and practices with regard to the 'vulnerable'.

Robin Gill is Professor of Applied Theology at the University of Kent. He was Chair of the Archbishop of Canterbury's Medical Ethics Advisory Committee 1993-2006. He has published a number of books on theological aspects of bioethics including Christian ethics and values, health care and genetics.

Roland Jackson is Executive Chair of Sciencewise and Chair of the Bioscience for Society Strategy Panel for the Biotechnology and Biological Sciences Research Council (BBSRC). He has a particular interest in science policy and in public involvement with research.

Vicki Marsh ('jobshare' with Sassy Molyneux) is a senior social scientist and public health researcher based in the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme in Kenya; University Research Lecturer in the Nuffield Department of Medicine, Oxford University; and Research Associate at the Ethox Centre, Oxford University. She has worked in Kenya since 1990, including a stint as a paediatric medical officer. Her current research interests focus on social and ethical aspects of international collaborative health research in low-income settings, including community engagement and deliberative forms of community consultation.

Sassy Molyneux ('job-share' with Vicki Marsh) is a senior social scientist based at the Kenya Medical Research Institute (KEMRI)-Wellcome Trust Research Programme in Kenya; Associate Professor in the Nuffield Department of Medicine, Oxford University; and Research Associate at the Ethox Centre, Oxford University. Her current research focuses on accountability: producing new thinking, evidence and recommendations around strengthening community involvement and internal accountability in biomedical research and health delivery in sub-Saharan Africa.

Helen Sammons is a General Paediatrician (Derbyshire Children's Hospital) and Associate Professor of Child Health at the University of Nottingham. She is a qualified Paediatric Clinical Pharmacologist with research interests around safe and effective use of children's medicines. Her interest in ethics have led to her being vice chair of the Derby NRES Ethics Committee and she has conducted research around why parents consent for their children to take part in clinical trials, and on physician viewpoints on key ethical issues. She is part of the ethical review boards for two major European projects, leading the ethics work package for the Treatment of Infection in Neonates (TINN) consortium projects, and a member of the ethics board for the ASTRO LAB project examining safety of asthma treatment in adults and children.

Mark Sheehan is Oxford NIHR Biomedical Research Centre Ethics Fellow at the Ethox Centre and a Research Fellow at the Uehiro Centre for Practical Ethics, University of Oxford. He currently serves as a National Research Ethics Advisor for the National Research Ethics Service, and has been a member of the NHS Advisory Group for National Specialised Services (AGNSS) and vice-chair of the Thames Valley Priorities Forum for the South Central Strategic Health Authority. He also sits on the University of Oxford's Social Sciences and Humanities Inter-Divisional Research Ethics Committee. He is Associate Editor of the Journal of Medical Ethics and is a Senior Research Fellow in Philosophy at St. Benet's Hall, University of Oxford.

Susan Tansey is Medical Director (Paediatrics) at Premier Research Group Limited. She trained as a paediatrician in the NHS before joining the pharmaceutical industry in 1998. She has since worked for various companies, including several years at Pfizer (formerly Wyeth) designing and conducting global paediatric vaccine trials. Susan is a Consultant Pharmaceutical Physician, a Member of the Royal College of Paediatrics and Child Health (RCPCH), and a Fellow of the Faculty of Pharmaceutical Medicine (FPM). She currently holds the position of Associate Director for Industry for the Medicines for Children Network in the UK and sits on the RCPCH/Neonatal and Paediatric Pharmacists Group (NPPG) as the FPM Observer.

Marc Taylor is Chair of ISRCTN, a not-for-profit organisation that manages the unique identification of randomised controlled trials worldwide, Vice Chair of the UK Research Integrity Office, and member of the Health Research Authority's Confidentiality Advisory Group. Until 2011, he was head of R&D Systems and Governance in the Department of Health's Research and Development Directorate, and was the lead official for research governance, including national policy on the NHS Research Ethics Committee system and the UK Ethics Committee Authority. He has a background in NHS finance policy and in overseas development.

Bridget Young is Professor of Psychology at the University of Liverpool. Her research investigates psychological and communicative processes in health care and clinical research. Her recent published work has focused on communication in the clinical care of patients with cancer and stakeholder experiences of clinical trials. She is co-lead for the Patient Perspectives Theme of the Medical Research Council North West Hub for Trials Methodology Research. She also has responsibility for the clinical communication education of medical and dental students at the University of Liverpool.

List of abbreviations

ALL	acute lymphoblastic leukaemia
ALSPAC	Avon Longitudinal Study of Parents and Children
AML	acute myeloid leukaemia
Cafcass	Children and Family Court Advisory and Support Service
CRN: Children	Clinical Research Network: Children (formerly MCRN)
CTIMP	clinical trial of an investigational medicinal product
EMA	European Medicine Agency
Enpr-EMA	European Network for Paediatric Research
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GHRN	Global Health Reviewers' Network
HRA	Health Research Authority
ICR	Institute of Cancer Research
IRB	institutional review board
JLA	James Lind Alliance
KEMRI	Kenya Medical Research Institute
KIDS	Kids and families Impacting Disease through Science
MCRN	Medicines for Children Research Network
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PDCO	Paediatric Committee (EMA)
PIP	paediatric investigation plan

PSP	priority setting partnership(s)
PUMA	paediatric use marketing authorisation
RCPCH	Royal College of Paediatrics and Child Health
RCT	randomised controlled trial
REC	research ethics committee
RGF	research governance framework
ScotCRN	Scottish Children's Research Network
SIDS	sudden infant death syndrome
UKALL	acute lymphoblastic leukaemia
WHO	World Health Organization
YPAG	young persons' advisory group

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