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## *Seen But Not Heard? Children in Clinical Trials*

**Emma Cave\***

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### **Key words**

Clinical trials, Gillick, consent, medical research, children

### **Abstract**

The Medicines for Human Use (Clinical Trials) Regulations<sup>1</sup> put into effect the European Union Clinical Trials Directive 2001<sup>2</sup>, which aims to facilitate and harmonise standards in research across Europe. The Regulations apply only to ‘clinical trials of investigational medicinal products’ (CTIMPs). The author discusses the consent requirements which restrict the ability of competent minors to consent or assent. Additionally, concerns are raised regarding the risk benefit ratio applied in paediatric clinical trials. The Regulations may prove overly restrictive of research

\* School of Law, University of Leeds. I am grateful to Dr. Helen Pickworth for her expert medical advice. Thanks also to the anonymous reviewers. Any remaining medical misunderstandings are my own. An earlier draft of this paper was presented at a seminar, ‘Legal and Ethical Issues Surrounding the Involvement of Children in Health Care Research’, held at Lancaster University on 20-21 September 2007 and funded by the M.L.R. Seminar Competition.

<sup>1</sup> S.I. 2004/1031.

<sup>2</sup> E.C. 2001/20.

which is not of direct benefit to the research participants, to the detriment of child health generally.

## I. INTRODUCTION

Whilst a body of law exists relating to medical treatment of children, the law is relatively undeveloped regarding clinical research. Even when the child stands to benefit directly from the research, it cannot be said to be synonymous with treatment. Research is experimental and may be placebo-controlled. It is difficult and sometimes impossible to say whether or not a child will benefit from inclusion. The emphasis in clinical trials is on the results. The investigators aim to do the research participants good and hope to do them no harm, but ultimately it is future patients who stand to benefit. The ethical requirement of clinical equipoise in many trials ensures that risks and benefits are appropriately balanced, but research is innovative and therefore risk-laden. There is an element of altruism in subjecting oneself to research, a factor which makes informed consent the cornerstone of ethical research. Young children and adults lacking the requisite mental capacity cannot give a valid consent, but in order to develop medicine in those specialist areas, research is allowed and encouraged with special requirements for proxy consent.<sup>3</sup> To put it plainly, the law must balance first the rights and interests of the child research participant with the rights and interests of other children; and second a paternalistic desire to do what is in the best interests of the child with the libertarian goal of respecting childhood autonomy.

In order to run a clinical trial there must be approval from the licensing authority; the Medicines and Healthcare Products Regulatory Agency (MHRA), and

<sup>3</sup> See A. Pierro, L. Spitz, 'Informed Consent in Clinical Research: The Crisis in Paediatric Research' (1997) 349(9066) *The Lancet* 1703.

from a licensed research ethics committee (REC). The latter face the difficult task of balancing the relevant ethical factors. Ethical guidance exists, but it emanates from a variety of sources with varying degrees of consistency.<sup>4</sup> The law, which should provide a minimum standard of protection for both children's rights and interests, and societies interest in the furtherance of research, is vague and at times contradictory. The Medicines for Human Use (Clinical Trials) Regulations 2004 (hereafter Clinical Trials Regulations) were enacted to implement the European Union Clinical Trials Directive 2001<sup>5</sup> as amended in 2006<sup>6</sup> to implement the Good Clinical Practice Directive 2005<sup>7</sup>. The dual aims of the 2001 Directive were to facilitate European research and to offer universal protection to research participants in clinical trials. Accordingly, the UK Clinical Trials Regulations demand that research ethics committees have the relevant paediatric expertise to assess protocols involving child participants, or bring in an expert who has;<sup>8</sup> and set down a list of conditions and principles which must be applied. Contravention of those conditions and principles, examined below, is an offence<sup>9</sup>, as is providing false or misleading information to an ethics committee, or when seeking authorisation from the MHRA.<sup>10</sup>

Different countries responded to the Directive in different ways.<sup>11</sup> Some changed the way *all* research was regulated. Others, like the UK, created a new set of

<sup>4</sup> S. D. Edwards and M. J. McNamee, 'Ethical Concerns Regarding Guidelines for the Conduct of Clinical Research on Children' (2005) 31 *Journal of Medical Ethics* 351.

<sup>5</sup> E.C. 2001/20.

<sup>6</sup> Medicines for Human Use (Clinical Trials) Amendment Regulations (S.I. 2006/1928). They were further amended by the Medicines for Human Use (Clinical Trials Fees Amendments) Regulations 2004 (S.I. 2004/1157); the Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 (S.I. 2006/2984); and the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (S.I. 2008/941).

<sup>7</sup> E.C. Directive 2005/28/EC.

<sup>8</sup> Regulation 15(6).

<sup>9</sup> Regulation 49(1)(d). The offence is punishable by fine or imprisonment: Regulation 52.

<sup>10</sup> Regulation 50.

<sup>11</sup> See (2008) 15(2) *European Journal of Health Law*: a special issue devoted to medical research involving children across Europe.

rules that apply only to ‘clinical trials of investigational medicinal products’.<sup>12</sup> Other research (which constitutes about 85% of research applications put to RECs) is regulated through other statutes<sup>13</sup> and common law. The Clinical Trials Regulations impose special rules relating to children involved in clinical trials. In particular, they impose requirements relating to the appropriate risk benefit ratio and they impose special consent requirements.

The 1989 UN Convention on the Rights of the Child states that ‘children have the right to good quality health care – the best health care possible’. Yet, in both the USA and Europe there is a persistent and dangerous problem with our medicines. Too few of them are licensed for use in children.<sup>14</sup> If ten year old Sam develops cancer of the throat then it may be that drugs tested on and licensed only for use on adults might help him. His doctor might decide to administer the drugs ‘off-label’, judging the appropriate dose according to Sam’s height and weight. But Sam is not a miniature adult. Over dosing might lead to resistance, adverse reactions, or permanent health problems.<sup>15</sup> Under dosing might be ineffective.<sup>16</sup> Sam does not have an adult physiology; he is still growing and developing.

This problem is being addressed. The EU Regulation on Paediatric Medicines, which came into force in January 2007, makes requirements and offers incentives for

<sup>12</sup> A term which poses its own definitional quandaries. See <http://www.mhra.gov.uk/home/groups/l-unit1/documents/websitesources/con009394.pdf> (last visited 7 July 2009).

<sup>13</sup> Such as the Mental Capacity Act 2005 which relates to ‘non-clinical’ research on adults lacking mental capacity.

<sup>14</sup> See Editorial, ‘Paediatric Research Should Take Centre Stage’ (2004) 364(436) *The Lancet*, 732.

<sup>15</sup> See for example the recent trial which demonstrated the unnecessary use of antibiotic ointment in some childhood eye infections. P. Rose, A. Harnden, A. Brueggemann, R. Perera, A. Sheikh, D. Crook, D. Mant, ‘Chloramphenicol Treatment for Acute Infective Conjunctivitis in Children in Primary Care: A Randomised Double-blind Placebo-controlled Trial’ (2005) 366(9479) *The Lancet* 37. And see Editorial, ‘Let Kids be Kids’, (2004) 5(1) *Lancet Oncology*, 641.

