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## Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

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# Protecting the Rights of Pediatric Research Subjects in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

Ann E. Ryan

## **Abstract**

This Comment argues that the parties to the International Conference on Harmonization of Technical Requirements for Regulation of Pharmaceutical Drugs (ITCH) should adopt more specific guidelines for pediatric research than those included in its Good Clinical Practice Guidelines (ICH GCP), and analyzes their attempt to do so in the Draft Guideline on Pediatric Trials. Part I of this Comment outlines the genesis of the current international guidelines for human research and how they relate to pediatric subjects. Part I also explains the human research guidelines of the three principal members of the ICH. Part II describes the function of the ICH and the provisions of the ICH GCP. Part II also discusses how the ICH GCP addresses pediatric medical research issues, and the provisions of the new Draft Guideline on Pediatric Trials. Part III argues that the Draft Guideline on Pediatric Trials represents a significant improvement in pediatric research guidelines, and should be accepted by the parties to the ICH with some modifications regarding the subject's consent and the role and composition of international review boards.

PROTECTING THE RIGHTS OF PEDIATRIC RESEARCH  
SUBJECTS IN THE INTERNATIONAL CONFERENCE ON  
HARMONISATION OF TECHNICAL REQUIREMENTS  
FOR REGISTRATION OF PHARMACEUTICALS  
FOR HUMAN USE

*Ann E. Ryan\**

*INTRODUCTION*

In the early 1990s, thirty-six healthy children between the ages of six and ten years old participated in a research study in New York City.<sup>1</sup> This study exposed its subjects to a drug that had been removed from the market by the U.S. Food and Drug Administration<sup>2</sup> ("FDA") for causing death in adult patients.<sup>3</sup> In the course of this three-year study, researchers forced children to fast for eighteen-hour periods and drew multiple blood samples from catheters inserted in their veins.<sup>4</sup> This process left some of the children feeling nauseous and complaining of headaches.<sup>5</sup>

Researchers exposed the children in this study<sup>6</sup> to doses of the diet drug fenfluramine, to help measure a hormone in their brains that may be linked to antisocial behavior.<sup>7</sup> The subjects agreed to participate only after they were offered US\$25 gift certificates to a popular toy store, and their parents gave permission after they were offered US\$100 for their children's partici-

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1. Rick Weiss, *Volunteers at Risk in Medical Studies; Complex Research Projects Strain System of Safeguards*, WASH. POST, Aug. 1, 1998, at A1.

2. See *Food and Drug Administration: An Overview*, (visited Mar. 8, 2000) <<http://www.fda.gov/opacom/hpview.html>> (on file with the *Fordham International Law Journal*) (explaining that U.S. Food and Drug Administration ("FDA") is public health agency charged with protecting U.S. consumers by ensuring that only wholesome food, and safe and effective cosmetics and pharmaceuticals are marketed in United States).

3. See Weiss, *supra* note 1, at A12 (explaining that fenfluramine has not been approved for use in children and was pulled from market as diet drug for adults).

4. See *id.* (explaining that blood samples were taken over several hours).

5. See *id.* (stating that trial methods left children feeling sick).

6. See *id.* (noting that all subjects were younger siblings of juvenile delinquents).

7. See *id.* (describing purpose of study).

pation.<sup>8</sup> Accordingly, the researchers proceeded with the study in the manner approved by an institutional review board (or "IRB").<sup>9</sup>

This case is only one example of a long history of abuses of pediatric research subjects, both in the United States and around the world.<sup>10</sup> The fact that this study was conducted in the United States, which is recognized as a leader in human research protections,<sup>11</sup> indicates that more protections are needed both nationally and globally to safeguard vulnerable pediatric subjects.<sup>12</sup> Particular areas of concern when conducting research on pediatric populations include the level of risk to which children may be exposed<sup>13</sup> and finding an age-appropriate sub-

8. *Id.*

9. *See id.* (describing institutional review board (or "IRB") approval of this study). An IRB is "any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research." 21 C.F.R. § 50.1 (1999).

10. *See* Susan E. Lederer & Michael A. Grodin, *Historical Overview: Pediatric Experimentation*, in CHILDREN AS RESEARCH SUBJECTS, 3, 19 (Michael A. Grodin & Leonard H. Glantz, eds., 1994) (stating that history of pediatric research is, essentially, history of abuses).

11. *See* Ileana Dominguez-Urban, *Harmonization in the Regulation of Pharmaceutical Research and Human Rights: The Need To Think Globally*, 30 CORNELL INT'L L.J. 245, 245-46 (1997) (stating that United States has very advanced and comprehensive laws regarding drug research and marketing); *see also* Keith Epstein & Bill Sloat, *U.S. Medical Researchers Flout Rules Around the World*, PLAIN DEALER, Nov. 8, 1998, at A1 (remarking that "[a] legacy of medical exploitation," including radiation experiments and syphilis studies on African-Americans "has led the United States to adopt some of the world's toughest protections for people on whom scientists test new drugs, devices and vaccines").

12. *See* THE INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE, TRIPARTITE GUIDELINE FOR GOOD CLINICAL PRACTICE (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) (1996), *also available in* <<http://www.ich.org>> (on file with the *Fordham International Law Journal*) [hereinafter ICH GCP]. The ICH GCP defines vulnerable populations as

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

*Id.* art. 1.61.

13. *See* William G. Bartholome, *Ethical Issues in Pediatric Research*, in THE ETHICS OF

stitute for informed consent.<sup>14</sup>

While most countries have already enacted national legislation addressing human research,<sup>15</sup> the international nature of the medical, and particularly the pharmaceutical industry, which is responsible for a large percentage of medical research worldwide,<sup>16</sup> has created a call for stronger international guidelines on this issue.<sup>17</sup> A new opportunity to address this issue as a global concern has arisen with the International Conference on Harmonisation of Technical Requirements for Regulation of Pharmaceutical Drugs ("ICH"), its Good Clinical Practice Guidelines<sup>18</sup> ("ICH GCP"), and its Draft Consensus Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population (or "Draft Guideline on Pediatric Trials").<sup>19</sup>

This Comment argues that the parties to the ICH should adopt more specific guidelines for pediatric research than those included in the ICH GCP, and analyzes their attempt to do so in the Draft Guideline on Pediatric Trials. Part I of this Comment outlines the genesis of the current international guidelines for human research and how they relate to pediatric subjects. Part I also explains the human research guidelines of the three principal members of the ICH. Part II describes the function of the ICH and the provisions of the ICH GCP. Part II also discusses how the ICH GCP addresses pediatric medical research issues,

RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY, 339, 349-56 (Harold Y. Vanderpool, ed. 1996) (describing debate over regulation of risks in U.S. regulations).

14. See Michael A. Grodin & Leonard H. Glantz, *Preface*, to CHILDREN AS RESEARCH SUBJECTS at i, vii (Michael A. Grodin & Leonard H. Glantz, eds., 1996) (explaining problems caused by pediatric subjects' inability to give legal consent).

15. See Dominguez-Urban, *supra* note 11, at 268 (stating that national regulations have little effect on international community).

16. See *id.* (noting that "[p]harmaceutical research is the predominant type of research using human subjects").

17. See *id.* at 273 (stating that because there are no international treaties on research, other international documents have been ineffective).

18. See ICH GCP, *supra* note 12, at Introduction (explaining that this document will create "international ethical and scientific quality standard for designing, conducting, recording and reporting trials").

19. DRAFT CONSENSUS GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION, released for Consultation Oct. 7, 1999 (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 1999) (visited Dec. 28, 1999) <<http://www.ifpma.org/ich5e.htm>> (on file with the *Fordham International Law Journal*) [hereinafter DRAFT GUIDELINE ON PEDIATRIC TRIALS].

and the provisions of the new Draft Guideline on Pediatric Trials. Part III argues that the Draft Guideline on Pediatric Trials represents a significant improvement in pediatric research guidelines, and should be accepted by the parties to the ICH with some modifications regarding the subject's consent and the role and composition of IRBs.

# I. DEVELOPMENT OF PEDIATRIC MEDICAL RESEARCH, INTERNATIONAL CONVENTIONS, AND DOMESTIC REGULATIONS

Abuses of clinical trial subjects, particularly children, has plagued human research.<sup>20</sup> These abuses led the international human rights and medical communities to create regulatory controls, although until recently, none of these attempts have resulted in binding international agreements.<sup>21</sup> Although there is only one binding international convention addressing human research,<sup>22</sup> many countries, including the parties to the ICH, have created their own regulations or guidelines addressing pediatric research.<sup>23</sup>

## A. Overview of Children in Medical Research

Pediatric research subjects have endured abuses in medical research settings for hundreds of years.<sup>24</sup> Despite these abuses, however, pediatric testing cannot be banned because of the scientific need to test drugs and other treatments on children.<sup>25</sup>

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20. See Lederer & Grodin, *supra* note 10, at 19-20 (stating that throughout history, convenience led scientists to exploit child subjects to further medical science).

21. See Dominguez-Urban, *supra* note 11, at 268 (explaining international scheme for regulation, but stating that there are still no binding regulations on human research).

22. See Peter Leuprecht, *Innovations in the European System of Human Rights Protection: Is Enlargement Compatible with Reinforcement?*, 8 TRANSNAT'L L. & CONTEMP. PROBS. 313, 325 (1998) (stating that Council of Europe Convention on Human Rights and Biomedicine is first binding international document on human rights in biomedicine).

