Chapter 1

Context and ethos

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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

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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 leukaemia[10]

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, Szmukler 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 Psychiatry* **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, Adjuik 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 living[39]),[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, 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.

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+09062014152000 for information on NICE's promise to developguidance 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. Alonside 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

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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, Comite de Etica 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.

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[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 cent[76]) 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 institution[84]) 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

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[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 parent[89]) 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_heardwbAZIg.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 doctors[95] 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

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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.