<sup>16</sup> See for example P. Paolucci, K. Pritchard Jones, M. delCarmen, C. Garcinuno, M. Catapano, A. Iolascon, A. Ceci, ‘Challenges in Prescribing Drugs for Children with Cancer’ 9(2) (2008) *The Lancet* 176.

paediatric research on new medicines.<sup>17</sup> The USA offered similar incentives years ago.<sup>18</sup> The 2008 revision of the World Medical Association Declaration of Helsinki *Ethical Principles for Research Involving Human Subjects*, adds the following: ‘... Populations that are underrepresented in medical research should be provided appropriate access to participation in research.’<sup>19</sup>

There are usually four phases of clinical trial. Phase I introduces the novel drug to a small group of humans. Participants rarely benefit from the small doses of the drug and Phase I trials often utilise healthy volunteers.<sup>20</sup> Phase II tests efficacy and toxicity amongst a larger number of participants. There may or may not be direct benefit to the group in this phase. Phase III trials are usually large scale, multicentre, randomised controlled trials which test efficacy and toxicity. They may be placebo controlled or compare a standard and novel treatment. They are usually double blinded so that neither the patient nor the doctor administering the drug knows which of the treatments the patient is receiving. Phase III trials usually offer the prospect of some benefit to the group. Phase IV involves post market surveillance. To fill the information gap relating to dose requirement and toxicity in children in drugs already licensed for use in adults, the investigator might run a Phase II or III trial: he can usually offer some prospect of benefit to his research participants, but because they are children, special consent requirements are imposed.

<sup>17</sup> EU Regulation on Medicinal Products for Paediatric Use Regulation (E.C.) No. 1901/2006. See also European Commission, *Communication from the Commission — Guidance on the Information Concerning Paediatric Clinical Trials to be Entered into the EU Database on Clinical Trials (EudraCT) and on the Information to be Made Public by the European Medicines Agency (EMA), in Accordance with Article 41 of Regulation (EC) No 1901/2006*, (E.C.) 2009/C 28/01.

<sup>18</sup> Pediatric Research Equity Act 2003. Previous attempts by the US Food and Drug Administration to encourage paediatric research were of limited success. The ‘Pediatric Rule’ was struck down in 2002. See Editorial, ‘Paediatric Research Should Take Central Stage’, above n. 14.

<sup>19</sup> World Medical Association, *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, (1964, as amended in 2008).

<sup>20</sup> See P.R. Ferguson, ‘Clinical Trials and Healthy Volunteers’ (2008) 16 *Medical Law Review* 23.

Some diseases affect only children or present so differently in children that entirely new medications are required. For these medications in particular, after initial safety tests, Phase I must be carried out on children. The Clinical Trials Regulations prohibit healthy children from being recruited,<sup>21</sup> but children with the disease in question might be enrolled. However, the Regulations further require that there must be direct benefit to the group of children involved in the trial.<sup>22</sup> In the next sections we will examine the consent requirements for children entering all stages of clinical trial, and will consider the particular problem of enrolling children in Phase I and II trials where direct benefit to the group is questionable, before going on to consider the implications for children's rights.

## II. CONSENT REQUIREMENTS<sup>23</sup>

### *Clinical Trials Regulations and Common Law Compared*

Let us begin by establishing the law relating to medical *treatment*. We will then go on to compare this with medical research. Children over 16 can consent to medical treatment under section 8 (1) of the Family Law Reform Act 1969.<sup>24</sup> Section 8 (3)<sup>25</sup> leaves open whether consent by a child under the age of 16 might be effective and in

<sup>21</sup> Schedule 1, Part 4, demands that minors are included in the trial only where: '9. The clinical trial relates directly to a clinical condition from which the minor suffers or is of such a nature that it can only be carried out on minors'; and '11. The clinical trial is necessary to validate data obtained - (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods.'

<sup>22</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 10.

<sup>23</sup> For a general appraisal of consent requirements in research on children see M. Brazier and E. Cave, *Medicine, Patients and the Law* (Penguin, 2007), para 16.10.

<sup>24</sup> Family Law Reform Act 1969, s 8 (1) 'The consent of a minor who has attained the age of 16 years to any surgical, medical or dental treatment which, in the absence of consent, would constitute a trespass to his person, shall be as effective as it would be if he were of full age; and where a minor has by virtue of this section given an effective consent to any treatment it shall not be necessary to obtain any consent for it from his parent or guardian.'

<sup>25</sup> Family Law Reform Act 1969, s 8 (3) 'Nothing in this section shall be construed as making ineffective any consent which would have been effective if this section had not been enacted.'

the landmark ruling of *Gillick v. West Norfolk and Wisbech Area Health Authority*<sup>26</sup> the House of Lords empowered a minor to consent to medical treatment when she reaches an age and maturity to judge what the treatment entails and assess its benefits and disadvantages.

At common law, a *Gillick* competent child can give consent to treatment, but she cannot always withhold it if it is deemed to be in her best interests to receive treatment, provided someone consents on her behalf.<sup>27</sup> A *Gillick* competent child's right to consent is not exclusive: currently, her parent or the court can provide the consent if she withholds it, though they must act in her best interests in doing so. The child's autonomy rights are not omnipotent: they must be balanced with her welfare rights,<sup>28</sup> or her 'developmental interests'<sup>29</sup>.

What if the parents of a minor refuse to consent to life saving treatment? Section 3 of the Children Act 1989 introduced the concept of 'parental responsibility' which incorporates rights and powers.<sup>30</sup> The parental power to consent to the medical treatment of their child or to access the medical information needed to make that consent is limited to those situations when the child lacks capacity; the child agrees to parental inclusion; or the child's health or welfare is threatened by her decision.<sup>31</sup> As the term 'parental responsibility' implies, parental powers to consent to treatment of

<sup>26</sup> [1984] QB 581. Confirmed post Human Rights Act 1998 in *R (Axon) v Secretary of State for Health* [2006] EWHC 37 (Admin).

<sup>27</sup> *Re R (A Minor) (Wardship: Consent to Treatment)* [1992] Fam. 11; *Re W (A Minor) (Medical Treatment: Court's Jurisdiction)* [1993] Fam. 64 discussed in E. Cave, 'Adolescent Consent and Confidentiality in the UK' (2009) 16(4) *European Journal of Health Law* (forthcoming).

<sup>28</sup> M. Freeman, 'Taking Children's Rights More Seriously' (1992) 6 *International Journal of Law, Policy and the Family* 52.

<sup>29</sup> J. Eekelaar, 'The Emergence of Children's Rights' (1986) 6 *Oxford Journal of Legal Studies* 161. For a contrasting view see M. Brazier, C. Bridge, 'Coercion or Caring: Analysing Adolescent Autonomy' (1996) 16 *Legal Studies* 84.

<sup>30</sup> Children Act 1989, s 3(1) 'In this Act "parental responsibility" means all the rights, duties, powers, responsibilities and authority which by law a parent of a child has in relation to the child and his property.'

<sup>31</sup> See for example, *Gillick v. West Norfolk and Wisbech Area Health Authority* [1984] Q.B. 581; *Re R* [1991] 3 W.L.R. 592; *Re W* [1992] 3 W.L.R. 758; *R (on the application of Axon) v. Secretary of State for Health & Another* [2006] E.W.H.C. 37 (Admin).

their child are limited by a duty to the child which is encapsulated in the welfare principle. Where treatment is in the best interests of a child, the parent's refusal may be overruled by the courts.<sup>32</sup>

Now that we have considered the child's right to give or withhold consent to *treatment*, let us turn to research. Research is different to treatment – even when the two are combined. Research is not wholly centred on the individual trial participant. The Declaration of Helsinki demands that 'concern for the interests of the subject must always prevail over the interests of science and society',<sup>33</sup> but the purpose of research is primarily to produce scientifically valid results.

