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# The Search for Minimal Risk in International Paediatric Clinical Trials

Tracy Evans Chan\*

Difficult ethical and regulatory challenges are raised whenever children are enrolled in non-beneficial research. Their resolution takes on new significance in the light of transnational pharmaceutical development trials in developing countries. This paper examines what international guidelines exist and how they address the challenges posed by involving children in non-beneficial clinical trials, focussing on the concept of 'minimal' risk as a legal and ethical standard to protect children from exposure to unwarranted risks presented by such trials. It reviews approaches to the question of minimal risk before evaluating the adequacy of existing international guidelines to address the needs of children and what can be done to strengthen them.

## I. Introduction

The cornerstone of research ethics involving human subjects in non-beneficial research is arguably the voluntary informed consent of the human subject.<sup>1</sup> While the principle of beneficence ensures that such research risks are minimised and appropriate in the light of the benefits to be gained from the knowledge gleaned from the protocol,<sup>2</sup> and that of justice seeks to ensure that the burdens of such

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1. TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10, VOL. 2, Nuremberg Code, Guideline 1, at 181-82 (Washington, D.C.: U.S. Government Printing Office, 1949), *available at* <http://www.nihtraining.com/ohsr/site/guidelines/nuremberg.html> [hereinafter Nuremberg Code].
2. *See, e.g.*, Council for International Organizations of Medical Sciences, INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, *General Ethical Principles* (CIOMS, Geneva 2002), *available at* [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm) [hereinafter CIOMS Guidelines].

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research are fairly distributed amongst the group or community that stands to benefit from that research,<sup>3</sup> ultimately it is the individual, autonomous choice to align oneself with the researcher's objectives that legitimates the imposition of the inevitable risks associated with research participation.<sup>4</sup> A duty to contribute to the biomedical research effort, while often articulated,<sup>5</sup> has so far not passed into the realm of universal or general ethical acceptance.

This autonomy paradigm for non-beneficial research raises serious ethical and regulatory challenges whenever children (or minors) are enrolled in non-beneficial research. For empirical and legal reasons, children are considered incapable of giving the necessary consent to expose themselves to research risk that offers no *direct* compensating benefit.<sup>6</sup> What is the moral or legal basis, if any at all, for involving children in such research? What protections and procedures ought to be put in place should this practice be justified? These issues have long been debated domestically, with different approaches adopted in various research jurisdictions.<sup>7</sup> However, their resolution takes on new significance in the light of international pharmaceutical development trials. This paper considers what international guidelines exist and how they address the challenges posed by involving children in non-beneficial clinical trials, particularly in developing countries. Part II of the paper describes the globalisation of pharmaceutical trials and the regulatory challenges vis-à-vis child subjects, while Part III reviews some domestic legal and ethical approaches to the issue of minimal risk. In the light of this review, Part IV then evaluates the adequacy of existing international guidelines in addressing the needs of this vulnerable group of persons, and what needs to be done to strengthen them.

3. *Id.*
4. Hans Jonas, *Philosophical Reflections on Human Experimentation*, *Daedalus* 219, 235-36 (1969).
5. See, e.g., R. Rhodes, *Rethinking Research Ethics*, 5(1) *Am. J. Bioethics* 7, 14-15; D. Brock, *Ethical Issues in Exposing Children to Risks in Research*, in *CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW* 90-93 (M. Grodin & L. Glantz eds., 1994) (in relation to incompetent subjects).
6. See David N. Weisstub et al., *Biomedical Experimentation with Children*, in *RESEARCH ON HUMAN SUBJECTS: ETHICS, LAW, AND SOCIAL POLICY* 380, 382-84 (David N. Weisstub ed., 1998).
7. See *infra* Part III.

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## II. The Globalisation of Pharmaceutical Trials and Their Impact on Children

### A. General

The past two decades have seen a noticeable rise in international pharmaceutical clinical trials in developing countries.<sup>8</sup> The reasons for this are both scientific and pragmatic. If investigational products seek to deal with diseases that are more common and widespread in developing countries, pharmaceutical companies are likely to conduct trials in countries where subjects with the relevant medical condition are to be found and recruited.<sup>9</sup> Further, human subjects in developing countries are less likely to have been exposed to pre-existing pharmaceutical agents that address the condition under investigation, thus allowing better efficacy data to be derived.<sup>10</sup> More significantly, there are important cost considerations in 'out-sourcing' clinical investigations to countries where manpower and recruitment costs associated with such research are much lower. Pharmaceutical companies also apparently stand to gain from greatly accelerated trial periods in countries where ethical and regulatory barriers are lower or non-existent as these countries may lack similar or basic ethical and regulatory controls as compared to the sponsoring jurisdiction, often because government officials and medical professionals lack adequate information and training in evaluating the propriety of these trials. Finally, there is (at the least) a perception that recruitment in these developing countries, where potential subjects are far more deferential to medical professionals and authority figures in general, is much easier.<sup>11</sup>

### B. Children as Therapeutic Orphans

Clinical investigations of pharmaceutical products in children is a scientific necessity due to the different ranges of diseases in and physiology of children.<sup>12</sup> There is currently inadequate paediatric testing of pharmaceutical products, principally by reason of a lack of adequate economic incentives on the part of

8. Draft Report of the Joint CIOMS/WHO Working Group, DRUG DEVELOPMENT RESEARCH IN RESOURCE-LIMITED COUNTRIES (CIOMS, Geneva Dec. 2005) ¶ 1.2 at 7, [http://www.cioms.ch/pv\\_in\\_rpc\\_final\\_14dec2005.pdf](http://www.cioms.ch/pv_in_rpc_final_14dec2005.pdf).
9. *Id.* ¶ 1.1 at 6.
10. Ruth Macklin, DOUBLE STANDARDS IN MEDICAL RESEARCH IN DEVELOPING COUNTRIES 7 (2004).
11. *Id.* at 7-9.
12. Ralph E. Kauffman, *Scientific Issues in Biomedical Research with Children*, in CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW, *supra* note 5, at 29, 34-37.

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pharmaceutical companies, resulting in widespread off-label prescriptions and interventions for children that are based on inexact extrapolations from the results of studies in adults.<sup>13</sup> This presents an inherent therapeutic risk whenever pharmaceuticals tested in adult-only clinical trials are used in children. As a matter of national health policy, some of the leading pharmaceutical development jurisdictions have gradually begun to work towards adopting overt regulatory or legislative action to encourage or mandate the inclusion of children in clinical trials, unless there are specific ethical or scientific reasons to exclude them.<sup>14</sup> The object is to improve the information available on dosage and safety information of pharmaceutical products for paediatric use. This policy is supported by major research groups and professional associations.<sup>15</sup> The frontrunner of these efforts is the U.S. *Paediatric Research Equity Act* of 2003,<sup>16</sup> which mandates such paediatric studies. Apart from legislation being considered in the European Union,<sup>17</sup> there is currently no similar legislation anywhere else in the world. Notwithstanding the likely greater risks that would be imposed on child subjects as part of this effort, mandatory testing in children is seen as a better strategy than allowing current off-label therapeutic practices, which might place even greater risks of harm on children, to continue.<sup>18</sup>

***C. Regulatory Challenges and the Search for Minimal Risk***

The confluence of these two trends suggests that paediatric clinical trials extending beyond the shores of country sponsoring the research (transnational trials) are likely to grow. This has been predicted by some commentators,<sup>19</sup> and indeed, domestic paediatric trials in the U.S. have increased since the regulatory and legislative measures were introduced by the Food and Drug Administration

13. Carol A. Tauer, *Testing Drugs in Pediatric Populations: the FDA Mandate*, in 7 ACCOUNTABILITY IN RESEARCH 37, at 39-41 (1999); Patrina H Y Caldwell, *Clinical Trials in Children*, 364 LANCET 803 (2004).
14. Caldwell, *supra* note 13, at 804-05.
15. *Id.*
16. 21 U.S.C.S. § 301 (2006). See Pub. L. No. 108-55, § 1, 2003 U.S.C.C.A.N. (117 Stat 1936). (providing that “[t]his Act may be cited as the ‘Pediatric Research Equity Act of 2003.’”).
17. Kathleen R. Gans-Brangs & Paul V. Plourde, *The Evolution of Legislation to Regulate Pediatric Clinical Trials: Present and Continuing Challenges*, ADVANCED DRUG DELIVERY REVIEWS 58 106-15 (2006).
18. Caldwell, *supra* note 13, at 806.
19. Gans-Brangs, *supra* note 17, at 114.