23. See Dominguez-Urban, *supra* note 11, at 269 (noting that most industrialized nations have some ethical review standards or mechanisms for human research).

24. See Lederer & Grodin, *supra* note 10, at 3-4 (explaining that medical studies on children in past would not comply with current standards of ethical research).

25. See American Academy of Pediatrics, Committee on Drugs, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, PEDIATRICS, Feb. 1995, 286, 286 (explaining that "[g]rowth, differentiation, and maturation can alter the kinetics, end organ responses, and toxicities of drugs in the newborn, infant, child, or adolescent as compared to the adult").

To conduct this research in an ethical manner, researchers and governmental actors regulating research must be cognizant of children's special physical and emotional vulnerabilities, as well as their liberty interests and dignity as human beings.<sup>26</sup>

### 1. History of Pediatric Research

Historically, children were exposed to a great deal of risky medical research.<sup>27</sup> The amount of pediatric research increased dramatically in the nineteenth century, along with the growth of pediatric medicine, in an attempt to improve children's health through superior vaccinations and inoculations.<sup>28</sup> The researchers conducting these trials made significant oncological contributions by curing serious childhood diseases.<sup>29</sup> They also, however, often placed pediatric research subjects at considerable risk.<sup>30</sup>

Similar high-risk experiments continued in the late nineteenth century, even as general recognition grew that children deserve special social protections.<sup>31</sup> During this period, researchers focused their experiments upon children who were institutionalized in asylums and orphanages<sup>32</sup> as control groups for

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26. See *id.* at 287 (stating that because children are particularly vulnerable, they must be provided added protection against violations of their rights and against risk, necessitating special considerations when soliciting participants, assessing risks and benefits, and ensuring equal representation of population and equal benefits).

27. See Leonard H. Glantz, *Research with Children*, 24 AM. J. L. & MED. 213, 215 (1994) (stating that "children have been particularly subjected to abuses by researchers and 'those who do research with children today have inherited the legacy of researchers who have come before them'").

28. See Lederer & Grodin, *supra* note 10, at 6 (explaining that poor social conditions in late 19th century led to further investigation into child health problems).

29. See *id.* at 4-5 (describing pediatric trials that led to smallpox vaccinations); see also *id.* at 7-8 (describing how pediatric research led to anti-toxins for diphtheria, which was main cause of death in 19th century children).

30. See Glantz *supra* note 27, at 215 (explaining that Edward Jenner, creator of smallpox vaccine, tested vaccine on his one-year-old son, and another eight-year-old boy, who was then exposed to smallpox virus). When the smallpox vaccine was shipped to the United States, it was tested on 48 children in a home for indigents. *Id.*

31. See Lederer & Grodin, *supra* note 10, at 6 (mentioning that "[c]hildren became a focus of social reform in the nineteenth century," and describing creation of American Pediatric Society to "establish pediatrics as a branch of the medical sciences"). The American Academy of Pediatrics (or "AAP") was established "to benefit the health and welfare of children." *Id.* During this time period, children were increasingly regarded as distinct from adults, and "childhood became a period of life worthy of being recognized and extended." *Id.*

32. David N. Weissstub, *et al.*, *Biomedical Experimentation with Children: Balancing the*

research on measles,<sup>33</sup> the germ theory,<sup>34</sup> and other diseases, theories, and medical treatments.<sup>35</sup> The dangers inherent in these trials were manifested in several cases,<sup>36</sup> particularly in one North Carolina orphanage where children were administered an experimental tuberculosis vaccine in 1912.<sup>37</sup> The children tested in this trial were later found to have a greater tendency to contract the disease than the children who had not received the experimental treatment.<sup>38</sup>

In the twentieth century, newer, more sophisticated drugs and medical tools, such as the x-ray, prompted continued medical research on children, focusing in particular on metabolism and digestion.<sup>39</sup> Some of these experiments caused their subjects to undergo unnecessary medical procedures, and endure a great deal of discomfort.<sup>40</sup> Due to the negative publicity surrounding these trials, however, experiments that abused children began to face increased scrutiny from members of the medical community and society-at-large.<sup>41</sup>

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*Need for Protective Measures with the Need To Respect Children's Developing Ability To Make Significant Life Decisions for Themselves*, in RESEARCH ON HUMAN SUBJECTS 380, 381 (David N. Weisstub, ed., 1998) (citing one New York pediatrician who commented that children in asylums were ideal research subjects because of researcher's ability to control subjects).

33. See *id.* at 380-81 (noting that trials similar to smallpox trials were conducted for measles).

34. See Glantz, *supra* note 27, at 216 (describing how germ theory was tested by injecting children and adults with various diseases).

35. See *id.* at 216 (explaining trial where doctor performed spinal taps on 29 children to determine if they are harmful, along with trials involving x-rays).

36. See Lederer & Grodin, *supra* note 10, at 7 (explaining that medical interest in diseases like cancer, leprosy, syphilis, gonorrhea, tuberculosis, and yellow fever prompted researchers to infect children and other research subjects deliberately); see also *id.* (describing Japanese experiments with scarlet fever in three to seven-year-old children).

37. See *id.* at 8 (describing tuberculosis study where 262 children at North Carolina orphanage were injected with experimental tuberculosis vaccine in 1912).

38. See *id.* (noting that when Public Health service tested North Carolina subjects in 1914, "guinea pigs who had received the [tuberculosis] vaccine yielded more quickly to tubercular infection than those not vaccinated").

39. See *id.* at 9 (explaining that doctors used x-rays to study normal development of children and fetuses *in utero*, and that there was great interest in studying digestion using stomach tubes in children and infants).

40. See *id.* at 10 (describing gastrointestinal tests that caused subjects to become ill and other studies where children had to be sedated and restrained to achieve compliance with protocol requirements).

41. See Glantz, *supra* note 27, at 216 (describing 1941 incident where editor of *Journal of Experimental Medicine* refused to publish study in which 12 healthy infants were



Despite this increased scrutiny,<sup>42</sup> pediatric subjects continued to endure abuses well into the second half of the twentieth century.<sup>43</sup> One of the most infamous examples of this exploitation was the hepatitis testing conducted at the Willowbrook State School beginning in 1955 and continuing through the early 1970s.<sup>44</sup> Even though researchers conducting this study obtained the subjects' parents' permission, the parents were not fully apprised of the risks involved in the protocol.<sup>45</sup> The head of the Willowbrook research team defended the study by explaining that research subjects were at no greater risk, and were, in fact, at lower risk of serious illness than the school's other students due to the poor conditions that existed at the school.<sup>46</sup> Despite this researcher's defenses, critics continued to question the merits of this study.<sup>47</sup> Even though this study and others similar to it<sup>48</sup> heightened awareness of pediatric research, abuses

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inoculated with herpes, even though these children were volunteered by parents for study).

42. See Lederer & Grodin, *supra* note 10, at 11-13 (explaining that groups opposing animal research began to oppose pediatric research subject abuse in late 19th century, and were later joined by members of medical community and journalists).

43. See Epstein & Sloat, *supra* note 11, at A12 (describing recent trials on pediatric subjects conducted by U.S. researchers in Slovak Republic and Egypt without proper informed consent).

44. Robert M. Nelson, *Children as Research Subjects*, in *BEYOND CONSENT: SEEKING JUSTICE IN RESEARCH* 47, 49 (Jeffrey P. Kahn, et al., eds., 1998). In this study, a group of mentally challenged students were exposed to a strain of the hepatitis virus intentionally, so that researchers could "understand the natural history and prevention" of this disease. *Id.*

45. See Lederer & Grodin, *supra* note 10, at 17 (explaining that researchers told parents that participants would be placed in special ward where they would be protected from other diseases running rampant in facility, and that there were questions regarding whether parents had been given adequate information regarding hepatitis risks); see also Nelson, *supra* note 44, at 51 (observing that "consent forms that parents signed to allow their children to be infected with the virus" read as though their children were to receive a vaccine").

46. See Nelson, *supra* note 44, at 50 (citing interviews with Saul Krugman, head of Willowbrook research team, in which Krugman states that because subjects were protected from common diseases at Willowbrook, including shigellosis and respiratory infections, participation in hepatitis study was safer than school's ordinary living conditions, and therefore ethical).

47. See *id.* at 50 (explaining that commentators questioned whether parents were coerced into consenting by promise of better conditions for their children, why similar tests were not conducted on adult staff members of facility, and why other sanitation and prevention measures were not taken to control spread of disease).