Imagine a research project designed to enhance the emotional and psychological wellbeing of participant children on transplant waiting lists. As this is not a clinical trial, the Clinical Trials Regulations do not apply and, in the absence of specific common law on this issue, we must look to guidance from professional bodies. The Medical Research Council (MRC) advises that, due to the inherent risks involved in research combined with treatment *Gillick* will *probably* apply, but dual parental consent should be encouraged.<sup>34</sup> Thus, a *Gillick* competent child should consent in addition to her parent or guardian. This matter has yet to be tested in court, but it is possible that a doctor who secures the consent of the *Gillick* competent child but not her parent or guardian may commit a battery when he treats her in the course of his research. A *Gillick* competent child who wishes to enter into a research project without her parent's consent would need to bring the matter before a court arguing that the research is in her best interests. If it is not in her best interests, her argument

<sup>32</sup> For example, *Re B* [1981] 1 WLR 1421 involving the authorisation of a life saving operation on an infant against the wishes of the parents.

<sup>33</sup> WMA, Declaration of Helsinki (1996), para 5.

<sup>34</sup> Medical Research Council, *Medical Research Involving Children* (2004), at paragraph 5.3.1.a. The General Medical Council, *0-18 Years: Guidance to All Doctors* (2007) para 38 advises that: 'If [children under the age of 18] are able to consent for themselves, [the doctor] should still consider involving their parents, depending on the nature of the research'.

that her parents have no right to withhold consent on her behalf will carry little weight. As we shall see, any right she has to autonomy and privacy under Article 8 (1) of the European Convention on Human Rights must be balanced with the Article 8 (2) limitations which include the protection of health.

Once enrolled in the hypothetical research project, can a *Gillick* competent child withdraw from it without her parent's consent? The General Medical Council (GMC) recommends that 'children and young people should *not usually* be involved in research if they object or appear to object in either words or actions, even if their parents consent'<sup>35</sup> (italics added). The implication is that in rare circumstances, their request to withdraw might be overruled. Arguably the GMC guidance mirrors the common law position in England and Wales in relation to children withholding consent to treatment. If withdrawal from the research might damage the child's mental health she might be forced to continue. But this has yet to be tested in a court of law. Research is inherently uncertain and it is difficult to conceive of a situation where forcing a child to undergo research against his wishes would be in his best interests.

In the above example, the research had potential to confer direct benefit on participants. Where it does not (imagine, for example, a project which aims to monitor rather than treat the emotional states of children on transplant lists) it is unlikely that *Gillick* would apply.<sup>36</sup> The researcher should seek the consent of the child's parents and the assent of the trial participant herself.

There is much debate as to whether *Gillick ought* to apply to therapeutic research, a thorough consideration of which is beyond the scope of this paper. Hunter and Pierscionek argue that an investigator has a personal interest in the research

<sup>35</sup> GMC, *0-18 Years: Guidance to All Doctors* (2007), para 38.

<sup>36</sup> *Re W (A Minor) (Medical Treatment)* [1992] 4 All ER 627, [635] per Lord Donaldson.

which may affect his ability to judge *Gillick* competency in his potential participants.<sup>37</sup> Only in two research situations, they argue, should *Gillick* competency apply: First when the research is of minimal risk and is of direct benefit to the participant and second when it is of minimal risk and great societal benefit. In both cases they argue that *Gillick* competency ought to be assessed by someone independent of the research project.

In clinical trials of investigational medicinal products, the Clinical Trials Regulations and not the Family Law Reform Act apply. The Regulations apply throughout the UK. They require that in trials involving minors, defined as children under the age of 16, the written consent of the person with legal responsibility (the parent / guardian / court) for minors must be obtained. In the words of Schedule 1, Part 4, Paragraph 13; ‘Informed consent given by a person with parental responsibility or a legal representative to a minor taking part in a clinical trial shall represent the minor's presumed will.’

There is no parallel to section 8 (3) of the Family Law Reform Act; *Gillick* does not apply here. However capable or mature, a minor is unable to give sole consent until the occasion of his 16<sup>th</sup> birthday. As we shall see in the next section, this position is supported in international ethical guidelines on the basis that the additional risks inherent in research over pure treatment warrant special controls. An arbitrary age limit for sole consent is at least compatible with the international guidance.

If a 15 year old has no legal right to give sole consent, might his assent be required in addition to his legal representatives’ consent? In essence the legal representative would give the legal consent, but the minor would provide permission to the limit of his understanding. There is evidence that younger children would be

<sup>37</sup> D. Hunter, B.K. Pierscionek, ‘Children, Gillick Competency and Consent for Involvement in Research’ (2007) 33 *Journal of Medical Ethics* 659.

capable of providing such assent.<sup>38</sup> But there is no such provision in the Clinical Trials Regulations. On a strict reading of the Regulations, a 15 years old has no autonomy right to give assent and he has no legal right to withhold it. The Regulations do require that the child is ‘given information according to his capacity of understanding’<sup>39</sup> and that: ‘The explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in the previous paragraph to refuse participation in, or to be withdrawn from, the clinical trial at any time is *considered* by the investigator.’ (Italics added).<sup>40</sup> But whilst they require that a minor’s explicit wishes are ‘considered’, they do not give his views or wishes any legal force unless the above provision is read in conjunction with the relevant and rather ambiguous provision of the Declaration of Helsinki, which I will examine in the next section. An examination of international guidelines reveals that they either promote dual assent or give the capable child a right to withdraw or refuse participation. Forcing an adolescent who is capable of understanding the nature and implications of his decision to participate in a clinical trial against his will is unethical and potentially unlawful. The Regulations should be amended to clarify a situation that is likely to confuse researchers and ethics committees.

### *Dual Consent and the International Guidelines*

<sup>38</sup> F. Baylis, J. Downie, ‘The Limits of Altruism and Arbitrary Age Limits’ (2003) 3(4) *The American Journal of Bioethics* 19, arguing that children of 14 and above could provide such assent; and T. M. Burke, R. Abramovitch, and S. Zlotkin, ‘Children’s Understanding of the Risks and Benefits Associated with Research’ (2005) 31 *Journal of Medical Ethics*, 715, suggesting that children as young and six can understand the necessary concepts involved in research if age-appropriate modules of information are used.

<sup>39</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 6.

<sup>40</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 7.

The international guideline most restrictive of children's rights to provide assent is the Council of Europe's Oviedo Convention.<sup>41</sup> The UK is not a signatory to this Convention but Plomer has persuasively argued that it will be hugely influential in the European Court of Human Rights when implementing the European Convention of Human Rights,<sup>42</sup> so it is worthy of our consideration. It was supplemented in 2005 with the *Additional Protocol Concerning Biomedical Research*. Like the Clinical Trials Regulations, it demands that a legal representative gives consent on behalf of the minor and there are no provisions for dual consent from a minor who is in fact able to consent. However, Article 15 demands that '...The opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity',<sup>43</sup> and further requires that the minor 'does not object'.<sup>44</sup> So whilst there is no requirement of assent of a child capable of understanding the implications, there is a requirement that he does not withhold assent. The Regulations, it will be remembered, merely require that the explicit wishes of a minor capable of understanding the relevant information to withdraw or refuse to participate are 'considered'.<sup>45</sup>

The Council for International Organisations of Medical Sciences (CIOMS) is clear. In addition to parental permission, it recommends that: '[T]he agreement

<sup>41</sup> Council of Europe, *Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine* (ETS No 164, 1997).