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(FDA) and Congress respectively.<sup>20</sup> What substantive and procedural protections ought to be in place before such children may be enrolled in clinical trials?

Some international consensus has arguably emerged on the basic ethical requirements for paediatric clinical trials, as reflected by both domestic state regulations and guidelines promulgated by international public and professional organizations. First and foremost, children must be protected from unwarranted research risk, especially since they are considered a vulnerable group of individuals who lack adequate autonomy to understand and evaluate research risks for themselves before enrolment.<sup>21</sup> This is seen as a specification of the ethical principle of respect for persons or beneficence.<sup>22</sup> What is not so clear is how this baseline threshold level of risk, beyond which no child should be exposed to, is to be defined and applied. A distinction is often drawn between beneficial and non-beneficial clinical research.<sup>23</sup> In respect of the former, the level of acceptable risk is a function of a balancing of that risk against the prospect of direct benefits offered by the intervention or pharmaceutical product.<sup>24</sup> More controversially, when it comes to non-beneficial clinical trials, it appears that there is widespread support for allowing such research that does not offer *any* direct benefit to the child subject where the risks imposed are “minimal”<sup>25</sup> or “low”,<sup>26</sup> although some jurisdictions are even prepared to go further than this if the countervailing benefits of the research are sufficiently important enough.<sup>27</sup>

Second, and arguably as a corollary to this, parental “permission” to enrol the

20. A.J. FLETCHER, PRINCIPLES AND PRACTICE OF PHARMACEUTICAL MEDICINE 183 (Lionel D. Edwards et al. eds., 2002).
21. CIOMS Guidelines, *supra* note 2, Guideline 9.
22. See CIOMS Guidelines, *supra* note 2; Robert Veatch, *Ranking, Balancing, or Simultaneity: Resolving the Conflict among the Belmont Principles*, in BELMONT REVISITED – ETHICAL PRINCIPLES FOR RESEARCH WITH HUMAN SUBJECTS 196 (James F. Childress et al. eds., 2005).
23. Compare United Nations Educational, Scientific and Cultural Organization [UNESCO], 33rd Session of the General Conference of UNESCO, Oct. 19, 2005, *Universal Declaration on Bioethics and Human Rights*, ¶ 7(b), available at [www.unesco.org](http://www.unesco.org) and CIOMS Guidelines, *supra* note 2, at Guideline 8 and Guideline 9 with ICH Harmonised Tripartite Guideline, *Clinical Investigation of Medicinal Products in the Pediatric Population; E11*, ¶ 2.6, Current Step 4 version (July 20, 2000), available at [www.ich.org](http://www.ich.org).
24. See World Medical Association, Declaration of Helsinki 2000, ¶ 16, available at <http://www.wma.net/e/ethicsunit/helsinki.htm>; CIOMS Guidelines, *supra* note 2, at Commentary to Guideline 8.
25. CIOMS Guidelines, *supra* note 2, at Guideline 9; UNESCO Declaration, *supra* note 23, at art. 7(b).
26. ICH Harmonised Tripartite Guideline, *Guideline for Good Clinical Practice E6(R1)* [10 June 1996], para. 4.8.14, available at <http://www.ich.org/cache/comp/276-254-1.html>.
27. 46 C.F.R. §46.407; see *infra* Part III.A.3.

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child is necessary.<sup>28</sup> “Permission”, rather than “consent”, is used to more accurately capture the ethical considerations involved in seeking parental approval before a child is enrolled in a clinical trial or research in general. It is not a matter of respecting the parent’s autonomy over his individual interests, but rather, at the least, a respect of the parent’s *prima facie* authority and responsibility to determine the proper development and upbringing of the child.<sup>29</sup> Furthermore, parental permission ensures that there is some external evaluation of a research protocol’s inherent risks, apart from that of the investigator and the institutional review board (IRB) or ethics committee. Although the latter are better positioned to objectively evaluate the risks created, parents are arguably in better placed to evaluate the possible subjective risks (psychological or otherwise) presented in relation to the particular child.<sup>30</sup>

Third, the “assent” of the child is required as well.<sup>31</sup> “Assent” roughly refers to the understanding and positive agreement of the child to participate in the trial, at least to the extent that he or she is capable of and depends on the age, maturity and psychological development of the particular child.<sup>32</sup> This essentially reflects the importance of respecting the developing autonomy of the child, especially if it is also desired to educate the child on the importance of becoming a morally conscious and contributing member of society. Furthermore, respecting the dissent of the child ensures that undue distress or harm is avoided, particularly when the research is non-beneficial in nature. Disagreement and uncertainty, however, exist over what age assent should be required, and if the dissent of a non-competent child should be respected in every situation.<sup>33</sup>

Finally, there should be just recruitment criteria and procedures in place to ensure the fair spreading of the benefit and burdens of such research between individuals and groups who actually stand to benefit from the knowledge gained from such research.<sup>34</sup> Following from this principle, it is always stipulated that it

28. See, e.g., CIOMS Guidelines, *supra* note 2, at Guideline 14; Cf. WMA Helsinki Declaration 2000, *supra* note 24, at para. 24, which refers to the “informed” consent of a legally authorised representative of the incompetent subject.

29. See Leonard H. Glantz, *Research with Children*, 24 Am. J.L. & Med. 213, at 219-20 (1998).

30. Weisstub, *supra* note 6, at 392-94.

31. CIOMS Guidelines, *supra* note 2, at Guideline 14: Research involving children; Helsinki Declaration 2000, *supra* note 24, at ¶ 25.

32. CIOMS Guidelines, *supra* note 2, at Commentary on Guideline 14.

33. See David Wendler & Seema Shah, *Should Children Decide Whether They Are Enrolled in Nonbeneficial Research*, 3(4) Am. J. Bioethics 1 (2003).

34. CIOMS Guidelines, *supra* note 2, at Guideline 12: Equitable distribution of burdens and benefits in the selection of groups of subjects in research.

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must be scientifically necessary to enrol children in the clinical trial in question because competent adults are unsuitable.<sup>35</sup> Further, enrolment should not unnecessarily target particularly vulnerable sub-groups of children, by reason of economic, social inequalities or simply because they are more easily accessible by reason, for example, of their poor health and institutionalization.<sup>36</sup>

In this paper, I focus on non-beneficial paediatric clinical trials, and in particular the application of first ethical principle of respect for persons above, because of the unique difficulties raised whenever incompetent and vulnerable subjects are sought for a trial or research that does not *per se* benefit them directly. The threshold of minimal risk essentially reflects a deontological moral threshold of risk, based on the respect for the individual child, beyond which it is impermissible to expose children to no matter what utility or beneficence the research offers for future child patients or society in general.<sup>37</sup> While all the requirements mentioned above are undoubtedly important, additional social, cultural and political complications are introduced by international paediatric clinical trials. The greater likelihood of exploitation of vulnerable populations (and parents in these communities) in developing countries and the general lack of adequate regulatory oversight in many developing countries,<sup>38</sup> for example, makes it all the more imperative that children are protected from unnecessary and unethical exposure to risk in non-beneficial clinical trials.