48. See *id.* at 52 (stating that U.S. Federal Regulations were designed to prevent abuses such as those occurring at Willowbrook and Fernald Schools). Circumstances similar to those existing at the Willowbrook School existed in radiation experiments

continue throughout the world.<sup>49</sup>

## 2. The Problem of Therapeutic Orphaning

Even though medical studies that are conducted on children may be controversial, the scientific need for such experimentation is apparent.<sup>50</sup> A child's physiology is significantly different from that of an adult or a child of a different age group.<sup>51</sup> These differences may have a significant impact on whether and how a drug can be used on a pediatric patient.<sup>52</sup> Drug studies conducted on adults, moreover, may not adequately predict

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conducted at the Walter E. Fernald School in Massachusetts, between 1950 and 1953. *Id.* at 51. In the course of these studies, 17 children were exposed to radioactive iron, and 57 were exposed to radioactive calcium. *Id.* Information letters sent to parents falsely indicated that this study was intended to benefit the subjects. *Id.*

49. See Epstein & Sloat, *supra* note 11, at A12 (describing study conducted by U.S. researchers in Slovak Republic on allergic diseases that was stopped because researchers were drawing blood samples from children without informing parents or children what study was about or asking for permission); see also *id.* (describing study conducted in Egypt in 1997 by U.S. researchers assessing blood levels in children, without telling children or parents blood was being drawn for research).

50. See National Institutes of Health ("NIH"), *NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects*, March 6, 1998, (visited Feb. 16, 2000) <<http://www.nih.gov/grants/guide/notice-files/not98-024.html>> (on file with the *Fordham International Law Journal*) (stating that NIH concluded that "there is a need to enhance the inclusion of children in clinical research," after reviewing "scientific information, demonstrated human need, and considerations of justice for children in receiving adequately evaluated treatments"); Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43900, 43901 (1997) (stating that pediatric testing is necessary to determine appropriate drug dosing guidelines, as incorrect dosing can lead to "unexpected adverse reactions," and ineffective treatment).

51. See NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN CHILDREN, CPMP/EWP/462/95, art. 1.2 (European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products ("CPMP") 1997), available at <<http://www.eudra.org/humandocs/PDFs/EWP/046295en.pdf>> [hereinafter GUIDELINE FOR CHILDREN] (on file with the *Fordham International Law Journal*) (stating that "[a]dequate evaluation of medicinal products for use in children cannot be achieved in adult studies because there are physiological differences between children and adults, and because children suffer from different diseases from adults, or show a different natural history for the same disease."). The Note for Guidance on Clinical Investigation of Medicinal Products in Children ("Guideline for Children") also sets forth specific pharmacokinetic, pharmacodynamic, and pathological differences between children and adults. *Id.* art. 1.2 (a)-(d).

52. See *id.*, art. 1.2 (a), (b) (explaining metabolic differences between children of different ages and differences in organ and tissue function); see also Ralph E. Kauffman, *Scientific Issues in Biomedical Research with Children*, in CHILDREN AS RESEARCH SUBJECTS 30, 38 (Michael A. Grodin and Leonard H. Glantz, eds. 1994) (stating that "capacity to metabolize and excrete drugs changes throughout infancy, childhood, and adolescence").

whether a drug will be toxic if prescribed to a child.<sup>53</sup> Pharmaceutical companies' failure to test medicines in children may result in death or serious illness.<sup>54</sup> Without adequate pediatric testing, doctors encounter a serious ethical dilemma: either prescribe medication or perform a procedure that potentially may benefit the child, or refrain from this treatment because it has not been adequately tested on children.<sup>55</sup> This problem, commonly referred to as therapeutic orphaning,<sup>56</sup> hampers the development and use of potentially life-saving therapies for pediatric patients.<sup>57</sup>

Pediatric patients are likely to become therapeutic orphans, as many pharmaceutical companies resist conducting research on children<sup>58</sup> because of ethical and legal issues involved in performing pediatric trials,<sup>59</sup> difficulty recruiting subjects,<sup>60</sup> and strains in raising adequate funds to conduct extra protocols.<sup>61</sup> This situation creates grave dangers and risks for pediatric pa-

53. See *GUIDELINE FOR CHILDREN*, *supra* note 51, art. 1.2 (explaining that adult tests "may not accurately predict the minimal effective dose, maximum titrated dose, therapeutic effect or adverse reactions in the child"); see also Committee on Drugs, *supra* note 25, at 286 (explaining that drug studies in adults cannot accurately predict the "pharmokinetic, pharmacodynamic, or toxic properties of drugs in children").

54. See Committee on Drugs, *supra* note 25, at 286 (explaining that when children were prescribed drugs with insufficient pharmacological studies, they suffered severe toxic effects, including death).

55. See *id.* at 286-87 (explaining that using nonvalidated drugs, which does not create data for future use, may create greater risk than administering drugs in controlled clinical trial).

56. See ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 239 (1986) (explaining that this term arose from orphaning clauses that appear on many prescription drugs conveying warnings such as "not to be used in children.").

57. See *id.* (stating that therapeutic orphaning occurs when drug manufacturers cannot adequately label drug for use in pediatric patients or other patient populations, due to absence of appropriate testing).

58. See Robert Pear, *FDA Prescribes New Rules for Conducting Pediatric Drug Tests/Companies Say Requirements Impractical*, *HOUS. CHRON.*, Nov. 28, 1998, at 2 (explaining that pharmaceutical industry offered strenuous objections to new U.S. regulation requiring greater testing of drugs on children, calling requirements impractical and burdensome).

59. See LEVINE, *supra* note 56, at 239 (noting that "uncertainties about the ethical propriety of and legal authority to do research on children," have impeded pediatric testing); see also Pear, *supra* note 58, at 2 (stating that drug companies stated that newly required tests on children would be costly and unethical because they may put children at risk).

60. See Kauffman, *supra* note 52, at 31 (stating that many protocols are impeded because researchers are not able to enroll sufficient number of subjects that conform to study's criteria).

61. See LEVINE, *supra* note 56, at 240 (explaining that often, pharmaceutical compa-

tients, as a large number of medications commonly prescribed for children are not tested on pediatric subjects.<sup>62</sup> The problem is particularly pronounced in medications used to treat serious illnesses, such as the human immunodeficiency virus ("HIV").<sup>63</sup> Certain age groups are also commonly left out of drug trials, resulting in incomplete and unreliable results concerning the safety and effectiveness of drugs for these patients.<sup>64</sup>

### 3. The Need for Greater Protections for Children

When scientists conduct research on pediatric subjects, they must address special concerns.<sup>65</sup> First, they must determine the degree to which a child can be exposed to risks involved in participating in a clinical trial.<sup>66</sup> Along with mere physical risks, researchers must also consider a child's psychological and emotional state because the child may be exposed to extreme discomfort, even in situations where physical risk is absent.<sup>67</sup> A child's inability to understand an experiment and his or her

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nies are reluctant to invest huge sums of money required by FDA for marketing, estimated at US\$70 million per product in 1981).

62. See NIH, *supra* note 50, at 43899 (stating that AAP has reported that "only a small fraction of all drugs and biological products marketed in the U.S. have had clinical trials for use in pediatric patients").

63. See *id.* at 43900 (noting that less than half of FDA approved drugs used to treat human immunodeficiency virus ("HIV") and opportunistic infections caused by HIV are labeled for use in children). According to the AAP, 81% of the drugs listed in the 1991 Physician's Desk Reference disclaimed all use in children, or at least disclaimed use in children of certain age groups. *Id.* In 1992, 79% of the 19 new molecular entities that were approved by the FDA were not labeled for use in pediatric patients. Committee on Drugs, *supra* note 25, at 286. In 1996, only 37% of new molecular entities with potential usefulness in children had some pediatric labeling. NIH, *supra* note 50, at 43902. Similar problems exist in Europe, where the British Medical Journal reported that 36% of children in U.K. hospitals received medications that were not approved for pediatric use. *Unlicensed/Off-Label Use and Testing in Children*, MARKETLETTER, June 22, 1998.

64. See NIH, *supra* note 50 (explaining that there is almost no information for most classes of drugs for use in children under age two).

65. See GUIDELINE FOR CHILDREN, *supra* note 51, art. 1.1 (listing risk of injury and legal dependence on parents to make decisions as "Ethical Considerations").

66. See Committee on Drugs, *supra* note 25, at 288 (describing determination of risks and benefits as area of concern).

67. See Barbara Conrad & Sharon Horner, *Issues in Pediatric Research: Safeguarding the Children*, 2 J. SOC. PEDIATRIC NURSES 163, 166 (1997) (explaining that there are critical development periods that should be considered in risk analysis, although, generally, trials involving deception, "induced anxiety, stress, fear of failure, lowered self-esteem, intrusions of privacy, guilt, embarrassment, or compromised trust present greater risks to children than adults").

emotional immaturity may affect the way he or she perceives the experience dramatically.<sup>68</sup> Similarly, physical risks vary according to the child's age and developmental level.<sup>69</sup> Because a child's emotional and physical vulnerabilities change with age, trials must be conducted accordingly.<sup>70</sup>

In addition to the physical and psychological risks involved in subjecting children to medical research, there is concern that children's liberty interests may be compromised because of their inability to give adequate consent.<sup>71</sup> One reason for this concern is that informed consent may be more difficult to regulate fairly in children than in other decisionally-impaired populations.<sup>72</sup> Any regulations addressing this issue must balance the child's growing capacity to participate in making important decisions with the child's need for protection.<sup>73</sup> As many children have not yet exhibited values that would allow others to determine what the child would decide if legally competent, it is often

68. See *id.* (explaining that children's cognitive limitations, underdeveloped assessment skills and coping strategies, and lack of maturity may influence perception of trial experience and explanation of cause and effect).

69. See *GUIDELINE FOR CHILDREN*, *supra* note 51, art. 2 (outlining specific risks that must be considered when conducting trials in various age groups, such as body composition, potential hazards, increased rate of drug penetration in brain for infants, growth rate, absorption rates, and sexual maturation).