<sup>42</sup> A. Plomer, 'Medical Research, Consent and the European Convention on Human Rights and Biomedicine' in A. Garwood-Gowers, J. Tingle, and T. Lewis (eds.), *Healthcare Law: The Impact of the Human Rights Act 1998* (Cavendish Publishing 2001) at 313–330; A. Plomer, *The Law and Ethics of Medical Research: International Bioethics and Human Rights* (London: Cavendish, 2005), chapter 1.

<sup>43</sup> Council of Europe, *Additional Protocol Concerning Biomedical Research*, (Strasbourg, 2005), article 15 (1) (iv).

<sup>44</sup> *ibid*, article 15 (1) (v).

<sup>45</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 7.

(assent) of each child has been obtained to the extent of the child's capabilities; and, a child's refusal to participate or continue in the research will be respected.'<sup>46</sup>

What of the Clinical Trials Directive 2001 which the Clinical Trials Regulations implement? Let us compare relevant provisions: Article 4 (a) of the Clinical Trials Directive provides that: '[T]he informed consent of the parents or legal representative has been obtained; consent *must* represent the minor's presumed will and may be revoked at any time, without detriment to the minor.' (Italics added). Schedule 1, Part 4, Paragraph 13 of the UK Clinical Trials Regulations provide that: 'Informed consent given by a person with parental responsibility or a legal representative to a minor taking part in a clinical trial *shall* represent the minor's presumed will.' (Italics added).

The Directive is ambiguous. Does it demand that the parent or representative represents the will of the minor? Or does it, as the Regulations have endorsed, presume it? The UK chose the course most restrictive of the adolescent's right to give assent.

The European Commission's Ad hoc Working Group on the Implementation of the Directive<sup>47</sup> reported in 2008 and recommended that in addition to the consent of the minor's legal representative, the assent of the minor should be sought and in the event of his express wish to withdraw from the trial, his 'will should be respected'. Whilst this is significant and may result in revision of the Clinical Trials Regulations, the report emphasises that whilst they advise that the assent of the capable minor is

<sup>46</sup> CIOMS, *International Ethical Guidelines for Biomedical Research Involving Human Subjects Guideline* (2002), guideline 14. Though see below page 000 for an exception to this rule.

<sup>47</sup> European Commission, Recommendations of the Ad Hoc Group for the Development of Implementing Guidelines for Directive 2001/20/EC Relating to Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population* (2008). [http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical\\_considerations.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/ethical_considerations.pdf) (last visited 7 July 2009).

sought, it is not a legal requirement. Thus it seems possible that in the UK supplementary guidance rather than clear and unambiguous legal provision may be opted for.

Yet the endorsement by both the Clinical Trials Directive and the UK Clinical Trials Regulations of the World Medical Association's Declaration of Helsinki, as amended in 1996,<sup>48</sup> strengthens the importance of both obtaining assent of the capable minor and recognising his right to withdraw that assent. Paragraph 1.11 provides that:

... when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever this minor child is *in fact* able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.<sup>49</sup> (Italics added).

There is some ambiguity here. The words '*in fact* able to consent' may, as I argue, impose a subjective test for capacity to consent. That is, for the purposes of this provision, competence should be judged according to capacity rather than status. Alternatively these words may connote the acceptability of an objective, status-based approach. A country which endorses a status-based test for consent whereby a minor can consent from the age of 16 would not, on this view, breach the guideline by refusing to recognise the right of a 15 year old to assent.

<sup>48</sup> World Medical Association, *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, (1964, as amended in 1996) Para I.11.

<sup>49</sup> World Medical Association, *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, (1964, as amended in 1996) Para I.11.

Version six clarified the matter in 2000, but other aspects of the Declaration, in particular its stance on placebo-controlled trials, were contentious.<sup>50</sup> The sixth version of the Declaration of Helsinki predated the Clinical Trials Directive by a year, the Regulations by four, and the GCP Directive<sup>51</sup> (on the basis of which the Regulations were amended) by five. Yet all refer expressly to the 1996 version. A seventh version was promulgated in 2008. The World Medical Association maintains that: ‘The current (2008) version is the only official one; all previous versions have been replaced and should not be used or cited except for historical purposes’,<sup>52</sup> but the 2008 version has no force in this context. The debate about whether the Clinical Trials Regulations should be amended to as to reflect the most recent version of the Declaration, we must leave to another time.

The 2008 version is more stringent in its provisions. Like the 1996 version, it demands that competent participants give informed consent,<sup>53</sup> but in addition it demands that an incompetent child’s assent should be obtained where he is capable of giving it.<sup>54</sup> The UK Clinical Trials Regulations do not expressly endorse the requirement that capable minors provide assent, but they do endorse the 1996 version of the Declaration and arguably ambiguity in the 1996 version should be resolved in the light of the clear 2008 provision.

<sup>50</sup> A summary of the reactions to the controversial 2000 revisions can be found at ‘The International Response to Helsinki VI’ [http://www.wma.net/e/ethicsunit/pdf/intl\\_response\\_helsinki.pdf](http://www.wma.net/e/ethicsunit/pdf/intl_response_helsinki.pdf) (last visited 7 July 2009).

<sup>51</sup> EC Directive 2005/28/EC.

<sup>52</sup> <http://www.wma.net/e/ethicsunit/helsinki.htm> (last visited 7 July 2009).

<sup>53</sup> World Medical Association, *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, (1964, as amended in 2008) Para 24: ‘... After ensuring that the potential subject has understood the information, the physician ... must seek the potential subject’s freely-given informed consent, preferably in writing.’

<sup>54</sup> World Medical Association, *Declaration of Helsinki*, (1964, as amended in 2008) Para 28: ‘When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject’s dissent should be respected.’

In conclusion, a failure to seek the assent of a capable 15 year old is unethical. It might also be unlawful. The European Convention on Human Rights protects everyone, regardless of age. If treatment were forced upon a competent adult, it would breach his rights under Articles 3, 5, 8 and 14. As Fortin points out, the European Court of Human Rights has asserted that ‘a measure which is a therapeutic necessity cannot be regarded as inhuman or degrading’<sup>55</sup> so if the research offers a non-consenting adolescent her only hope of life then it will not breach Article 3. A similar argument exists in relation to Article 5 which confers a right to liberty and security of persons subject to a number of exceptions including Article 5 (1) (e) which allows the detention ‘of persons of unsound mind’. Article 8<sup>56</sup> protects the privacy<sup>57</sup> and autonomy<sup>58</sup> rights of both parents and minors. We might accept Fortin’s contention<sup>59</sup> that Article 8 (1) should be read so as to amalgamate welfare and rights. Consequently, if the trial is the minor’s only chance of life, or indeed, if it offers her substantial health benefits, it might be argued that there is no breach of Article 8 (1). Alternatively, if Article 8 (1) were viewed as offering prima facie protection to the minor’s right to autonomy, her ‘conflicting’ welfare interests could be balanced against this right by invoking Article 8 (2).<sup>60</sup> This argument is strengthened further by

<sup>55</sup> J. Fortin, ‘Accommodating Children’s Rights in a Post Human Rights Act Era’ (2006) 69(3) M.L.R. 299, at 316 referring to *Herczegalvy v. Austria* (1992) 15 E.H.R.R. 437, at [82].