### III. Non-Beneficial Clinical Trials Under Domestic Legal and Ethical Standards

As a starting point, it is useful to survey what limits are placed on non-beneficial paediatric clinical trials under domestic law. Standards and procedures governing research in children take varied forms. There is often a mix of legal and ethical guidelines, and in federal systems, overlapping and possibly conflicting federal and state rules.<sup>39</sup> What follows is a brief, selective survey of the relevant rules in the U.S., U.K. and Singapore that serves to highlight the main approaches taken and difficulties involved.<sup>40</sup>

35. *Id.* at Guideline 14 (research involving children).

36. *Id.* at Guideline 13 (research involving vulnerable persons).

37. See Veatch, *supra* note 22 at 196; L. Kopelman, *Minimal Risk as an International Ethical Standard in Research*, 29(3) *J. Med. and Philo.* 351, 352 (2004) [hereinafter Kopelman, *Int'l Ethical Standard*].

38. See *infra* Part IV.

39. See Glantz, *supra* note 29, at 229-32.

40. See Kopelman, *Int'l Ethical Standard*, *supra* note 37, for a more detailed survey of the



## **A. The U.S. Federal Regulations' Multi-layered Approach**

### **1. Minimal Risk Research**

The U.S. Federal Regulations, or Common Rule, represent the most multi-layered approach to non-beneficial research involving children. At the baseline, the Common Rule provides for the commonly adopted “minimal risk” standard for non-therapeutic paediatric research.<sup>41</sup> Minimal risk in the Common Rule means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those encountered in daily life *or* during the performance of routine physical or psychological examinations or tests.<sup>42</sup> The ethical justification for such “minimal risk” research is two-fold. It reflects a shared, communal judgment that the community benefits of such activity clearly outweigh exposure to a level of risk that is unavoidable and accepted as part of daily life.<sup>43</sup> Therefore, it cannot be said that that child is necessarily made worse off by participating, if not better off. Further, even if such research may not offer direct therapeutic benefit, children benefit by participation in a community practice in which all members have some mutual ties of responsibility to each other that advances their common interests, and this is also part and parcel of their socialisation and growth as responsible moral beings.<sup>44</sup>

The Common Rule offers a dual test for what constitutes this “minimal” risk. The first limb ambiguously refers to risks encountered in daily life, which could be interpreted from an objective standpoint as representing some notional common level of unavoidable risk to which the average child in a community is exposed. It would therefore reflect an absolute standard. Alternatively, the first limb could be interpreted as reflecting a subjective level of risk dependent on the daily risks encountered by the individual paediatric subject in question.<sup>45</sup> Fortunately, this alternative approach seems to be largely rejected in the U.S. on grounds that it could produce unjust outcomes by placing greater risk on child subjects simply because social, medical and economic circumstances already expose them higher levels of risk than more fortunate and privileged children, infringing the justice

<sup>41</sup> ‘minimal risk’ standard.

41. 45 C.F.R. § 46.404 (2005). *See also* 21 C.F.R. § 50.51 (2006) (the equivalent FDA regulation).

42. 45 C.F.R. § 46.303(d) (2005); 21 C.F.R. § 50.3(k) (2006).

43. Brock, *supra* note 5, at 87-88.

44. *Id.* at 89-90.

45. Kopelman, *Int'l Ethical Standard*, *supra* note 37, at 361-63.

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principle outlined above.<sup>46</sup> A subjective approach would also frustrate the intended purpose of expediting ethical and regulatory review on the assumption that the risk exposure of a given clinical trial or research protocol reflects an objectively minimal level of risk that obviates the necessity for closer scrutiny.<sup>47</sup>

Unfortunately, even the former absolute everyday risks standard suffers from a serious shortcoming. It assumes that common every day risks are easily identifiable, uniform and stable. The U.K. Institute of Medical Ethics examined this approach in its 1986 report.<sup>48</sup> After surveying a wide array of voluntarily accepted and daily risks for different members of the British population, it concluded that an everyday standard of risk (that is, risk less than that run in everyday life) is effectively meaningless since daily life can actually be quite hazardous in a variable variety of ways, dangerous sport and the like aside.<sup>49</sup> Comprehensive empirical data on the range of these types of risk is also lacking, leaving IRB members to rely on their own subjective perceptions in making risk assessments.<sup>50</sup> Many of these ‘everyday’ risks are also unconsciously accepted or involuntarily imposed as an adjunct to activities chosen by parents for the social and educational developmental of the child (e.g. road travel to attend school and participate in sports, playing on sidewalks or playgrounds close to roads). It does not follow that the same level of risk is ethically appropriate for *intentionally* chosen risk-laden activities like non-beneficial research.<sup>51</sup>

Some commentators have defended this “‘everyday risks’” standard on the basis that it ought only to focus risks that are common to us all (including driving to work) and is meant to be a *qualitative* and categorical judgment made by an IRB, not a *quantitative* test.<sup>52</sup> The problem with the former comment is that activities common to us all are liable to vary, if not substantially within a community, then

46. See Loretta M. Kopelman, *When is Risk Minimal Enough for Children to be Research Subjects*, in CHILDREN AND HEALTH CARE: MORAL AND SOCIAL ISSUES 89, 95 (L. Kopelman & J. Moskop eds., 1989); Robert M. Nelson, *Children as Research Subjects*, in BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH 59-60 (Jeffrey P. Kahn et al. eds., 1998).
47. Kopelman, *Int'l Ethical Standard*, *supra* note 37, at 363.
48. MEDICAL RESEARCH WITH CHILDREN: ETHICS, LAW AND PRACTICE (Richard H. Nicholson ed., 1986).
49. *Id.* at 84-87.
50. David Wendler et al., *Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research Without a Prospect of Direct Benefit*, 294(7) J. AM. MED. ASS'N. 826, 827 (2005).
51. Terrence F. Ackerman, *Moral Duties of Parents and Nontherapeutic Clinical Research Procedures Involving Children*, 2(2) BIOETHICS Q. 94, 105-06 (1980).
52. Benjamin Freedman et al., *In Loco Parentis: Minimal Risk as an Ethical Theshold for Research Upon Children* 23(2) HASTINGS CENTER REP. 13, 15-16 (1993).

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most certainly between different geographical and economically under-privileged communities across the globe. Further, the assumption that IRB members are likely to apply such a qualitative standard consistently has been proven otherwise. Various studies have been conducted where researchers and IRB members gave widely varying responses to what they considered to be minimal risks associated with invasive and non-invasive research procedures acceptable in research<sup>53</sup> and non-beneficial research specifically.<sup>54</sup> In short, perception of risk and its acceptability depends very much on the individual consulted, and it is reasonable to expect that IRB members who are personally involved or supportive of research are likely to be more optimistic about research risk than other professionals and laypersons.<sup>55</sup> This does not bode well for a regulatory standard ultimately meant to protect the interests of children otherwise dependent on parents who may often have difficulty understanding the nature of research or the clinical trial in question.<sup>56</sup>

This leaves us with the alternative “routine examinations” standard. Susceptible to the same subjective approach criticisms as the everyday risk standard, an objective interpretation focussing on routine examinations all healthy people might ordinarily encounter in the interests of both personal and public health is preferable.<sup>57</sup> Examinations of the latter sort arguably approximate more closely with the more attenuated notions of benefit presented by clinical trials as compared with research that offers direct clinical benefit.<sup>58</sup> It is also the approach commonly adopted by various paediatric professional boards making recommendations in respect of paediatric research.<sup>59</sup> However, it must be said that this is a rather restrictive standard that is likely to rule out most, if not all, non-beneficial clinical