70. See Conrad & Horner, *supra* note 67, at 167 (noting psychological differences between children of different age groups). Researchers conducting studies involving pre-school age children must be sensitive to the fact that these children have underdeveloped coping strategies and assessment skills, and may be made particularly uncomfortable by changes in their every day routine and exposure to unfamiliar environments. *Id.* Consequently, changes in the child's schedule, time restraints, or frightening themes or environments may be stressful to children in this age group. *Id.* Children between the ages of 6 and 11 tend to be uncomfortable in situations that challenge their independence, or comparisons, especially unfavorable comparisons, with their peers. *Id.* These children are sensitive to peer group tensions, and being assigned names with negative connotations, such as "special needs." *Id.* Adolescents are also susceptible to studies that may damage their self-esteem, particularly those that affect the subject's appearance, or that deal with sexuality or sexual attractiveness. *Id.*

71. See Glantz, *supra* note 27, at 218 (explaining that because children may not be competent to volunteer to participate, child may be participating in study nonvoluntarily or involuntarily); see also LEVINE, *supra* note 56, at 235 (expressing view of those who believe that involving subjects who cannot give legal consent is objectionable, "[b]ecause the Nuremberg Code identifies voluntary consent as absolutely essential, it is clearly problematic to involve subjects who lack free power of choice.").

72. See Weisstub, *supra* note 32, at 384 (stating that two major problems are "the need to obtain substitute consent" with "need children have to develop their own capacity to give consent").

73. See *id.* at 383-84 (expressing difficulties assessing child's desire to participate in research studies).

difficult for a parent or guardian to provide a true substitute consent for a minor.<sup>74</sup> Additionally, at least one commentator believes that complete reliance on proxy consent<sup>75</sup> exposes the child to the possible ulterior motives of the substitute decision-makers or researchers, who may not always prioritize the child's best interests.<sup>76</sup>

Some commentators suggest that involving the child in the research participation decision is necessary in order to show respect for the child as an autonomous human being.<sup>77</sup> Although some commentators believe that proxy consent is sufficient for non-therapeutic, low risk experiments,<sup>78</sup> others believe that failing to respect a child's decision not to participate in a research protocol may affect the child's future ability to trust adults and

74. See *id.* (noting reasons why substituted consent presents unique problems for research on minors as opposed to other incompetent populations). David Weistub lists the differences as:

The "universality of childhood dependency," making the need to establish and maintain mechanisms for others to make health care decisions for children universally accepted.

1. As opposed to other vulnerable groups, children have "a clearly defined class of persons" to make medical and other decisions for them.
2. The need for substitute decision making changes with the child's age and maturity.
3. Many children have not expressed values to enable a substitute decision-maker to "assess what the child would do if competent."

*Id.*

75. See, e.g., Eric T. Juengst, *Protecting Human Subjects in Genome Research: A Preliminary Policy Agenda*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY* 401, 410 (Harold Y. Vanderpool, ed., 1996) (explaining problems caused by proxy consent, or when family members or authorized representatives give consent for incompetent subjects).

76. See Glantz *supra* note 27, at 219 (observing that parents are not obligated to make decisions in child's best interests, and that they may make "idiosyncratic decisions for their children for personal or religious reasons").

77. See Sanford Leikin, *Minors' Assent, Consent, or Dissent to Medical Research*, 15 I.R.B. 1, 1 (1993) (explaining that principle of respect for persons extends not only to respect for those capable of making autonomous decisions, but also to those who are not legally competent to make autonomous decisions).

78. See Willard Gaylin, *The Competence of Children: No Longer All or None*, HASTINGS CTR. RPT., Apr. 1982, 33, 37 (arguing that child's right to refuse participation in low risk/low gain experiments should be overridden if child's parent agrees to child's participation). Willard Gaylin espouses the view that parents and doctors should be able to ignore a child's refusal to participate in a low risk study to teach the child "moral responsibility." *Id.*; see also Lainie Friedman Ross, *Children as Research Subjects: A Proposal to Revise the Current Federal Regulations Using a Moral Framework*, 8 STAN. L. & POL'Y REV. 159, 171 (1997) (expressing view that parental permission alone is sufficient for minimal risk, non-therapeutic research, if parents feel that participation will "guide her development according to their vision of the good life").

members of the medical community negatively.<sup>79</sup> Some commentators also believe that respecting the child's decision may contribute to the trial's success, since it reduces the child's level of stress and anxiety, and increases the child's willingness to cooperate in the elements of the protocol.<sup>80</sup> There is also evidence indicating that participation in this type of decision making helps to develop a child's psychological well-being, and positive feelings of self-esteem and self-image.<sup>81</sup> Participation also gives the child access to making important life decisions in a controlled environment.<sup>82</sup>

These theories on why children should be given the oppor-

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79. See Bartholome, *supra* note 13, at 358-59 (arguing that ignoring child's refusal to participate may undermine child's trust of adults and sense of control over his or her life); see also Leikin, *supra* note 77, at 5 (stating that not only is failure to accept child's dissent disrespectful, but it may also undermine child's trust of people involved in protocol and compromise future relationships with health care providers); Committee on Drugs, *supra* note 25, at 298 (stating that all children over age seven should have right to refuse to participate in non-therapeutic research).

80. See Lois A. Weithorn & David G. Scherer, *Children's Involvement in Research Participation Decisions: Psychological Considerations*, in CHILDREN AS RESEARCH SUBJECTS 133, 135 (Michael A. Grodin & Leonard H. Glantz, eds., 1994) (stating that involving child in research decisions creates positive psychological benefits including, "greater feelings of competence and effectiveness, increased sense of self-esteem, reduced depression, decreased anxiety, and generally less psychopathology"). Additionally, involving children in research decision making, "may increase the child's compliance with the research endeavor, may improve their performance in the required tasks (including promoting their compliance with treatment regimens), and may lead to an improved treatment outcome."). Weisstub, *supra* note 32, at 394. Weisstub states that

To the child, rather than serving as an obstacle to participation in research, the process of consent may instead present an opportunity to develop the ability to evaluate the potential benefits to others and to medical science against the potential harm to herself, and to place this evaluation in the context of her own personal priorities.

*Id.*

81. See Weithorn & Scherer, *supra* note 80, at 133, 134 (stating that "it is in the interests of children, parents, and researchers to maximize the children's involvement in research participation decisions to the greatest extent to which the children are capable"); see also Bartholome, *supra* note 13, at 358 (arguing that "[r]espect for the child as a moral agent requires respect for the developing capacity of the child for autonomy," and that participation in this type of decision-making is essential to fostering development of children's self-esteem and self-image, and contribute to the child's psychological and moral growth); Weisstub, *supra* note 32, at 394 (stating that "considerable benefits may be derived from the dynamic involvement of the child in the consent process").

82. See Weithorn & Scherer, *supra* note 80, at 135 (describing benefits that children accrue by enabling them to practice decision-making skills that may be helpful in later determinations, such as whether to use illegal drugs). Participation in this type of decision-making helps develop a child's sense of responsibility and general decision-making abilities. *Id.* at 394.

tunity to participate in research decisions are strengthened by further evidence that even young children have the capacity to make rational choices concerning their involvement in research trials.<sup>83</sup> These studies have shown that children over the age of nine years old have the cognitive capacity to participate in making this decision.<sup>84</sup> The child's ability to make a rational choice, however, may vary depending on the type of research and interventions involved<sup>85</sup> and the child's own psychology.<sup>86</sup> Accordingly, factors other than age must be considered when determining whether a child is old enough to consent to participation, such as intellectual capacity, reasoning ability, life experience, the environment in which the research is to be conducted, and the child's personality.<sup>87</sup>

### B. *International Conventions and Their Effect on Pediatric Research*

The long history of human research abuses has led to numerous national and international human research regulations. The first major document setting forth guidelines in this field was the Nuremberg Code<sup>88</sup> (or "Code") in 1947.<sup>89</sup> Although the

83. See Leikin, *supra* note 77, at 2 (stating that "[a]lthough most experts still believe that the cognitive systems of early childhood, middle childhood, and adolescence are qualitatively different from one another, there is growing doubt that the differences between them are as radical as formerly thought."); see Conrad & Horner, *supra* note 67, at 166 (stating that children 7 to 12 years old can generally express preference regarding participation and understand risk and benefit and provide assent).

84. See Leikin, *supra* note 77, at 4 (stating that generally, children over age nine have sufficient cognitive capacity to provide assent to research participation). Many researchers and professional groups have asserted that children over the age of seven can be involved in deciding whether to participate in a research study. *Id.*; see also Weisstub, *supra* note 32, at 400-01 (citing studies suggesting that children between ages of 7 and 14 are capable of providing assent and consent, respectively, but stating that, as individual capacities differ, capacity must take into account functional criteria more than mere age). But see Committee on Drugs, *supra* note 25, at 290 (stating "[a]ssent must be obtained from any child with the intellectual age of 7 years or more. The protection provides the opportunity for a child 7 years or older to refuse participation in studies or procedures done for research purposes.").