<sup>56</sup> Human Rights Act 1998, Article 8(1): ‘Everyone has the right to respect for his private and family life, his home and his correspondence.’

<sup>57</sup> Parental and child privacy rights under Article 8 are discussed by J. Loughrey, ‘Medical Information, Confidentiality and a Child’s Right to Privacy’ (2003) 23 L.S. 510; and J. Loughrey, ‘Can you Keep a Secret?’ [2008] CFLQ 312.

<sup>58</sup> See for example, S. Choudhry, H. Fenwick, ‘Taking the Rights of Parents and Children Seriously: Confronting the Welfare Principle under the Human Rights Act’ (2005) 25 OJLS 253; A. Hall ‘Children’s Rights, Parents’ Wishes and the State: The Medical Treatment of Children’ [2006] Fam Law 317; J. Fortin, ‘Children’s Rights – Substance or Spin?’ [2006] Fam Law 757; R. Taylor, ‘Reversing the Retreat from Gillick? R (Axon) v Secretary of State for Health’ [2007] CFLQ 81.

<sup>59</sup> J. Fortin, n. 55 above, at 311.

<sup>60</sup> Human Rights Act 1998, Article 8(2): There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.

the positive obligation under Article 2 to protect life. Thus, a minor under the age of 16, whose life or health is dependent upon enrolment in the clinical trial will be unable to assert a right to assent. In other cases the status-based test endorsed in the Clinical Trials Regulations may, if utilised to force non-consensual treatment on a de facto capable 15 adolescent, breach his human rights.

The solution is to recognise the capable child's right to assent and to withhold assent, preferably by amending the Regulations. The right to assent might be framed so as to incorporate an exception where the research is of direct benefit to the health of the child. Children would have the power to withhold assent in most circumstances and would, in these circumstances, also hold the power to prevent disclosure to parents. Only where research is of direct medical benefit would disclosure be made to parents contrary to the wishes of the child, and the child could be obliged to undergo the research. Other countries have successfully legislated to this effect,<sup>61</sup> though a full consideration of an exception to the right to assent or withdraw in the best interests of the child are beyond the scope of this paper. Alternatively the 1996 version of the Declaration of Helsinki might be interpreted so as to require dual consent of capable under 16 year olds, but, as we have seen, this right would be difficult to restrict where the capable child withholds consent against his best medical interests.

### III. THE RISK BENEFIT RATIO

<sup>61</sup> In the USA, for example, the legal requirement in clinical trials that capable children give assent is subject to two exceptions: (1) The child is incapable of giving assent. (2) There is 'a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research'. Department of Health and Human Services, *Regulations for the Protection of Human Subjects* 45 C.F.R. 46.408. See also CIOMS, n. 46 above, Commentary to Guideline 14: Guideline 14 requires that, in addition to parental permission, the assent of the child is obtained where the child is *in fact* capable of giving it.

Debates about the appropriate risk benefit ratio in research are frequent features in the research ethics literature. Space does not allow me to recount them all. In the next section I shall compare the legal provisions contained in the Regulations with international guidance to monitor consistency and compliance, before going on to analyse the effects of the Clinical Trials Regulations for paediatric research.

### *The Clinical Trials Regulations*

The Clinical Trials Regulations state that children should only be enrolled in research where it ‘can only be carried out on minors’<sup>62</sup> and more prohibitively, that ‘some direct benefit of the group of patients involved in the clinical trial is to be obtained from that trial’.<sup>63</sup>

Part 2 of Schedule 1 sets down principles and conditions which apply to all trials. They include the provisions that:

2. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and shall prevail over interests of science and society.

Risk is relevant, but the benefit against which it is balanced, may be to future patients.

Part 4 of Schedule 1 imposes additional conditions relating to the balancing of risk

<sup>62</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 9.

<sup>63</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched 1, Part 4, Para 10.

and benefit in research on minors. It demands that there must be a direct benefit to the group enrolled in the research. Thus placebo controlled research is not unlawful, provided the 'group' will benefit. However a research project that confers no direct benefit on the group cannot be sanctioned even if it would help future children suffering from the condition, cannot be carried out on adults, child and parental consent is obtained and the research is of minimal risk.<sup>64</sup> A Phase I clinical trial designed to test toxicity and tolerability to a new drug is unlikely to confer direct benefit to the group, but it may represent the only chance of survival to minors who have exhausted all other treatment options. Even a small chance of benefit may satisfy those minors and their parents, but it is insufficient to satisfy the Regulations.

#### *Direct Benefit and the International Guidelines*

The Regulations impose a 'direct positive benefit' test. International guidance recommends a significantly less restrictive stance. The Council for International Organisations of Medical Sciences (CIOMS), for example, recommends a 'low risk' standard.<sup>65</sup> Research that does not confer a direct benefit on the participant is acceptable if the risk of the procedure is sufficiently low.

The 1996 version of the Declaration of Helsinki is difficult to reconcile with the Regulations, despite their endorsement of the Declaration, because it uses different language. Rather than requiring 'direct benefit', it separates therapeutic and non-therapeutic research and imposes additional restrictions on the latter where

<sup>64</sup> This point was made by M. Brazier and E. Cave, n. 23 above, p 425.

<sup>65</sup> CIOMS, n. 46 above, para 9: 'Special limitations on risk when research involves individuals who are not capable of giving informed consent: When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.'

participants must be volunteers,<sup>66</sup> and the research must not cause harm to the participants.<sup>67</sup> No specific additional requirements relate to the appropriate risk benefit ratio for research involving minors, though, as we have seen, the Declaration of Helsinki does require that the minor, where capable, gives his assent alongside his legal representative's consent. Still, the requirement of voluntariness might be seen to preclude minors incapable of giving consent, and clearly non-therapeutic research would be inappropriate if against the medical best interests of the minor, but it does not go so far as to demand that the group actually benefit. Research that is neutral in terms of benefit would be acceptable, subject to consent requirements.<sup>68</sup>

Like the Clinical Trials Regulations, the 2008 version of the Declaration of Helsinki drops the therapeutic / non-therapeutic research distinction. Therapeutic research usually involves treatment but it does not necessarily confer benefit. Trials usually compare a novel treatment with an existing treatment or with a placebo. A patient assigned to the latter arm of the trial cannot expect any benefit. Also, the risks involved might be high due to the experimental nature of the drug. Non-therapeutic research, on the other hand, may be of smaller risk or no risk at all if, for example, samples are collected at the same time as samples necessary for treatment are collected. The 2008 version is not endorsed by the Regulations but it does provide further guidance as to what level of benefit is required by incompetent minors participating in research.

The 2008 version of the Declaration states that '[Incompetent minors] must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential

<sup>66</sup> Section III, para 2.

<sup>67</sup> Section III, para 3.

<sup>68</sup> For a supporting stance, see Royal College of Paediatrics, 'Child Health: Ethics Advisory Committee Guidelines for the Ethical Conduct of Medical Research Involving Children (2000) 82 *Archives of Disease in Childhood* 177.

subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.<sup>69</sup> A clinical trial that does not promise direct benefit to the individual or group but does hold out the prospect of benefiting other children with similar health problems would potentially be acceptable under the Declaration of Helsinki 2008, but not under the Clinical Trials Regulations.