53. Jeffrey Janofsky & Barbara Starfield, *Assessment of Risk in Research on Children*, 98 J. PEDIATRICS 842 (1981).
54. C. Lenk et al., *Non-therapeutic Research With Minors: How Do Chairpersons of German Research Ethics Committees Decide?*, 30 J. Med. Ethics, 85 (2004).
55. Nicholson, *supra* note 48, at 104-06.
56. This is an extrapolation from studies on adults concerning the ‘therapeutic misconception’ in clinical research: see A. CATO ET AL., *CLINICAL DRUG TRIALS AND TRIBULATIONS* ch.12, pt. III (2002). See also Michelle Obermann & Joel Frader, *Dying Children and Medical Research: Access to Clinical Trials as Benefit and Burden* 29 AM. J. L. & MED. 301, 308-10 (2003).
57. Kopelman, *Int’l Ethical Standard*, *supra* note 37, at 365-67.
58. Cf. Wendler et al., *supra* note 50, at 830.
59. See, e.g., Samuel Gidding, et al., *A Policy Regarding Research in Healthy Children*, 123 J. PEDIATRICS 852 (1993); Ethics Advisory Committee, Royal College of Paediatrics and Child Health, *Guidelines for the Ethical Conduct of Medical Research Involving Children*, 82 ARCHIVES DISEASE CHILDHOOD 177 (2000).

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trials which necessarily pile on the risks of exposure to the investigational product over and above any routine medical procedures associated with the trial.<sup>60</sup>

## 2. Minor Increase Over Minimal Risk Research

Secondly, the Common Rule allows non-beneficial research involving a ‘minor increase over minimal risk’ only if, *inter alia*, the intervention presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations<sup>61</sup> and is likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition.<sup>62</sup> It must be obvious that this provision compounds the uncertainty by adding another subjective concept of “minor” to the ambiguous “minimal risk” conception. No guidance is offered as to how one resolves what amounts to a minor increase over the baseline “minimal risk.”<sup>63</sup> One could infer that the drafters of the rule envisaged that such “minor” increases to the baseline threshold are justified by the fact that child subjects with the disorder or condition are likely by reason of their own past experiences to be better able to cope with the interventions proposed under the trial in question (thus minimising potential psychological harm) and are more likely than subjects without the relevant disorder or condition under investigation to potentially benefit at some *future* point should therapeutic applications for the disorder or condition materialise sooner.<sup>64</sup>

An ethical justification offered for this standard seems to be that this higher level of risk exposure is nonetheless within the realm of legitimate and responsible parental discretion in allowing children to gain new experiences that may pose incrementally higher than usual “everyday” risks.<sup>65</sup> This moves away from the strict best interests of the child viewed from an ideal perspective and recognises that parents are given leeway in exposing children to risk in familial or altruistic activities that have no ostensible direct and immediate benefit to them apart from developing their moral character.<sup>66</sup> Critics respond that, notwithstanding this

60. Wendler et al., *supra* note 50, at 830.

61. 45 C.F.R. § 46.406(c) (2005).

62. 45 C.F.R. § 46.406 (2005). *See also* 21 C.F.R. § 50.53 (2006).

63. Loretta M. Kopelman, *Pediatric Research Regulations Under Legal Scrutiny: Grimes Narrows Their Interpretation*, 30 J. L. MED. & ETHICS 38, 44 (2002).

64. *See* David Wendler et al., *Non-beneficial Research with Individuals Who Cannot Consent: Is it Ethically Better to Enrol Healthy or Affected Individuals?*, 25(4) IRB: ETHICS & HUMAN RESEARCH 1, 2 (2003).

65. Charles Weijer, *The Ethical Analysis of Risk*, 28 J. L. MED & ETHICS 344, 356 (2000).

66. *Id.* *See also* Lanie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*,

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parental authority, the §46.406 rule as drafted will actually doubly burden sick children who are more likely to be exposed to increased daily risk simply because of their existing misfortune, and runs counter to the justice principle. What is more, clinical trials may also impose uniquely greater risk on sick children for some types of trials, so the implicit assumption that past experience will tend to minimise current risks is not invariable.<sup>67</sup> They reason that §46.406 should not categorically be confined to affected children; instead recruitment should first be determined by a requirement of scientific necessity, which incorporates due consideration of the particular experiences and special risks of affected children.

That said, the responsible or scrupulous parent standard offers a more defensible approach to determining acceptable risk thresholds, from both a normative and practical perspective.<sup>68</sup> It seeks to determine “whether the probability and magnitude of physical and psychological harm is no more than that to which it is appropriate [for a responsible parent] to *intentionally* expose a child for educational purposes in family life situations.”<sup>69</sup> This directs the IRB to compare the risks presented by a clinical trial with those attendant on analogous decision-making scenarios that parents are presented with in disciplining and educating their children, thus resonating with an existing socially acceptable risk threshold in respect of all children in a particular community. The responsible parent standard also resists a purely quantitative exercise for which empirical data specific to a community or country may simply be lacking, or the nature of the risks examined are incommensurable.<sup>70</sup> It could actually subsume the basic §46.404 “minimal risks” rule since *ex hypothesi*, the responsible parent would not object to an exposure to minimal risks, provided this is measured by reference to analogous character-building activity that is *intentionally* chosen.<sup>71</sup> However, as drafted, §46.406 does not explicitly mandate such an approach.

### 3. The 407 Approval Process

Finally, the Common Rule envisages exceptional situations where research offers a reasonable opportunity to further the understanding, prevention or

30 J. LAW MED & ETHICS 50, 54 (2002).

67. Wendler et al., *supra*, note 64, at 3.

68. See Lanie Friedman Ross, *Do Healthy Children Deserve Greater Protection In Medical Research?* 142 J. PEDIATRICS 108, 110 (2003); Ackerman, *supra* note 51, at 106-09.

69. Ackerman, *supra* note 51, at 106 (emphasis added).

70. Freedman et al., *supra* note 52, at 16-17.

71. Ross, *supra* note 68, at 110-11.

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alleviation of a serious problem affecting the health or welfare of the children, and it will be conducted “in accordance with sound ethical principles”.<sup>72</sup> This provision is interesting at it seems to envision exposure of child subjects to even greater levels of risk in the cause of the greater good of children, and perhaps even suggests that it might be possible to perform a utilitarian calculation to justify significant increases over minimal risk to further the ends stipulated. It is unsettling that §46.407 does not provide any explicit ethical guidelines particularly on the threshold protection from research risk. What it does seem to acknowledge is that we should not rule out the possibility that the importance of the research or harm is so great that it may occasion a community or societal reconsideration of the level of risk from which individual children should qualitatively be shielded. The protections under §46.407 essentially move from the substantive to the procedural.<sup>73</sup> §46.407 provides that such research can only proceed if (a) the Secretary of the Department of Health and Human Services, (b) in consultation with a panel of experts in pertinent disciplines and (c) following the opportunity for public review and comment, has determined that the non-beneficial research (notwithstanding ineligibility under §§46.404 and 46.406) can nonetheless ethically proceed because envisaged ethical standards may adapt in the light of unforeseen circumstances. There will doubtless be detractors who argue that non-beneficial research cannot move beyond the moral compass envisaged by either or both §§46.404 or 46.406.<sup>74</sup>

On the whole, the Common Rule provisions on paediatric research reflect two second-order strategies<sup>75</sup> to cope with the inherent ethical difficulties in deciding if and when children may be enrolled in non-beneficial clinical trials. Although the more stringent rule-bound approaches under §§46.404 and 46.406 possess serious conceptual and practical difficulties in their formulation of risk thresholds, they provide greater controls over what IRBs may approve in respect of children as compared to §46.407. The latter attempts to compensate for the absence of any explicit risk threshold by delegating the decision to a more trustworthy decision-maker coupled with a more publicly transparent decision-making process.

72. 45 C.F.R. § 46.407 (2005). *See also* 21 C.F.R. § 50.54 (2006).