85. See Leikin, *supra* note 77, at 4 (explaining that where research involves simple interventions, such as weighing child, very young child would be able to provide assent, however, in research involving more complex risks and interventions, such as drug trials, greater cognitive ability may be required). *Id.*

86. See *id.* at 2-4 (stating that child should be able to understand research, reason about research, and express their will without undue influence from outside sources).

87. See Weithorn & Scherer, *supra* note 80, at 165-71 (detailing factors that should be considered when determining whether child may provide meaningful assent).

88. See Sharon Perley, *et al.* *The Nuremberg Code: An International Overview*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE*, 149, 150 (George J. Annas & Michael A.



Nuremberg Code was significant in promoting informed consent, its shortcomings, including its lack of guidance on consent for incompetent subjects, caused the World Medical Association (or "WMA") to develop the Helsinki Declarations in 1964, with continual revisions through 1996.<sup>90</sup> The Helsinki Declarations represented a significant step forward in the area of pediatric research, by introducing the concept of proxy consent,<sup>91</sup> and allowing incompetent subjects to be involved in research participation decisions.<sup>92</sup> The World Health Organization ("WHO") and

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Grodin, eds., 1992) (stating that while Nuremberg Code (or "Code") was "almost certainly the first *international* code" it had several significant national and ancient predecessors).

89. *Id.*

90. See DECLARATION OF HELSINKI I (18th World Medical Assembly 1964), reprinted in THE NAZI DOCTORS AND THE NUREMBERG CODE 331 (George J. Annas & Michael A. Grodin, eds. 1992) [hereinafter HELSINKI I]. The World Medical Association ("WMA") doctors that formulated the Helsinki Declaration realized that the Code did not provide adequate guidance for many populations, including minors, and attempted to ameliorate this problem by adding proxy consent in the first Helsinki Declaration. Robert J. Levine, *International Codes and Guidelines for Research Ethics: A Critical Appraisal*, in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS, 235, 236 (Harold Y. Vanderpool, ed. 1996).

91. HELSINKI I, *supra* note 90, art. II (1), art. III (3a). Article II, "Clinical Research Combined with Professional Care," states

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In the case of legal incapacity consent should also be procured from the legal guardian; in the case of physical incapacity the permission of the legal guardian replaces that of the patient.

*Id.* art. II (1). Similarly, Article III, "Non-Therapeutic Clinical Research," paragraph 3a, states "[c]linical research on a human being cannot be undertaken without his free consent, after he has been legally informed; if he is legally incompetent, the consent of the legal guardian should be procured." *Id.* art. III (3a). Article II, paragraph 3(b) however, limits proxy consent in non-therapeutic trials by stating that the "subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice." *Id.* art. III (3b). Proxy Consent is consent to research given by a proxy consentor, who is "an individual authorized to exercise parental rights on behalf of or a spouse or guardian of the trial subject, or a person equivalent thereto." GUIDELINE FOR GOOD CLINICAL PRACTICE Ordinance No. 28 (Ministry of Health and Welfare 1997) [hereinafter NEW JAPANESE GCP].

92. See DECLARATION OF HELSINKI III, (35th World Medical Assembly 1983), reprinted in THE NAZI DOCTORS AND THE NUREMBERG CODE 336 (George J. Annas & Michael A. Grodin, eds., 1992) [hereinafter HELSINKI III]. Although the concept of involving minors in research participation decisions, at least in therapeutic trials, may be implied in Article II, paragraph 1, in the case of a psychologically incompetent person, informed consent should also be obtained from the legal guardian. *Id.* This idea is specifically enumerated in Article I, paragraph 11 of Helsinki III, which states,

In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or

the Council for International Organizations of Medical Science ("CIOMS") further developed these concepts in its International Ethical Guidelines for Biomedical Research Involving Human Subjects<sup>93</sup> ("CIOMS/WHO Guidelines" or "Guidelines") in 1993, devoting an entire section to research on children.<sup>94</sup> Although the Code, the Helsinki Declarations, and the CIOMS/WHO Guidelines are not legally binding, the Council of Europe recently passed the first binding international document that discusses human research.<sup>95</sup> The rights and protections outlined in these documents embody the growing international movement for children's rights exemplified by the United Nations Convention on the Rights of the Child (or "CRC").<sup>96</sup> Although there are many challenges incumbent in international research regulation,<sup>97</sup> the growing multinationalism of the phar-

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mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the 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.

*Id.* art. I (11).

93. INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Council for International Organizations of Medical Science (CIOMS) in collaboration with the World Health Organization ("WHO") 1993) [hereinafter CIOMS/WHO GUIDELINES].

94. *Id.*

95. See *Innovations in the European System of Human Rights Protection: Is Enlargement Compatible with Reinforcement?*, 8 TRANSNAT'L L. & CONTEMP. PROBS. 313, 325 (1998) (noting that Convention on Human Rights and Biomedicine ("Biomedical Convention") was first binding international document on bioethics).

96. See *United Nations Convention on the Rights of the Child*, G.A. Res. 44/25, U.N. GAOR, 44th Sess., Supp. No. 49, at 174, U.N. Doc. A/44/736 (1989), 28 I.L.M. 1448 (1989) [hereinafter CRC].

97. See Dominguez-Urban, *supra* note 11, at 253 (explaining that divergent cultural and regulatory systems impede harmonization efforts). Varying cultural values, with regard to the manner in which clinical testing is conducted, and the testing requirements themselves, have caused a significant barrier to regulatory harmonization. *Id.*; see also *id.* at 260 (explaining differences in regulatory ideals, stating that while United States requires randomized testing, France considers such testing "cruel and inhumane"); *id.* at 270 (describing different priorities placed on informed consent in European Union, United States, and Japan); Carel B. Ijsselmuiden & Ruth R. Fadden, *Medical Research and the Principle of Respect for Persons in Non-Western Cultures*, in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS 281, 287-88 (Harold Y. Vanderpool, ed., 1996) (describing anthropological reasons why individual informed consent may not be best model for certain non-Western Countries). In past attempts at international regulation, as ultimately recognized by the International Ethical Guidelines for Biomedical Research Involving Human Subjects ("CIOMS/WHO Guidelines"), a major problem was achieving consensus on informed consent. Perley, *supra* note 88, at 161. In many tribal cultures, and particularly in developing nations, individual informed consent may

maceutical and medical industries has created a demand for stronger and more cogent guidelines in pediatric research.<sup>98</sup>

### 1. The Nuremberg Code

The Nuremberg Code<sup>99</sup> was one of the first international instruments to define ethical standards for conducting medical research.<sup>100</sup> Although it has no concrete legal authority, the Code has served as a moral guide for researchers since its promulgation in 1947<sup>101</sup> by a panel of U.S. judges<sup>102</sup> at the conclusion of the Nuremberg Medical Trial.<sup>103</sup> The Nuremberg Medical Trial began on December 9, 1946, as a trial against twenty-three Nazi physicians for war crimes and crimes against humanity.<sup>104</sup> In the course of this trial, the judges received detailed information regarding the atrocities that Nazi physicians com-

not be as important as achieving consent from a tribal leader, family member, or community at large. See Dominguez-Urban, *supra* note 11, at 280 (explaining group consent mentality in non-Western cultures).

98. See Dominguez-Urban, *supra* note 11, at 245-46 (explaining how growth of harmonization of pharmaceutical regulation and mutual acceptance of clinical data has led to greater need for "regulations extending beyond national borders to protect human subjects").

99. United States v. Karl Brandt, *et al.*, 2 TRIALS OF WAR CRIMINALS BEFORE THE NUREMBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW 10, Case 1, Oct. 1946-Apr. 1949, 181-82 (1949) [hereinafter Nuremberg Code].

100. See Jonathan D. Moreno, *The Dilemmas of Experimenting on People; Striking a Balance Between Human Rights and Medical Progress*, MASS. INST. TECH. ALUMNI ASS'N TECH. REV., July, 1997, at 31 (stating that Nuremberg Trial prosecutors faced absence of internationally recognized codes of medical ethics regarding experimentation); see also Weithorn & Scherer, *supra* note 80, at 132 (describing absence of universal principles for human experimentation during Nuremberg Trials).

101. See Moreno, *supra* note 100 (calling Code powerful moral force, despite its lack of legal authority); see also Harold Y. Vanderpool, *Introduction and Overview: Ethics, Historical Case Studies, and the Research Enterprise*, in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY 501 (Harold Y. Vanderpool, ed., 1996) (remarking that some regard Nuremberg as fundamental standard for research in competent adults).

102. See Jonathan Moreno, *Reassessing the Influence of the Nuremberg Code on American Medical Ethics*, 13 J. CONTEMP. HEALTH L. & POL'Y 347, 348 (1997) (noting that Nuremberg panel was composed of three U.S. judges).

103. *Id.* The Nuremberg Medical Trial is another name for *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law 10*, Case 1 *United States v. Karl Brandt, et al.*, Oct. 1946-Apr. 1949, 1-1004; 2 *id.* [hereinafter Nuremberg Medical Trial].