Analysis of the Oviedo Convention reveals a similar conclusion. Article 6 (1) demands that research on individuals unable to consent must confer upon him or her, direct benefit. However exceptions to this rule are contained in Articles 17 (2):

Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to ... the following additional conditions:

- i.* the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
- ii.* the research entails only minimal risk and minimal burden for the individual concerned.

Again, the stance is less restrictive of research than the stance taken in the UK Clinical Trials Regulations. Research that is neutral in terms of benefit to the individual or group might be sanctioned if other conditions are satisfied.

<sup>69</sup> World Medical Association, *Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects*, (1964, as amended in 2008) Para 27.

A similar picture emerges when the Clinical Trials Regulations are contrasted with ethical guidance in place in the UK prior to the implementation of the Regulations, and co-existing in relation to the 85% of research which does not fall into the clinical trial category.

The Medical Research Council (MRC) states that ‘it is ethical for a healthy child to participate in research as long as appropriate consent has been obtained, there is no more than minimal risk and the research is not against the child’s interests’.<sup>70</sup> In cases where there is no benefit to the child but the research will help others with a similar condition, the MRC advises that even if it poses greater than minimal risk, it might be acceptable after ‘serious ethical consideration’,<sup>71</sup> for the research to go ahead. Research ethics committees will consider a range of factors such as the magnitude of the condition, probability of the research achieving its aims, resources and timing. The next section considers the implications of the restrictive stance taken in the Clinical Trials Regulations and analyses the meaning of ‘direct benefit’.

#### *Direct Benefit to the Group*

We have seen that the 1996 Helsinki Declaration recommends that non-therapeutic research must not cause harm to the participants and I have argued that this might be interpreted so as to prohibit research which is against the medical interests of the participant. But it does not go so far as to demand that research is of positive direct benefit to the group. The word ‘benefit’ connotes the *enhancement* of well being. It must produce a benefit that would not be attainable without being entered into the research project.

<sup>70</sup> Medical Research Council, *Medical Research Involving Children* (2004), para. 4.3.1.

<sup>71</sup> MRC *ibid.*, para. 4.3.

And what of the word ‘direct’? This signifies an immediate bearing. It can be contrasted with the parallel requirement in the Clinical Trials Regulations protecting adults lacking mental capacity, where benefit need not be ‘direct’. There the Clinical Trials Regulations require that: ‘There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit to the subject outweighing the risks or produce no risk at all.’<sup>72</sup> Imagine a trial testing two licensed medicines to limit the effects of Alzheimer’s disease. There is clinical equipoise as to which is preferential. This is the preferred ethical basis for a randomised controlled trial because the doctor can fulfil his ethical duties to participants assigned to each arm of the trial by way of offering each the best proved treatment, whilst also producing scientifically valid results.<sup>73</sup> Subject to consent requirements, it is not unlawful to enrol an adult lacking the mental capacity to consent into this trial because he will benefit from the medication (though not ‘directly’ in that he would have received one of the medicines in any event) and the risks are minimal. Similarly, if there was evidence that a new medicine might be preferential to the existing best proven treatment, it would be acceptable for the research to go ahead, even though the participant might be assigned the existing rather than the novel treatment, because he would not be considered to have engaged in additional risk.

For minors however: ‘Some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial’.<sup>74</sup> This leads to two potential problems. First, a trial to test a drug which is significantly cheaper to produce but just as efficacious as the existing best proven treatment will not lead to direct benefit for the group and therefore cannot be sanctioned. Second, because research is by nature

<sup>72</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched. 1, Part 5, Para. 9.

<sup>73</sup> B. Freedman, ‘Equipoise and the Ethics of Clinical Research’ (1987) 317 *The New England Journal of Medicine*, 141.

<sup>74</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched. 1, Part 4, Para. 10.

experimental it is uncertain whether or not investigators can promise direct benefit as the Clinical Trials Regulations demand. Ethically a trial should only commence if there is collective equipoise at the outset, and during the course of the trial, that equipoise will be disturbed – that is, the trial will prove that one treatment is in fact preferable to the other.<sup>75</sup> The ease with which direct benefit to the group might be predicted depends on the type of trial. A Phase III trial comparing placebo with a novel treatment is likely to result in direct benefit to the group. A Phase IV trial determining which of two licensed treatments are most efficacious will also reveal that one treatment is preferable to the direct benefit of those assigned to that arm of the trial. A Phase III trial comparing a novel drug with an existing drug, however, should only go ahead if there is strong evidence that the novel drug will have advantages over the existing one. If it is proved more efficacious then those assigned the novel drug will have benefited from the trial, but if it is not then neither those assigned the novel drug, nor those assigned the existing drug (which they would have received in any event) would have directly benefited *from the trial*. Such a trial could proceed using consenting adult participants, or even non-consenting adults with mental incapacity (provided other safeguards were followed), but not in children under 16. There is a resulting tension between collective clinical equipoise and the Regulations. The greater the certainty that the trial drug is preferable to existing treatment, the easier it is to satisfy the requirement that there is direct benefit to the group, but the harder it is to satisfy the ethical requirement of collective equipoise.

### *Defining Direct Benefit*

<sup>75</sup> B. Freedman, n. 73 above. According to Freedman, clinical equipoise arises where there 'exists . . . an honest, professional disagreement among expert clinicians about the preferred treatment'. Freedman demands that '...the results of a successful trial should be convincing enough to resolve the dispute among clinicians'.

To avoid this conclusion, a wider interpretation of the term ‘direct benefit’ might be considered. I shall contrast two definitions: The first incorporates wider benefits to the group such as the benefits altruism will bring to their emotional well being. The second involves direct *medical* benefit.

The requirement of direct benefit to the group may incorporate non-medical benefits such as emotional or social benefits. This inevitably involves a balancing exercise, but it may be argued that at times the risks to the child participant are so small or are non-existent so that wider interests (societal or emotional interests) warrant inclusion of the child. Essentially, the argument is that where research is not *against* their medical interests or their autonomy interests (individuals should have the right to refuse if capable of making that decision), it could be viewed as being in their social or emotional interests to participate and this in turn could be viewed as a direct benefit.

John Harris argues that patients and research participants benefit from living in a society where good research is prioritised.<sup>76</sup> He argues that, where risks are minimal and the research is not contrary to their own interests ‘if any assumptions are made, they should be that people are public spirited and would wish to participate’.<sup>77</sup> It might therefore be assumed that for children capable of ‘public spiritedness’ but still not old enough to consent, participation might be of benefit to them even if it is not of *medical* benefit to them.

The ethical arguments for the inclusion of children in some types of research, despite their inability to provide a valid consent are strong. However, whilst inclusion might be viewed as being in the interests of children, it cannot be said on these

<sup>76</sup> J. Harris, ‘Scientific Research is a Moral Duty’ (2005) 31 *Journal of Medical Ethics* 242. But see I. Brassington, ‘John Harris’ Argument for a Duty to Research’ 21(3) (2007) *Journal of Medical Ethics* 160 and S. Shapshay, K.D. Pimple, ‘Participation in Biomedical Research is an Imperfect Moral Duty: A Response to John Harris’ (2007) 33 *Journal of Medical Ethics* 414.

<sup>77</sup> J. Harris, *ibid.*, at 245.

grounds alone to be to their ‘direct benefit’ as the Clinical Trials Regulations require. As we have seen, the Clinical Trials Regulations require ‘benefit outweighing the risks or produce no risks at all’ in relation to adults lacking the mental capacity to consent. The benefits to society or altruistic motives might be relevant in this context, but the stricter requirement of ‘direct benefit to the group’ in trials involving children demands more.