73. *See* Loretta Kopelman & T. Murphy, *Ethical Concerns About Federal Approval of Risky Pediatric Studies*, 113(6) *Pediatrics* 1783 (2004). *See also* 21 C.F.R. § 50.54 (2006).

74. *See, e.g.*, Ackerman, *supra* note 51, at 108.

75. Second-order strategies are decisions about the appropriate strategy for reducing the problems associated with making a first-order decision. *See* C. Sunstein & E. Ullmann-Margalit, *Second Order Decisions*, 110 *Ethics* 5, 7 (1999).

### ***B. The Prohibitive Approach***

In contrast, it appears that in the United Kingdom, a paediatric clinical trial must relate “directly to a clinical condition from which the minor suffers or is of such a nature that it can only be carried out in minors”,<sup>76</sup> and “some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial.”<sup>77</sup> The first elaborated condition reflects the requirement of scientific necessity, but also implicitly suggests that healthy children without any medical condition should not be involved in clinical research. The latter condition is rather curious since it raises the immediate question of what constitutes group benefit. If every child in the group must benefit, then would it not have been easier to simply provide for direct benefit to each trial participant?<sup>78</sup> Perhaps what was envisaged was the possibility of enrolling children with a relevant medical condition in a randomised controlled trial (RCT). In this scenario, while it is demonstrable that a majority of child subjects will randomly receive an investigational product that has some proven efficacy in adults, the control group will not – save perhaps for any demonstrable placebo effect.<sup>79</sup> If this be the case, then the U.K. Regulations arguably do not provide sufficiently explicit requirements that there must still be some form of *direct* medical benefit to *every* individual child enrolled in the trial, even though on average there is a direct benefit to the group as a whole. Even if this were not necessary, there should still be some threshold limit of risk protecting children in the control group who do not receive the medicinal product under investigation for the period of the trial. Some other commentators acknowledge the uncertainty but take a conservative interpretation of the provision to suggest that it precludes *any* non-therapeutic research – conferring no personal benefit on the research participant.<sup>80</sup>

The position in Singapore is arguably much more explicit. Although

76. The Medicines for Human Use (Clinical Trials) Regulations 2004, S.I. 1031/2004 [hereinafter U.K. Regulations], Schedule 1, Part 4, Condition 9, available at [www.opsi.gov.uk/si/si2004/20041031.htm](http://www.opsi.gov.uk/si/si2004/20041031.htm).

77. *Id.* at Condition 10.

78. In respect of incapacitated adults, Condition 9 of Part 5 of the U.K. Regulations provides: “[t]here 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” (emphasis added).

79. On the placebo effect in pediatric clinical trials, see Franklin Miller et al., *When Do The Federal Regulations Allow Placebo-Controlled Trials in Children?*, 142 J. PEDIAT. 102, 105 (2003).

80. Lynn Hagger & Simon Woods, *Children and Research: A Risk of Double Jeopardy?*, in CHILDREN’S HEALTH AND CHILDREN’S RIGHTS 54-55 (Michael Freeman ed., 2006).

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professional guidelines issued by the National Medical Ethics Committee similarly allow for non-beneficial research in children where the risks are not greater than those in their “everyday lives” or alternatively interventions that only constitute a “minor legal assault” like venepuncture.<sup>81</sup> In contrast, the *Medicines (Clinical Trials) Regulations 2001* provides that subjects may only be enrolled in a clinical trial with the appropriate consent.<sup>82</sup> Persons who are under 21 years of age may be enrolled in a clinical trial in three different circumstances. First, if the minor is married, then the consent of that individual shall suffice to legitimate enrolment in a clinical trial.<sup>83</sup> Second, if the minor *and* his parent, guardian or legal representative (“proxy”) *both* give consent.<sup>84</sup> However, in this instance, a minor can only jointly consent if he has “sufficient understanding” to give such consent – in short, if he is competent.<sup>85</sup> Thirdly, and more pertinently, the proxy’s consent alone will suffice only if the minor lacks capacity to consent *and* “there is a reasonable prospect that participation in the clinical trial *will directly benefit that person*”.<sup>86</sup> Thus, in the case of a minor who lacks the requisite decision-making capacity, non-therapeutic trials are simply not permissible.<sup>87</sup> The foregoing U.K. and Singapore provisions arguably reflect a pre-emptive judgment that the risks associated with non-beneficial clinical trials, the inherent risks presented by the investigational product, the shortcomings of the review process, the open textured

81. National Medical Ethics Committee, *Ethical Guidelines on Research Involving Human Subjects*, in NATIONAL MEDICAL ETHICS COMMITTEE, A REVIEW OF ACTIVITIES (1997)(Sing.), ¶ 2.5.5.1, available at [http://www.moh.gov.sg/corp/publications/details.do?cid=pub\\_reports&id=13991964](http://www.moh.gov.sg/corp/publications/details.do?cid=pub_reports&id=13991964).
82. Medicines (Clinical Trials) Regulations, r. 11 (1978 (amended 1990 and 2000)) (Sing.).
83. *Id.* at r.11(1)(a).
84. *Id.* at r.11(1)(b).
85. *Id.* at r. 11(2)(a).
86. *Id.* at r. 11(2)(b) (emphasis added).
87. This conclusion must be qualified by the provisions of the SINGAPORE GUIDELINE FOR GOOD CLINICAL PRACTICE [SGGCP], which throws a spanner [wrench] in the works. SINGAPORE MINISTRY OF HEALTH, SINGAPORE GUIDELINE FOR GOOD CLINICAL PRACTICE (1999). Paragraph 4.8.14 of the SGGCP provides that non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative if several conditions are met. These conditions mirror those in para. 4.8.14 of the ICH GCP, *infra* note 119. Paragraph 4.8.13 defines a non-therapeutic clinical trial to mean a trial in which there is no anticipated direct clinical benefit to the subject. These paragraphs are patently inconsistent with r. 11(2)(b) of the *Medicines (Clinical Trials) Regulations* discussed in the main text, at least in so far as paediatric clinical trials are concerned. Paragraph 4.8.14(d) of the SGGCP also requires that the non-therapeutic trial not be prohibited by law, which presumably includes subsidiary legislation represented by r. 11(2)(b). I surmise therefore that Paragraph 4.8.14 of the SGGCP is ineffectual and the full import of r. 11(2)(b) (first promulgated on 24 March 1978) was not appreciated when the SGGCP, based substantially on the ICH GCP, was introduced in 1999.



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nature of the “minimal risk” standards available, and even possibly the disparate impact of parental permission to enrol on children of less-privileged families,<sup>88</sup> are simply too high a price to pay without any compensating direct benefit to the individual child.

It is obvious from the illustrative survey above that there is no uniform domestic approach to paediatric risk threshold protection. The threshold of “minimal risk” is more easily stated than stipulated. Much disagreement and uncertainty exists over its formulation and adequacy. While the use of some conception of the “minimal” or “low” risk approach is common, this will likely produce different results depending on how “everyday” risks are perceived and interpreted by IRB members. Contrariwise, very strict thresholds also exist that rule out non-beneficial clinical trials altogether. The literature on the subject, however, reveals a promising alternative approach based on the exercise a responsible or scrupulous parent standard. Nevertheless, the U.S. Common Rule is prepared to go even further by providing for exceptional situations where appropriately transparent and public processes and more trustworthy institutions are persuaded that the research imposing greater than minor increases over minimal risk is ethically warranted.