104. See Evelyne Shuster, *The Nuremberg Code: Hippocratic Ethics and Human Rights*, 351 LANCET 974 (1998) (explaining that Nuremberg Medical Trial involved U.S. judges sitting in judgment of 23 Nazi physicians and doctors for murder and torture in conducting medical experiments).

mitted on human subjects in the name of medical research.<sup>105</sup> Although these experiments left the Nuremberg judges profoundly disturbed,<sup>106</sup> they found themselves at a loss for international guidelines by which to judge the defendants' behavior.<sup>107</sup>

To resolve the dilemma caused by the absence of universally accepted guidelines, the judges adopted their own set of standards, known as the Nuremberg Code.<sup>108</sup> The judges sought information from a variety of sources in order to form a consensus on the appropriate limits for human research.<sup>109</sup> By using these resources, the judges created a Code that represents not only the opinion of a single war crime tribunal, but also serves as a statement of universally-accepted principles of medical ethics.<sup>110</sup>

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105. See Telford Taylor, *Opening Statement of the Prosecution, December 9, 1946*, 1, *Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law 10*, 27-74 (detailing concentration camp experiments). Children, particularly twins, were subjected to numerous experiments in concentration camps. Eva Mozes-Kor, *The Mengele Twins and Human Experimentation: A Personal Account*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE* 53 (George J. Annas & Michael Grodin, eds. 1992). These trials included germ experimentation where one twin would be injected with a germ, and then, if that twin died, the other would be killed as well, to compare the autopsies of the infected child with the uninfected child. Mozes-Kor, *supra*, at 56. Among others, children were also engaged in tests to see how much blood a person could lose before they died, genetic studies involving cross-transfusions to try to "make boys into girls," and studies trying to create "Siamese twins" by joining a set of twins together. *Id.* at 57.

106. See *Judgement and Aftermath*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE* 94, 104 (George J. Annas & Michael Grodin, eds. 1992) (describing evidence of revolting physical conditions to which prisoners were exposed, and extreme pain or torture experienced by prisoner research subjects).

107. See Moreno, *supra* note 102, at 348 (explaining how Nuremberg judges had no preexisting international frame of reference by which to evaluate defendants' behavior, as defense attorneys were able to use ambiguity of human research protocol in defense arguments).

108. See George J. Annas & Michael Grodin, *Introduction*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE*, 3, 4 (George J. Annas & Michael Grodin, eds., 1992) (explaining that 10 point code was enumerated at end of judgment in Nuremberg Medical Trial).

109. See Michael A. Grodin, *Historical Origins of the Nuremberg Code*, in *THE NAZI DOCTORS AND THE NUREMBERG CODE*, 121, 139 (George J. Annas & Michael A. Grodin, eds., 1992) (explaining that Code was based on combination of testimony and memoranda prepared by representatives of American Medical Association ("AMA"), doctors Andrew Ivy, M.D., and Leo Alexander, M.D., Hippocratic Oath, writings of several medical ethicists, and notably, human research regulations promulgated in pre-war Germany and Third Reich).

110. See Moreno, *supra* note 102, at 348-49 (describing how Nuremberg judges believed that they were codifying pre-existing moral values among doctors); see also Nuremberg Medical Trial, *supra* note 103 at 181 (stating that "all agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts"). There is, however, some debate on whether the Code truly represented a universal set of guidelines. See LEVINE, *supra* note 56, at 240 (arguing that content of

## a. The Principles Embodied in the Code

The principle of informed consent is the most significant element of the Code,<sup>111</sup> and is outlined in its first principle.<sup>112</sup> The first principle of the Code states that all subjects must give voluntary, informed consent to participate in medical trials.<sup>113</sup> This principle also defines the requirements for informed consent, stating that an experiment should be explained to a subject in a manner that is free from duress, force, or deception.<sup>114</sup> Similarly, the subject must be at liberty to withdraw from the trial at any time.<sup>115</sup>

In addition to the informed consent provisions, the Code contains limitations on the degree of risk to which subjects can

Code was heavily influenced by fact that medical trial was heard by U.S. judges, relying heavily on testimony of two U.S. physicians, and is therefore product of Western ideas and culture).

111. See, e.g. George Annas, *Mengele's Birthmark: The Nuremberg Code in United States Courts*, 7 J. CONTEMP. HEALTH L. & POL'Y 17, 21 (1991) (describing Code as "most complete and authoritative statement of the law of informed consent to human experimentation").

112. See *id.* (stating that although informed consent is included in paragraph one, Code's other requirements regarding trial design must be satisfied before trial gets to consent stage).

113. Nuremberg Code, *supra* note 99, para. 1. The first principle states that "[t]he voluntary consent of the human subject is absolutely essential". *Id.*

114. *Id.* para. 1. The first principle of the Nuremberg Code states in full:

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

*Id.*

115. See *id.* para. 9. (stating that "[d]uring the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.").

be exposed.<sup>116</sup> Under the Code, the level of risk must be proportional to the trial's expected benefits, and no trials should be conducted where death or disabling injury may result.<sup>117</sup> The judges also provided adequate provisions in the event that the subject is injured or becomes ill as a result of the trial.<sup>118</sup>

### b. The Code and Pediatric Research

Although the Code pioneered international human research regulation, it has several widely recognized weaknesses.<sup>119</sup> Foremost among these weaknesses, the Code fails to provide for conducting research on subjects who are incapable of providing legal informed consent.<sup>120</sup> This omission led to widespread debate among members of the medical and ethical communities on whether research should be conducted on children at all.<sup>121</sup>

116. See *id.* para. 6. (explaining that "[t]he degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.").

117. See *id.* para. 5. (instructing that "[n]o experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps in those experiments where the experimental physicians also serve as subjects."). The level of risk is to be determined through prior animal experimentation and knowledge of the disease. *Id.* para. 3.

118. See *id.* para. 7 (stating that laboratory in which study takes place should also be inspected to "protect the experimental subject against even remote possibilities of injury, disability, or death.").

119. See Annas, *supra* note 111, at 24 (explaining physician's groups' complaints that Code was too legalistic and was irrelevant to normal medical experimentation).

120. See Nuremberg Code, *supra* note 99, para. 1 (stating that "the person involved should have legal capacity to consent."). There are no statements in the Code that allow for proxy consent, or any type of legal permission for subjects who are not personally capable of providing legal, voluntary consent. See Ross, *supra* note 78, at 159 (explaining that Code makes no mention of proxy consent and that subject must personally consent to research participation, thereby implying that children who are not capable of informed consent cannot participate).

121. See Ross, *supra* note 78, at 159-60 (describing problem created by Code's mandate that voluntary consent is absolutely essential when children are involved). Leading figures in this debate, beginning in the 1970s, were two Christian theologians, Paul Ramsey and Richard McCormick. *Id.* Ramsey posited that under the Code, children and other legal incompetents could never legally consent to participation in non-beneficial research. Paul Ramsey, *The Enforcement of Morals: Nontherapeutic Research on Children—A Reply to Richard McCormick*, HASTINGS CTR. REP., Aug. 1976, at 21. Ramsey further believed that because the Code never mentioned proxy consent, a parent's consent on behalf of a minor child is ethically invalid, and is, in fact, a breach of the fiduciary duty that a parent owes to his or her child. Ross, *supra* note 78, at 159. He calls research conducted under these conditions "offensive touching." Richard McCormick, *Experimentation in Children: Sharing in Sociality—A Reply to Paul Ramsey*, HASTINGS CTR. REP., Dec. 1976, at 41. McCormick, on the other hand, used a natural law argu-

In this regard, critics have and continue to view the Code as too restrictive to allow for human experimentation using any subjects other than competent adults.<sup>122</sup> Commentators felt that the limitations imposed by the Code would significantly hinder the study of childhood disease and conditions arising in the mentally ill.<sup>123</sup> Additionally, many doctors and researchers shared the view that the Code was inapplicable to their research.<sup>124</sup> These doctors felt that the extreme circumstances surrounding the Nuremberg Medical Trial and the atrocities committed in concentration camps had little relevance to their daily practices.<sup>125</sup> Consequently, although the Code formed the basis for modern regulations, the international medical community recognized the need for more practical and comprehensive guidelines.<sup>126</sup>

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ment to suggest that parental consent for a child's participation is valid because, presumably, the child would want to participate. Ramsey, *supra*, at 21. McCormick argues that as a social being, the child would want to participate in non-beneficial research that poses no harm to him because he ought to for the good of society as a whole. Ramsey, *supra*, at 22. Ramsey rebuts this argument, stating that a child's primary interest is his or her own physical well-being and to force a child to participate in this type of research amounts to compulsory altruism, which would be unacceptable if imposed on adults. *See id.* at 23 (stating that child's main interest is "preservation of [an] unimpaired life"). Ramsey's second argument is based on the Canteen theory that to use children as subjects in non-beneficial research is to use them solely as a means, rather than as an end. Ross, *supra*, at 160. McCormick replies to this argument by stating that the child is treated as an end, even in non-beneficial research, as the child benefits through helping society as a whole. *Id.*

122. See Harold Y. Vanderpool, *Introduction and Overview: Ethics, Historical Case Studies, and the Research Enterprise*, in *THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS: FACING THE 21ST CENTURY* 1, 8 (Harold Y. Vanderpool, ed., 1996) (stating that Code has been viewed as "politically naïve and unduly restrictive with respect to research involving children and other populations of patients").

123. See Perley, *supra* note 88, at 155 (noting that U.S. researcher Henry Beecher asserted that Code would "effectively curtail the study of mental illness and children's diseases").