Now let us turn to the concept of direct *medical* benefit. In practical terms, it might be argued that any minor entering a clinical trial will enjoy direct medical benefit purely by virtue of the extra monitoring they will receive. Where research is combined with medical treatment this argument is counteracted by the 1996 Helsinki Declaration’s recommendation that the ‘refusal of the patient to participate in a study must never interfere with the physician–patient relationship’.<sup>78</sup> In principle, if the patient should suffer no medical detriment by withdrawing from the trial he should receive no direct medical benefit merely by virtue of enrolling. It is the medical treatment received that must confer the benefit rather than the benefits in kind associated with extra health monitoring.

But what of research which is not combined with treatment? Can there be direct benefit in this case? Imagine that twenty children between aged 8 and 12 are enrolled in a trial designed to monitor their sleep patterns following the administration of a 5 mg dose of the hypothetical drug, *Child-Rem*, a paracetamol-based children’s medicine. All receive a comprehensive health check. None are harmed by the low dose of paracetamol. Might we argue that they have directly benefited from the research?

<sup>78</sup> Paragraph II.4. This is endorsed in the Declaration of Helsinki (2004) para. 31.

On the 1996 version of the Declaration of Helsinki it might be argued that the children have benefited though it is debatable as to whether that benefit is direct. The benefit comes from the extra monitoring rather than the research itself. The 2008 version abandons the concept of non-therapeutic research in favour of the concept of 'no direct benefit'. It envisages direct benefit to be a matter of medical advantage (i.e. *benefit*) related to the trial product rather than the incidental monitoring (i.e. the benefit must be *direct*). Arguably the 1996 version should be interpreted in this light. Further it would be counter-intuitive, given the intention of the Declaration to impose additional safeguards on non-therapeutic research, to insist that extra monitoring cannot lead to direct benefit in therapeutic research but can in non-therapeutic research.

King distinguishes direct benefit from aspirational benefit (the benefits of altruism, society and future patients) and collateral benefit (such as the wider benefits from extra monitoring and health checks).<sup>79</sup> It is direct medical benefit to which the Regulations refer. Otherwise the framers would not have inserted the additional requirement that benefit be direct into the provision relating to minors whilst omitting the crucial word from the provisions relating to adults lacking mental capacity to consent. The imposition of this rule might have far reaching consequences for paediatric clinical trials, not only, as we saw in the previous section, in Phase III trials in which it might be difficult to predict the benefits of the trial drug, but also when it is not possible to forecast direct benefit due to the early stage of the research.

### *Phase I Trials*

<sup>79</sup> N. King, 'Defining and Describing Benefit Appropriately in Clinical Trials' (2000) 28 *Journal of Law and Medical Ethics* 332.

Not all Phase I studies involve healthy volunteers. After initial safety tests,<sup>80</sup> treatments relating directly to childhood diseases often need to be tested on children. The Clinical Trials Regulations demand that: ‘A trial should be initiated and continued only if the anticipated benefits justify the risks.’<sup>81</sup> Proving direct benefit and balancing risk and benefit pose particularly difficult problems when dealing with rare diseases which manifest only in children. Let us first assess the problems inherent in proving direct benefit.

Phase I trials are designed to test the safety of the procedure and any benefit to the research participants is usually a bonus, but in the UK paediatric Phase I clinical trials cannot be conducted on this basis. Research is experimental and investigators can only talk in terms of potential harms and benefits, yet the Clinical Trials Regulations do not merely require that ‘some direct benefit to the group is *anticipated*’ (my italics). They require the demonstration through previous research on adults or other means that ‘some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial’.<sup>82</sup> In the USA there is provision for an Institutional Review Board (the equivalent of our Research Ethics Committees) to waive the requirements of direct benefit and minimal risk ‘in accordance with sound ethical principles’.<sup>83</sup> A lack of a similar exception in the UK Clinical Trials Regulations may prove particularly restrictive of research into cures for rare childhood diseases.

Canavan disease, for example, is a rare disorder which usually kills children before they reach their teens by preventing the body from producing myelin, which

<sup>80</sup> Under the Medicines for Human Use (Clinical Trials) Regulations 2004 Sched. 1, Part 4, para. 11, a trial involving minors can only proceed if it is necessary to validate data from clinical trials involving adults, or from other research.

<sup>81</sup> Medicines for Human Use (Clinical Trials) Regulations 2004, Sched. 1, Part 2, para. 2.

<sup>82</sup> Medicines for Human Use (Clinical Trials) Regulations 2004 Sched. 1, Part 4, para. 10.

<sup>83</sup> Department of Health and Human Services, *Regulations for the Protection of Human Subjects* 45 C.F.R. 4645, subpart D.

allows the brain to send messages to the spinal cord. Affected children cannot usually walk and lose the ability to speak and, eventually, to swallow. Early Phase I trials enabled children to regain some muscle control but the gene did not reach many parts of the brain. Building on these results, later research proved more successful.<sup>84</sup> It is doubtful, given the known potential risks of gene therapy trials and the limited benefits of a Phase I trial, whether the early trials searching for a cure for Canavan disease would have been sanctioned today under the protective umbrella of the Clinical Trials Regulations.

Similarly, when developing a novel treatment for a childhood cancer the investigator might have difficulty promising direct benefit in a Phase 1 trial, even if the slim chance of benefit provides the only hope of a cure for participants. The reader will recall that the relevant test is direct benefit to the group, not best interests of the individual research participant.

There is evidence that consent forms are frequently overly optimistic with regard to the potential of direct benefit in Phase I trials and there have been calls to state clearly to potential participants the true likelihood of benefit.<sup>85</sup> Alternatively, the investigator might adopt a different type of trial methodology which more readily offers direct benefit to the group. He may combine Phase I and II in order to promise direct benefit to some of the children in the group. Alternatively, a dose escalation study will not benefit the first group of children receiving the small dose, but is likely to benefit those who receive higher doses at the end of the trial and therefore satisfy the Clinical Trials Regulations. The four phase randomised controlled trial is recognised as the ‘gold standard’ of scientific validity, but the restrictive stance of the

<sup>84</sup> See for example, S. McPhee, C. Janson. R. Samulski et. al., ‘Immune Responses to AAV in a Phase I Study for Canavan Disease’ (2006) 8(5) *Journal of Genetic Medicine* 577.

<sup>85</sup> J. Kimmelman and N. Palmour, ‘Therapeutic Optimism in the Consent Forms of Phase 1 Gene Transfer Trials: An Empirical Analysis’, (2005) 31 *Journal of Medical Ethics*, 209.

Clinical Trials Regulations may force investigators to turn to other, arguably less rigorous, methodologies.

We have seen that investigators are required to promise direct benefit rather than simply hope it occurs as a side effect of the Phase I trial, but an additional problem lies in the balancing of risks and benefits. It might be thought that for children whose treatment options have run out, any potential benefit is worth the risks inherent in a Phase I trial. But this is not necessarily the case where there is a considerable risk of a more painful or less dignified death. This is not merely a decision for the legal representative and child, but will also be considered by the research ethics committee, which must give its approval of the proposal before research can proceed.