#### **IV. The International Protection of Children in Clinical Trials**

##### ***A. Helsinki Declaration 2000***

What international principles or guidelines are in place to ensure adequate protection of child subjects, particularly in developing countries that often do not have adequate regulatory institutions or standards governing clinical research? There is unfortunately, but not surprisingly, no truly international treaty on the pharmaceutical testing.<sup>89</sup> Paediatric clinical research was only first recognised in

88. See Ross, *supra* note 68, at 110 (citing William A. Silverman, *The Myth of Informed Consent in Daily Practice and in Clinical Trials* 15 J. MED ETHICS 6 (1989)); S.C. Harth et al., *The Psychological Profile of Parents Who Volunteer Their Children for Clinical Research: A Controlled Study*, 18 J. MED. ETHICS 86 (1992); Cf. J.A.F. Zupancic et al., *Determinants of Parental Authorization for Involvement of Newborn Infants in Clinical Trials*, 99 PEDIATRICS 117 (1997).
89. See, e.g., Dawn Miller, *Research and Accountability: The Need for Uniform Regulation of International Pharmaceutical Drug Testing*, 13 PACE INT’L L. REV. 197, 202-11 (2001). The *Convention on Human Rights and Biomedicine*, 4 Apr. 1997, Eur. T.S. 164, only binds Council of Europe signatories: Benjamin Meier, *Int’l Protection of Persons Undergoing Medical Experimentation: Protecting the Right of Informed Consent*, 20 BERK. J. INT’L L. 513, 527-29 (2002).

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the World Medical Association's Declaration of Helsinki 1964, which permitted proxy consent for all subjects who were legally incompetent in accordance with national legislation.<sup>90</sup> As far as risk assessment and acceptable thresholds are concerned, rule 16 of Helsinki 2000 provides that "[e]very medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject *or to others*. This does *not* preclude the participation of *healthy volunteers* in medical research . . . ."<sup>91</sup> This rule seems to allow the weighing of third party or community interests in determining acceptable risk-benefit ratios, suggesting that these may be weighed in against research risks even though there is no compensating direct benefit for a child subject. Rule 18 provides that such research "should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers."<sup>92</sup> Finally, in addition to the recognition of proxy "informed consent," rule 24 requires that research for incompetents must be necessary to promote the health of the population represented and cannot be performed on legally competent persons, while rule 25 requires the investigator to obtain the incompetent's assent where this capability exists.<sup>93</sup>

The provisions are silent on whether any risk thresholds exist for the recruitment of incompetent subjects or if any direct benefit is necessary. Much turns on the unusual concept of "healthy volunteer" in rules 16 and 18 (which is undefined) since rule 18 recognises that research objectives must be weighed against risks and burdens to the subject even if no potential benefit *to the subject* exists. Thus non-beneficial medical research may enrol such "healthy volunteers."<sup>94</sup> The entire context suggests two possibilities. "Volunteers" either refers to subjects without a pre-existing relationship with the medical investigator (whatever their mental capacity), or only to subjects capable of giving free individual consent to participate (quite apart from whether they are adequately informed under rule 22). If the former, then children may be enrolled in non-beneficial research provided its importance outweighs the risks to the child. The

90. World Medical Association 18<sup>th</sup> General Assembly, Declaration of Helsinki, June 1964, art. I.11, available at [www.cirp.org/library/ethics/helsinki](http://www.cirp.org/library/ethics/helsinki); Cf. Nuremberg Code, *supra* note 1, at Guideline 1.

91. World Medical Association 52<sup>nd</sup> General Assembly, Declaration of Helsinki, Oct. 2000, available at: <http://www.wma.net/e/policy/b3.htm>.

92. *Id.* at art. 18.

93. *Id.* at art. 24.

94. *Id.* at art. 16.

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weight of this overriding research importance is not specified. Otherwise, their incapacity precludes them from being “volunteers” in non-beneficial research. Helsinki 2000 is equivocal on this issue.

**B. WHO Guidelines 1995**

This latter interpretation reflects the approach taken in the World Health Organization’s Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products (“WHO Guidelines”),<sup>95</sup> which have been of significant influence in the formulation of national good clinical practice guidelines.<sup>96</sup> Paragraph 3.3(g) stipulates that consent must always be given by the subject in a non-therapeutic study, while paragraph 3.3(f) provides that the inclusion of children in a trial may be acceptable if, *inter alia*, it is “permitted by local laws and regulations”, and “the investigator thinks that participation will promote the welfare and be in the interest of the subject.”<sup>97</sup> Taken together, these provisions appear to preclude child enrolment in non-beneficial research, which cannot be said to *promote* the welfare of the child subject instead of merely not being contrary to his welfare and interests. This prohibitive stance is also reflected in the recent European Directive on Good Clinical Practice in the Conduct of Clinical Trials (“EDGCP”).<sup>98</sup> Article 4(e) of the EDGCP requires that a clinical trial on minors can only be undertaken if some direct benefit for the group of patients is obtained from the clinical trial.<sup>99</sup> As discussed above in relation to the similarly worded U.K. provisions, this at most accepts risk exposure for the control group in RCT trials, and not non-beneficial trials in general.<sup>100</sup>

95. World Health Organization, *Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products*, WHO Technical Report Series No. 850, Annex 3 (1995), available at <http://www.vghtpe.gov.tw/~mre/goodexp/Fercap-Survey/WHO-GCP-1995.pdf>.

96. Draft Report of the Joint CIOMS/WHO Working Group, *supra* note 8 at 30, ¶ 4.5, lines 29-31.

97. World Health Organization, *supra* note 95, at ¶ 3.3(f). The agreement of a legally acceptable representative of this effect should also be recorded by a dated signature.

98. Council Directive 2001/20/EC, 2001 O.J. (L121) 1 (EC), available at [http://eudract.emea.eu.int/docs/Dir2001-20\\_en.pdf](http://eudract.emea.eu.int/docs/Dir2001-20_en.pdf). This presumably overrides the *Convention on Human Rights and Biomedicine*, *supra* note 89, at art. 17(2), which permits non-beneficial research where, *inter alia*, it has the aim of contributing to the ultimate attainment of results capable of conferring benefit on the person concerned, or to other persons in the same category, and entails only minimal risk and minimal burden for the individual concerned.

99. *Id.* at L121/38.

100. *See supra* Part III.B.

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### ***C. CIOMS Guidelines 2002***

A more nuanced interpretation of Helsinki 2000 is embodied in the latest Council for International Medical Organisations' International Ethical Guidelines for Biomedical Research on Human Subjects, 2002 ("CIOMS Guidelines").<sup>101</sup> A particular objective of these guidelines, developed in collaboration with the WHO, is to reflect the conditions and needs of "low-resource" countries in applying the Helsinki Declaration and developing biomedical research policies and ethical guidelines.<sup>102</sup> Notwithstanding the ambiguities in Helsinki 2000, the CIOMS Guidelines make special provision for research involving children. Guideline 9 specifically provides for limitations in respect of non-beneficial research involving incompetent individuals:

- (1) 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 risk attached to routine medical or psychological examinations.
- (2) Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases.<sup>103</sup>

Guideline 9 prudently adopts a routine examinations standard, obviating the potential for abuse inherent in an "everyday risks" standard that takes advantage of the heightened health and other risks disadvantaged children in the developing world are likely to be exposed to in their daily lives.<sup>104</sup> There is some doubt as to whether this routine examinations standard is to be applied subjectively (for the particular individual) or objectively (those encountered by every healthy individual). For reasons of fairness in the distribution of research risk mentioned above, the latter approach is to be preferred.

In respect of the alternative minor increase over minimal risk standard, the commentary on Guideline 9 closely mirrors the stipulations of the Common Rule §46.406, but candidly acknowledges that there is no internationally agreed or precise standard of such an upper threshold of risk for non-beneficial research.<sup>105</sup> The suggested solution is that its meaning "is to be inferred from what various

101. CIOMS Guidelines, *supra* note 2.

102. *Id.* at Background.

103. CIOMS Guidelines, *supra* note 2, at Commentary on Guideline 9.

104. *Id.* at para. 2.