124. See Moreno, *supra* note 102, at 349 (explaining that many doctors felt that Code only applied to Nazi doctors, not to them).

125. See *id.* at 349 (listing four rationales that explain why many doctors do not think that Nuremberg applies to them: that conduct of Nazi doctors was so extreme that Code would have no relevance to civilized, moral physicians; that concentration camps were far removed from normal circumstances attending medical research; that Hippocratic Oath was sufficient to guide doctors in everyday practice and research activities; and that requirement of "absolute consent" was unreasonable and inapplicable to important research protocols on children and other cognitively impaired populations); see also Shuster, *supra* note 104, at 976 (explaining that Code's link to Nazi atrocities, murder, and torture led average physicians to believe that Code was only relevant to Nazi Doctors).

126. See Perley, *supra* note 88, at 150-51 (stating that many believe that Nuremberg

## 2. The Helsinki Declarations

The criticisms surrounding the Code led physicians to call for a set of research guidelines that would be more relevant to their daily practices.<sup>127</sup> The World Medical Association's Committee on Medical Ethics ("Ethics Committee") first undertook this challenge in 1953<sup>128</sup> by creating the Resolution on Human Experimentation: Principles for Those in Research and Experimentation<sup>129</sup> ("Resolution").<sup>130</sup> The five principles embodied in this document placed primary ethical responsibilities on the researcher.<sup>131</sup> Furthermore, it clarified that personal informed consent was necessary for healthy subjects, while proxy consent was sufficient for those who were too ill to give consent.<sup>132</sup>

After the Resolution, the Ethics Committee continued to study medical research issues.<sup>133</sup> In 1964, the WMA's General Assembly in Helsinki adopted the result of the Ethics Committee's efforts, the Declaration of Helsinki<sup>134</sup> ("Helsinki I").<sup>135</sup>

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provided "starting point" for examining ethical issues regarding experimentation and brought "issue of human experimentation to the forefront of public debate"); Kevin M. King, Note, *A Proposal for the Effective International Regulation of Biomedical Research Involving Human Subjects*, 34 STAN. J. INT'L L. 163, 179 (1998) (stating that Nazi experiments highlighted need for more comprehensive guidelines to deal with human research).

127. See Robert J. Levine, *International Codes and Guidelines for Research Ethics: A Critical Appraisal*, in THE ETHICS OF RESEARCH INVOLVING HUMAN SUBJECTS 235, 242 (Harold Y. Vanderpool, ed., 1996) (citing WMA's Committee on Medical Ethics 1953 statement recognizing "need for professional guidelines designed by physicians for physicians" and that Code was not merely legal document created for use in specific trial).

128. See Perley, *supra* note 88, at 157 (explaining that WMA Committee on Medical Ethics began to deal with human experimentation in 1953, realizing need for professional guidelines to cure Code deficiencies, such as failure to recognize difference between therapeutic and non-therapeutic research).

129. *Resolution on Human Experimentation: Principles for Those in Research and Experimentation*, adopted by the WMA General Assembly 8th Sess. (Rome, 1954).

130. *Id.*

131. See Perley, *supra* note 88, at 157 (stating that Resolution on Human Experimentation placed primary responsibility for ethical conduct on researcher).

132. See *id.* (describing fourth principle as stating that researchers must attempt to obtain fully informed, free consent from healthy subjects, but may obtain consent of incompetent patient's next of kin, after informing subject or legal guardian of nature, reason, and risks involved in trial).

133. See *id.* at 158 (stating that between 1954 and 1960 Ethics Committee continued to study human experimentation, and presented first draft of Helsinki Declaration to WMA's 15th Assembly in 1961).

134. See *id.* at 158 (stating that after first draft was presented at 15th Assembly, Code underwent several revisions, and was adopted at WMA's 18th Assembly in Helsinki, Finland, in 1964); see also Zbigniew Bankowski, *International Ethical Considerations for Research on Human Subjects*, in ETHICAL ISSUES IN RESEARCH, 177, 181 (Darwin Cheney,



Although Helsinki I was influenced by the Code, it included several significant differences.<sup>136</sup> First, Helsinki I distinguished between therapeutic research<sup>137</sup> and non-therapeutic research,<sup>138</sup> ensuring the rights of patients receiving experimental therapeutic care, as well as the rights of volunteers.<sup>139</sup> Additionally, Helsinki I required that the level of risk inherent in the medical trial must be proportional to the trial's expected benefits.<sup>140</sup> Moreover, with regard to pediatric research, Helsinki I permitted proxy consent for all subjects who were legally incompetent.<sup>141</sup> Thus, Helsinki I enabled researchers to conduct trials on subjects who were not able to give legally competent consent, including pediatric and other vulnerable populations.<sup>142</sup> Although many physicians praised Helsinki I as providing an eth-

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ed. 1993) (explaining that need for ethical guidelines created by physicians was realized at 18th WMA Assembly in 1964, when Declaration of Helsinki was adopted).

135. *Id.*

136. See Perley, *supra* note 88, at 158 (mentioning that although Code is never explicitly mentioned in Helsinki I, Executive Director of WMA confirmed that Helsinki drafters consulted text of Code and Code was discussed at WMA Assembly meetings).

137. See Shuster, *supra* note 104, at 976 (distinguishing "therapeutic research" as that which benefits patient and which "[saves] life, re-establish[es] health or alleviat[es] suffering" from nontherapeutic research, which is defined as purely scientific.)

138. HELSINKI I, *supra* note 90, at Introduction. The Introduction to Helsinki I states, "a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and clinical research the essential object of which is purely scientific and without therapeutic value to the person subjected to the research." *Id.*

139. See Perley, *supra* note 88, at 158 (stating that Helsinki I's distinction between therapeutic and non-therapeutic research is important because it emphasized that patients who are receiving experimental therapies must be afforded same rights and respect as healthy patients).

140. HELSINKI I, *supra* note 90, art. 1.3. Paragraph 3 of the Basic Principles states, "[c]linical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject." *Id.*

141. *Id.* art. II (1). Article II, "Clinical Research Combined With Professional Care," states in paragraph 1,

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity consent should also be procured from the legal guardian; in case of physical incapacity the permission of the legal guardian replaces that of the patient.

*Id.* Regarding non-therapeutic research, article III (3a) states, "[c]linical research on a human being cannot be undertaken without his free consent, after he has been fully informed; if he is legally incompetent the consent of the legal guardian should be procured." *Id.* art. III (3a).

142. See Lederer & Grodin, *supra* note 10, at 16 (stating that Helsinki "recognized a place in medical research for experimentation in special populations and called for some protection for these groups, including a process of surrogate decision-making").

ical, rather than a legal, solution to the problems facing medical researchers,<sup>143</sup> others found that it was too paternalistic and vague.<sup>144</sup>

As a result, Helsinki I was revised at the twenty-ninth annual WMA meeting in Tokyo in 1975, creating the Declaration of Helsinki II<sup>145</sup> ("Helsinki II").<sup>146</sup> Several major concepts were introduced in this revision, such as an independent committee review requirement for all research protocols.<sup>147</sup> Further, Helsinki II supplemented Helsinki I's risk protections, as it emphasized protecting both the subject's physical<sup>148</sup> as well as psychological well-being.<sup>149</sup> Helsinki II also placed greater emphasis on the principle of informed consent by devoting three paragraphs of the Basic Principles to this topic,<sup>150</sup> instead of merely placing it among

143. See Annas & Grodin, *supra* note 109, at 26 (citing U.S. physician Henry Beecher, President of Council for International Organizations of Medical Sciences, praising Helsinki I). Beecher summarized the feelings of the international medical community in relation to Helsinki when he stated, "[t]he Nuremberg Code presents a rigid set of legalistic demands . . . . *The Declaration of Helsinki*, on the other hand, presents a set of guides. It is an ethical, as opposed to a legalistic document, and is thus a more broadly useful instrument than the one formulated at Nuremberg." *Id.*

144. See *id.* at 26 (citing Jay Katz's statement that Codes are "painfully vague").

145. DECLARATION OF HELSINKI II (29th World Medical Assembly, 1975), *reprinted in*, THE NAZI DOCTORS AND THE NUREMBERG CODE, 333 [hereinafter HELSINKI II]. See Perley, *supra* note 88, at 159 (stating that Helsinki I was largely unrevised for more than 10 years).

146. HELSINKI II, *supra* note 145.

147. See *id.* art. I (2) (stating that all experiments involving human subjects should be "transmitted to a specially appointed independent committee for consideration, comment and guidance").

148. See *id.* art. I (7) (stating that "[d]octors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.").

149. See *id.* art. I (6) (stating that "[e]very precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.").

150. *Id.* art. I, (9)-(11). Paragraph 9 of the Basic Principles defines the general requirements of informed consent under Helsinki II, stating

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely -given informed consent, preferably in writing.