Take as an example the genetic condition Severe Combined Immune Deficiency (SCID). Unless the genetic defects of a child with SCID are corrected, she will usually die within two years of birth. A pharmaceutical company developing a new form of gene therapy to combat SCID will usually need to run a Phase I trial (or a combined Phase I and II trial) involving child participants with SCID. Participants are recruited only where alternative treatments have failed or are unavailable. The risks may be high. In an early SCID trial, 5 patients who were cured of SCID went on to develop leukaemia as a direct result of the gene therapy.<sup>86</sup> The trial was halted in France, but continued in the UK: The potential benefits outweighed the risks – leukaemia is frequently successfully treated.

The benefits of a Phase I trial might be weighed against palliative care, but, in rare cases where animal models of Phase I trials have already demonstrated potential, it might also be weighed against unlicensed innovative treatment. Such treatment is

<sup>86</sup> See UCL Institute for Child Health *Gene Therapy for X-SCID; Additional Briefing* December 18 2007 see [http://www.ich.ucl.ac.uk/pressoffice/pressrelease\\_00592](http://www.ich.ucl.ac.uk/pressoffice/pressrelease_00592) (last visited 7 July 2009).

tailored to the needs of the individual. Direct benefit is the aim rather than a much hoped for side effect as is frequently the case in a Phase 1 trial. Where the innovative treatment exists, the patient must find a doctor willing to administer it. Even then the doctor will want to know that his treatment of the patient with experimental drugs will not be considered negligent. The High Court authorised such treatment for legally incompetent variant Creutzfeldt-Jakob Disease sufferers, Jonathan Simms and JA (aged 18 and 16 respectively) on the basis that the treatment was in their best interests – there were no available alternatives and the prognosis was dire.<sup>87</sup> In America the refusal of a small pharmaceutical company to provide experimental treatment that had undergone Phase I testing to a terminally ill patient was recently held to violate her constitutional rights under the 5<sup>th</sup> Amendment of the US Constitution, which demands that ‘... no person shall be ... deprived of life ... without due process of law...’.<sup>88</sup> However, this decision was overturned by an 8:2 majority ruling of the District of Columbia Court of Appeal.<sup>89</sup> For the present, at least, in England and America there is no legal right to a potentially toxic experimental drug of no proven benefit. For many, Phase I trials with their slim chance of benefit offer the only hope.

There is a clear need to enable and encourage research of scientific value to target childhood diseases and extend licensing of drugs used in adults, to children. Whilst some Phase I studies involving children will still proceed in the UK, it is questionable whether a more permissive approach might have been developed to enable non-therapeutic studies and studies which do not confer direct benefit when the

<sup>87</sup> *Simms v. Simms and An NHS Trust* [2002] E.W.H.C. 2734, Fam. See J.A. Harrington, ‘Deciding Best Interests: Medical Progress, Clinical Judgment and the ‘Good Family’’ [2003] 3 *Web Journal of Current Legal Issues*.

<sup>88</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 445 F.3d 470 C.D.C. Cir. (2006).

<sup>89</sup> *Alliance for Better Access to Developmental Drugs v Von Eschenbach*, No. 04-5350, 2007 W.L. 2238914, (C.D.C. Cir. Aug 7, 2007). The Supreme Court has declined to hear an appeal. See A. Caplan, ‘Is it Sound Public Policy to let the Terminally Ill Access Experimental Medical Innovations?’ (2007) 7(6) *American Journal of Bioethics* 1.

risks are low or non-existent and future children stand to benefit, and the research cannot be conducted on adults. It might also be questioned whether it is ever possible to promise direct benefit in Phase I studies involving children who require innovative treatment in order to survive. Even if a child will die without treatment, the potential of benefit to the group may be too low to satisfy the Regulations. Limiting Phase I studies involving children may prove disastrous for children suffering rare conditions where treatments cannot be developed on adult volunteers. Yet the emotional benefits to parents and children wishing to help develop a cure for future children may provide a good reason for the research to go ahead, even if the benefits do not amount to 'direct benefit' to the study group.

Enrolling minors in Phase I studies is frequently problematic in terms of demonstrating direct benefit.<sup>90</sup> Phases II-IV might incorporate minors more readily. Phase I might be omitted where the disease or condition in question affects both adults and children and there is already a drug licensed for use in adults. Direct benefit can be demonstrated, subject to the potential conflict with collective equipoise outlined above. As I have shown, if investigators are of the opinion that a new drug is likely to be of equal value to an existing drug, the trial should not go ahead, regardless of the potential for the new drug to be produced more cheaply.

## V. CONCLUSION

I have identified three problems with the Clinical Trials Regulations in relation to research on minors.

<sup>90</sup> E. Dorenzo and J. Moss, *Writing Clinical Research Protocols: Ethical Considerations* (Elsevier Academic Press, 2006) at 50: 'A blanket condemnation of no-direct-benefit research is not an answer but a demonstration of lack of appreciation of the appropriate and necessary risks that are essential parts of a sound, deliberative, medical progress.'

First, the fact that capable minors under the age of 16 are not necessarily required to assent to the research is a worrying invasion of their autonomy rights. Fortin suggests a radical reappraisal of children's rights to assent and withhold consent, arguing that the *Gillick* competence test should be, and is gradually being 'spliced' onto Article 8 rights<sup>91</sup> - children's competency should be judged according to their ability to comprehend and assimilate the information, not merely on their status as an under 16 year old. The additional safeguard of the consent of a legal representative when child participants are under the age of 16 is sensible given the potential influences on the investigator and the fact that the goal of research is primarily the generation of knowledge, but this should not entail the diminishing of the child's right to assent to a mere 'consideration'. Indeed, the European Commission has recently recommended that capable minors assent to their inclusion in clinical trials and that their requests to withdraw command respect.<sup>92</sup>

Second, the fact that a child who is capable of understanding the nature of his decision has no legal right to withdraw or refuse to participate is confusing for researchers and ethics committees given the contrary message emerging from domestic courts interpreting Article 8 of the ECHR.<sup>93</sup> An adolescent who disagrees with his legal representative is in an unenviable position. The Declaration of Helsinki requires dual assent and the Regulations should be interpreted in this light. The 'consideration' of a child's express wish to withdraw or withhold assent to participation should be given elevated strength. Forcing a child to participate in a trial should be limited to cases where the child is incapable of giving assent due to an

<sup>91</sup> Fortin n. 55 above, at 320.

<sup>92</sup> European Commission n. 47 above.

<sup>93</sup> For example *Mabon v. Mabon* [2005] EWCA Civ 634 and; *R (on the application of Axon) v. Secretary of State for Health & Another* [2006] E.W.H.C. 37 (Admin).

inability to comprehend the information, and, potentially, in cases of direct medical benefit available only in the context of research.<sup>94</sup>

Finally, the requirement of direct benefit for the group may prove restrictive to the development of paediatric medicines for conditions peculiar to children. Unless a wide definition of the term ‘direct benefit’ is taken, and I have argued that such a definition cannot be supported, the Regulations may prove restrictive - especially in Phase I trials and trials where it is difficult to convince an ethics committee that the group will benefit because the comparator drugs are too similar. There should be an exception to this rule to allow research that does not confer a direct benefit to the group where the risk is minimal. Another exception should be developed to accommodate research into rare childhood diseases where the research cannot be conducted on adult participants, even at Phase I. An ethics committee should be able to consider all the facts and determine whether or not the research should be sanctioned. The Clinical Trials Regulations avoid convoluted rules and exceptions in paediatric research, but the price for this simplicity is too high.

<sup>94</sup> As supported by USA statute: 45 C.F.R. 46.408 (a).