105. *Id.* at para. 4.

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ethical review committees have reported as having met the standard.”<sup>106</sup> This is problematic since it may devolve a large amount of discretion to a local IRB to determine what constitutes a “slight” or “minor” increase, which is an inherently subjective exercise. Given the problems seen in variable determinations of minimal risk by IRB members in well established research jurisdictions,<sup>107</sup> and the problems of a lack of expertise and independence in developing world regulatory institutions,<sup>108</sup> this is arguably an inappropriate second-order decision making strategy to adopt. Furthermore, local IRB determinations on acceptable research risks are rarely made publicly available,<sup>109</sup> let alone the detailed reasons for those determinations. In the absence of any substantive principle or concept grounding these determinations, and the general lack of comprehensive study and information on risk profiles,<sup>110</sup> there is a real likelihood that such an approach would encourage information cascades on acceptable risk analogues for non-beneficial clinical trials, without adequate consideration of the relevant information, ethics and local culture and circumstances utilised by a “reporting” IRB in coming to its decision.<sup>111</sup> This could have implications both ways, to stifle needed paediatric research or allow inordinate levels of risk exposure on children in developing countries.

I suggest that a responsible or scrupulous parent standard advocated by Ackerman and Ross would provide an ethically sounder foundation on which developing world IRBs could make their deliberations.<sup>112</sup> This would direct IRB members to make qualitative assessments on the socially acceptable levels of *intentionally imposed* risk that the host country is prepared to accord parents in the educational upbringing of their children. In doing so, it mitigates against the exploitation of differing everyday risk levels across countries by focussing on analogous voluntary or charitable activities chosen by parents for the moral education of the child. The legitimate scope of parental duty and prerogative are arguably questions of universal deliberation and would be a more recognizable

106. *Id.* at Commentary on Guideline 9, para. 4.

107. *See supra* notes 53 and 54 and accompanying text.

108. *See infra* notes 122-124 and accompanying text.

109. This is the situation in the U.S., where greater transparency is only likely under the §46.407 national review process. However, such 407 reviews are exceptional, *see* Kopelman & Murphy, *supra* note 73, at 1787.

110. Wendler et al., *supra* note 50, at 827.

111. In an information cascade, people cease relying on their private information or opinions and decide instead on the basis of signals conveyed by others, *see* CASS SUNSTEIN, WHY SOCIETIES NEED DISSENT 55 (2003).

112. *Supra* notes 51, 68, 70 and accompanying text.

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standard compared to appeals to essentially subjective perceptions of degrees of risk. Practically speaking, there are concrete examples of appropriate parental interventions from which an IRB may draw inspiration or which serve as tangible starting points for risk investigation, such as the discipline of children, involvement in familial chores and charitable activities. Furthermore, it is a standard that includes the consideration of subjective harms and developmental maturity of the particular age group in formulating acceptable risk thresholds.<sup>113</sup> In this vein, a responsible parent standard, having resonance with more commonly understood conceptions of parental authority in a local setting, would also facilitate greater public understanding and feedback in the articulation and development of local analogues of acceptable risks. Finally, it is to be expected that societies and communities may arrive at differing determinations as to the levels of risk a responsible parent may permit.<sup>114</sup> This accords respect to the varying cultural, familial and community norms across the globe, rather than ascribe normative significance to the differing “everyday” risks of life in those communities over which parents may have little or no choice over.

Nevertheless, it must be acknowledged that differing risk thresholds are prone to exploitation by investigators impeded by stricter standards in their home country. Guideline 3 of the CIOMS Guidelines provides a ready solution to this:

An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and *the ethical standards applied should be no less stringent than they would be for research carried out in that country*. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs and priorities of the host country and meets the requisite ethical standards.<sup>115</sup>

In short, there must be dual scientific and ethical review by an IRB in the host and sponsoring country, with each committee paying particular attention to matters within their competence.<sup>116</sup> This review strategy affords a means of preventing potentially exploitative trials on children in host countries who are unlikely to

113. See Ackerman, *supra* note 51, at 107-09.

114. Freedman et al., *supra* note 52, at 17-18.

115. CIOMS Guidelines, *supra* note 2, at Guideline 3 (emphasis added). See also Freedman et al., *supra* note 52, at 18.

116. The commentary to Guideline 3 also recommends that the host country ethical review committee must have members or consultants who have a thorough understanding of a community’s customs and traditions, while Guideline 2 requires the inclusion of a variety of professional as well as lay persons qualified to represent cultural and moral values of the community.

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benefit from them. It could be further augmented by requiring host nation IRBs to provide greater public transparency and participation in evaluating appropriate risk thresholds given the features of the responsible parent standard discussed above. No doubt, this will necessarily entail greater cost and delay. However, since the need to enroll children in non-beneficial trials is widely acknowledged to be exceptional,<sup>117</sup> then this would be a price worth paying.

**D. The ICH Good Clinical Practice Guideline 1996**

It is unfortunate that the highly influential<sup>118</sup> International Conference on the Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use's ('ICH') Harmonized Tripartite Guideline for Good Clinical Practice ('GGCP')<sup>119</sup> provides considerably less clear guidance on non-beneficial trials. Under the rubric of informed consent, paragraph 4.8.14<sup>120</sup> of the GGCP provides that non-therapeutic trials may be conducted in subjects with the consent of a legally acceptable representative on the condition that:

117. See, e.g., FLETCHER et al., *supra* note 20, at 186.; U.S. Federal Drug Administration Pediatric Advisory Subcommittee, Ethics Working Group Consensus Statement (15 Nov. 1999), ¶ 1, available at <http://www.fda.gov/cder/pediatric/ethics-statement.htm>.
118. The ICH GCP has been adopted in various non-ICH participating countries in Asia, either with modifications or a wholesale importation. C.G. Fenn et al., *The Contemporary Situation for the Conduct of Clinical Trials in Asia*, 15 INT'L JOURNAL OF PHARMACEUTICAL MEDICINE 169, 170 (2001). Further, many other countries in the Asia-Pacific region are attempting to develop their regulatory systems to be compatible with ICH guidelines, and various regional harmonization initiatives in Asia Pacific Economic Co-operation, Association of South East Asian Nations, Pan American Health Organisation and the South African Development Community participating in ICH consultations and consideration step-wise implementation of ICH guidelines, including the GGCP. Y. Hayashi, *Impact of the Int'l Conference on Harmonisation in Asia*, 37 DRUG INFORMATION JOURNAL 129, 135-36 (2003).
119. ICH Harmonised Tripartite Guideline, *supra* note 26.
120. The more specific *Clinical Investigation of Medicinal Products in the Pediatric Population: E11* does not provide any elaboration of the requirement of 'low' risk under 4.8.14(b), merely stating that paediatric participants are generally expected to benefit from the clinical trials. ICH Harmonised Tripartite Guideline, *Clinical Investigation of Medicinal Products in the Pediatric Population; E11*, ¶ 2.6, (July 2000), available at <http://www.ich.org/cache/compo/276-254-1.html> [hereinafter *Clinical Investigation*].

