Chapter 5

Developing research proposals: professionals' responsibilities

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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 Service[547] 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 lumber 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=WC0b01ac05801df74a.

[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

of the application of the Paediatric Regulation, available at: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf, at page 42.

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 Innvoative

[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.