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- (1) the objectives of the trial cannot be met by means of a trial on subjects who can give informed consent personally,
- (2) the foreseeable risks to the subjects are low;
- (3) the negative impact on the subjects well-being is minimised and low;
- (4) the trial is not prohibited by law;
- (5) the approval of the IRB or IEC is expressly sought and written approval covers this aspect.<sup>121</sup>

Paragraph 4.8.14 suffers from the usual shortcomings entailed in adopting a relative “low” risk threshold discussed above. It apparently also conflates various distinct ethical justifications for such research in children and in doing so, delegates a large amount of discretion on a local IRB without any normative direction on how it should go about the task. This is understandable in respect of ICH participating countries who have well developed ethical guidelines, regulatory mechanisms and expertise in place, but would not be a prudent stance in ensuring that adequate protections for paediatric subjects are in place for transnational clinical trials in developing countries. In its report on Clinical Trials in Developing Countries, the former U.S. National Bioethics Advisory Committee (“NBAC”) observed that:

the requirement for local review is occasionally tested and sometimes weakened when research is conducted in developing countries (something that can also happen within U.S. borders) . . . Although several developing countries have instituted national research ethics guidelines, and ethics review in some countries is becoming more established, many difficulties and challenges to local review remain, including lack of experience with and expertise in ethics review principles and processes; conflict of interest among committee members; lack of resources for maintaining the committees; length of time it can take to obtain approvals . . . .<sup>122</sup>

Further, while acknowledging that sufficient empirical evidence of the efficacy of local IRB review is not readily available,<sup>123</sup> Macklin draws together sufficient anecdotal evidence of review lapses in clinical trials conducted in developing countries that suggest that we cannot assume local review processes have sufficient expertise and resources to ensure that ethically appropriate risk thresholds are adhered to, or even that an independent review will always take place in the face of serious conflicts of interest that exist even amongst these IRBs.<sup>124</sup>

In the midst of a growing call for greater international harmonisation of clinical

121. *Id.* at ¶¶ 2.6.3-2.6.5.

122. National Bioethics Advisory Commission, ETHICAL AND POLICY ISSUES IN INTERNATIONAL RESEARCH: CLINICAL TRIALS IN DEVELOPING COUNTRIES 13 (2001), available at <http://www.georgetown.edu/research/nrcbl/nbac/pubs.html>.

123. Macklin, *supra* note 10, at 159.

124. *Id.* at 133-58.



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practice standards, it is unfortunate that the more recent ICH Guideline on Paediatric Clinical Trials has not seen it as necessary to improve on the requirements of Paragraph 4.8.14 of the ICH GCP, particularly with respect to clearer substantive risk thresholds and effective review of such non-beneficial trials.<sup>125</sup> This, it is submitted, is a serious lapse. In the midst of a rise in transnational clinical trials, there may also be a perverse race to the bottom on the part of developing countries to ensure they possess more facilitative levels of regulatory requirements, in order to encourage more clinical trials in their countries and reap their direct and ancillary benefits.<sup>126</sup> There is thus no assurance that these countries will also voluntarily heed the more specific CIOMS Guidelines or more stringent WHO Guidelines on standards of protection for children. The success of the first phase of the ICH harmonization initiative, relating to technical requirements,<sup>127</sup> which is strongly supported by the international pharmaceutical industry,<sup>128</sup> suggests that it likely to emerge as the gold standard of not only technical requirements but also good clinical practices.<sup>129</sup> Led by drug development jurisdictions representing 75% of the global pharmaceutical market and the pharmaceutical industry,<sup>130</sup> the ICH is in the driving seat for setting the appropriate bar for paediatric subject protections in transnational clinical trials as pharmaceutical companies would have a strong economic incentive to ensure that trials adhere to ICH GCP rooted standards in order for product safety and efficacy data to be accepted in seeking product registration in ICH countries.

For the reasons discussed above, two particular modifications to Paragraph

125. *Clinical Investigation*, *supra* note 120.

126. Kevin M. King, *A Proposal for the Effective International Recognition of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L. 163, 202 (1998).

127. Draft Report of the Joint CIOMS/WHO Working Group, *supra* note 8, at 34 ¶ 4.6.

128. C. Nutley argues that industry has three compelling reasons to support ICH and its harmonization efforts; (a) reduced development times and resources, (b) easier simultaneous launch of new drugs in many countries and (c) the facilitation of intra-company globalization by the recognition of a common standard. C. NUTLEY, THE VALUE AND BENEFIT OF ICH TO INDUSTRY (Jan. 2000), <http://www.ich.org/cache/compo/276-254-1.html> (follow "SC Reports and Other Documents" hyperlink)(last visited Dec. 9, 2006).

129. The Joint CIOMS/WHO working group has agreed on the universality of the ICH principles relating to both scientific and ethical issues and sought to encourage and assist resource limited countries in their implementation by providing relevant commentaries to the original ICH text. *See* draft Report of the Joint CIOMS/WHO Working Group, *supra* note 8, at 36 ¶ 5.0.

130. Harvey. Bale Jr., M.D., *Background and History of the ICH Global Cooperation Group in ICH*, SUMMARY REPORT OF THE 6<sup>TH</sup> ICH – NEW HORIZONS AND FUTURE CHALLENGES (Osaka, Japan, 13-15 Nov. 2003) at 32, *available at* <http://www.ich.org/LOB/media/MEDIA1383.pdf>.

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4.8.14 of the ICH GCP are recommended. First, the “low” risk standard should be replaced by the responsible parent standard to determine acceptable risk levels for non-beneficial trials. As defined, the CIOMS Guidelines’ routine examinations standard is likely to rule out non-beneficial clinical trials insofar as they go beyond routine interventions by exposing subjects to the investigational product.<sup>131</sup> Under the responsible parent standard, this may be permissible even in the absence of direct clinical benefit, after taking into account the child subject’s prevailing health risks, past experiences, mental capacity, maturity and the prevailing social norms in his society or community. Secondly, to counter the problem of possible exploitation of differing risk thresholds, dual review by sponsoring and host country IRBs as prescribed by CIOMS Guideline 3 should be implemented under Paragrah 4.8.14.<sup>132</sup>

It should be noted that the ICH GCP only lays down the minimum standards for non-therapeutic paediatric trials. Countries or regions are free to ratchet up protections by simply prohibiting non-beneficial trials in children, and many have done so.<sup>133</sup> This works against achieving a consistent international approach to the problem, and may disproportionately expose children in countries with anything less than an absolute prohibition to the burdens imposed by such trials. Should the ICH GCP instead simply follow the tack of the WHO Guidelines 1995 and the EDGCP? Some commentators point out that an absolute prohibition on such research involvement would be to the long term detriment of children’s health and well-being.<sup>134</sup> If properly applied and reviewed, the responsible parent standard in fact reflects a stringent objective standard pegged to the overall developmental welfare of child and thus should ensure their interests are not unfairly compromised. It also seeks to accommodate the legitimate interests and values of different societies and communities, faced with their particular paediatric health challenges, in the search for the appropriate balance between the valid competing interests of encouraging clinical trials responsive to the health needs of those children and the respect and protection due to each individual child from research risks.

131. See G. Koren, *Healthy Children as Subjects in Pharmaceutical Research*, 24 THEORETICAL MED. 149, 152 (2003).

132. This is also the position adopted by the recent *Universal Declaration on Bioethics and Human Rights*, *supra* note 23, at art. 21(2).

133. See *supra* notes 76, 86 and 98.

134. Freedman et al., *supra* note 52, at 17.

## **V. Conclusion**

In conclusion, the international guidelines on non-beneficial paediatric trials differ substantially in approach to the determination of risk thresholds. This is reflective of the domestic treatment of issue, and the difficult ethical evaluations involved in balancing therapeutic risks inherent in untested pharmaceuticals and the imposition of research risks on child subjects. Improvements to the current difficulties should start at the ICH GCP forum given the influence this conference has on the general move towards greater international harmonisation on drug development regulations. Ethically appropriate risk thresholds for non-beneficial clinical trials should be assessed by a responsible parent standard pegged to the socially accepted levels of risk exposure associated with the moral and educational development of children. Enhanced, dual reviews by the sponsoring and host country IRBs should also be required by the GCP. This would significantly improve the current voluntary international framework that lacks binding enforcement mechanisms and perhaps also encourages more focussed empirical study of comparable familial risk analogues for non-beneficial paediatric clinical trials in order to improve the ethical assessment of research risk in such clinical trials.