*Id.* Paragraph 10 provided further informed consent requirements for subjects with a special relationship to the investigator. *Id.* para. 10. Paragraph 11 enumerates informed consent requirements for incompetent adults and children. *Id.* para. 11.

the guidelines for specific types of research.<sup>151</sup> Furthermore, Helsinki II sets incompetent subjects apart from other groups by devoting an entire paragraph to substituted consent.<sup>152</sup> This paragraph specifically mentioned minors as a distinct class of legally incompetent subjects.<sup>153</sup> Helsinki II's provisions allowed researchers to conduct trials after obtaining permission from a responsible relative, as permitted by national legislation.<sup>154</sup>

Following Helsinki II, the WMA revised the Helsinki Declaration three more times, in 1983,<sup>155</sup> 1989,<sup>156</sup> and 1996.<sup>157</sup> The Declaration of Helsinki III ("Helsinki III"), further developed the notion of informed consent in pediatric subjects by advancing the idea that children can share in the decision-making process.<sup>158</sup> The Basic Principles of Helsinki III specified that when dealing with a subject who is legally incompetent, the researcher must obtain not only the consent of the legal guardian, but also the consent of the child to the extent that he or she is able to provide such consent.<sup>159</sup> The Declaration of Helsinki IV ("Hel-

151. *Id.* art. I (11). Unlike Helsinki I, which listed the informed consent requirement in Article II and Article III and which specifically dealt with requirements for therapeutic and non-therapeutic trials, Helsinki II places informed consent in Article I, paragraph 11, which states:

In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

*Id.*

152. *Id.* art. I (11). Paragraph 11 of the Basic Principles states that

In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

*Id.*

153. *Id.*

154. *Id.* art. I (11). Section 1.11 states, "permission from a responsible relative replaces that of the subject in accordance with national legislation." *Id.*

155. HELSINKI III, *supra* note 92.

156. DECLARATION OF HELSINKI IV (41st World Medical Assembly, 1989) [hereinafter HELSINKI IV].

157. DECLARATION OF HELSINKI V (48th World Medical Assembly, 1996) [hereinafter HELSINKI V].

158. See HELSINKI III, *supra* note 92, art. I (11).

159. *Id.* Article I states,

In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or

sinki IV") and the Declaration of Helsinki V ("Helsinki V") largely retained this language, although the provision regarding consent of a capable minor was further emphasized by turning this sentence into a separate paragraph in Helsinki IV.<sup>160</sup>

The Helsinki Declarations, like the Code, are not legally-binding documents.<sup>161</sup> Like the Code, the Helsinki Declarations have significantly impacted later international, national, and regional regulations.<sup>162</sup> The Helsinki Declaration also stressed the importance of allowing children to participate in medical research decision making,<sup>163</sup> and of including the medical commu-

mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the 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.

*Id.* (emphasis added). It should be noted that the child's consent, when the child is able to provide such consent, is mandatory, as opposed to other provisions of Helsinki that are permissive. Compare with *id.* art. I (10). Article I, paragraph 10 states

When obtaining informed consent for the research project the physician *should* be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent *should* be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

*Id.* art. I (10) (emphasis added).

160. HELSINKI IV, *supra* note 156, art. I (11). Article I, paragraph 11 finds that In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. . . . Whenever the 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.

*Id.*

161. See Bankowski, *supra* note 134, at 182 (stating that similar to Code, Helsinki is not legally binding).

162. See, e.g., *Good Clinical Practice for Trials on Medicinal Products in the European Community*, III/3976/88, (adopted May 1990), art. 1.1, 1.2. [hereinafter EU GCP]. Article 1.1 of the Good Clinical Practice for Trials on Medicinal Products in the European Community (or "EU GCP") states "[t]he current revision of the Declaration of Helsinki is the accepted bases for clinical trial ethics, which must be fully known and followed by all engaged in research on human beings." *Id.* art. 1.1. Article 1.2 of the EU GCP states, "[t]he personal integrity and welfare of the trial subjects is the ultimate responsibility of the investigator in relation to the trial; but independent assurance that subjects are protected is provided by an Ethics Committee and freely obtained informed consent." *Id.* art. 1.2.

163. See HELSINKI IV, *supra* note 156, art. I (11) (stating that child must agree to participation if able to do so).

nity's opinion in formulating human research regulations.<sup>164</sup>

### 3. The CIOMS/WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects

In 1983, the CIOMS and WHO produced the CIOMS/WHO Guidelines.<sup>165</sup> The authors of the CIOMS/WHO Guidelines intended to clarify Helsinki IV, and to make its provisions more easily applicable.<sup>166</sup> They also sought to assist developing countries in formulating guidelines for human research.<sup>167</sup> Because the Guidelines address research conducted in developing countries, its drafters were forced to recognize divergent intercultural ethical standards.<sup>168</sup> The document was drafted in three CIOMS Round Table Conferences, in consultation with health ministries and medical schools from more than sixty countries.<sup>169</sup> The Guidelines were first introduced in 1982,<sup>170</sup> and later revised and reissued in 1993.<sup>171</sup>

The authors of the Guidelines sought to create protections

164. See Levine, *supra* note 90, at 243 (stating that Helsinki recognized need for professional guidelines drafted for and by physicians).

165. See CIOMS/WHO GUIDELINES, *supra* note 93.

166. See Sev S. Fluss, *The Regulation of Human Experimentation: Historical and Contemporary Perspectives*, in RESEARCH ON HUMAN SUBJECTS 222, 229 (David Weissstub ed., 1998) (explaining that CIOMS/WHO Guidelines were intended to "amplify and give effect" to Helsinki IV).

167. See Perley, *supra* note 88, at 161 (citing WHO/CIOMS PROJECT PROPOSAL FOR THE DEVELOPMENT OF GUIDELINES FOR ESTABLISHMENT OF ETHICAL REVIEW PROCEDURES FOR RESEARCH INVOLVING HUMAN SUBJECTS 4 (WHO & CIOMS, 1978)). The CIOMS/WHO's objectives were to

develop the guidelines for the establishment of ethical review procedures for research involving human subjects [so as to] enable countries to: (a) define a national policy on the ethics of medical and health research and to adopt ethical standards appropriate to their specific local needs; and (b) to establish adequate mechanisms for ethical review of research activities involving human subjects.

*Id.*

168. See CIOMS/WHO GUIDELINES, *supra* note 93, at Guideline 8 (stating that investigators must seek review from ethical review boards that are "thoroughly familiar with the customs and traditions of the community").

169. See Perley, *supra* note 88, at 161 (explaining that CIOMS sent out more than 100 questionnaires to Health Ministries and medical schools in developing nations, and more than 60 responses were received).

170. See Bankowski, *supra* note 134, at 182 (stating that CIOMS and WHO first released Proposed International Guidelines for Biomedical Research Involving Human Subjects in 1982 for comment and revision).

171. *Id.*

for vulnerable subjects, including children.<sup>172</sup> In fact, the Guidelines devote an entire section to informed consent and risk issues pertaining to pediatric subjects both in therapeutic and non-therapeutic trials.<sup>173</sup> Guideline Five spends three paragraphs explaining that a parent must give proxy consent, that the child must consent to the extent he or she is able, and that the child's refusal to participate in non-therapeutic research must always be respected.<sup>174</sup> Furthermore, Guideline Five explains that the level of risk in pediatric trials must be low and, at the very least, in proportion to the knowledge that the research is likely to yield.<sup>175</sup> Indeed, despite early concerns that international guidelines must be general to accommodate varying opinions,<sup>176</sup> the CIOMS/WHO Guidelines recognized that research on children and other vulnerable groups required specialized attention.<sup>177</sup>

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172. See *id.* at 183 (describing how CIOMS/WHO Guidelines drafters attempted to clarify when experimentation on vulnerable populations was ethical).

173. CIOMS/WHO Guidelines, *supra* note 93, at Guideline 5. Guideline 5 states: Before undertaking research involving children, the investigator must ensure that:

- Children will not be involved in research that might equally well be carried out with adults;
- The purpose of the research is to obtain knowledge relevant to the health needs of children;
- A parent or legal guardian of each child has given proxy consent;
- The consent of each child has been obtained to the extent of the child's capabilities;
- The child's refusal to participate in research must always be respected unless according to the research protocol the child would receive therapy for which there is no medically-acceptable alternative;
- The risk presented by interventions not intended to benefit the individual child-subject is low and commensurate with the importance of knowledge to be gained; and
- The interventions that are intended to provide therapeutic benefit are likely to be at least as advantageous to the individual child-subject as any available alternative.

*Id.*

174. *Id.*

175. *Id.*

176. See Perley, *supra* note 88, at 160 (quoting March 1978 WHO document, WHO/CIOMS Project Proposal for the Development of Guidelines for the Establishment of Ethical Review for Research Involving Human Subjects, stating that "by their very nature, international declarations can only be general.").

177. See *id.* at 163 (noting that CIOMS/WHO Guideline paid particular attention to children, pregnant and nursing women, and mentally ill).

#### 4. The Council of Europe and the Biomedical Convention

The Council of Europe Convention on Human Rights and Biomedicine<sup>178</sup> ("Biomedical Convention") represents the first binding international instrument protecting human rights in biomedicine.<sup>179</sup> The long process culminating in the Biomedical Convention began in June 1990, with recommendations from both the European Ministers of Justice and the Parliamentary Assembly.<sup>180</sup> In response to these recommendations, the Committee of Ministers instructed the Steering Committee on Bioethics ("CAHBI") to create a general framework convention protecting human rights in the biomedical field.<sup>181</sup> The Biomedical Convention was adopted by the Committee of Ministers on November 19, 1996,<sup>182</sup> and opened for signature on

178. Council of Europe, Convention on Human Rights and Biomedicine and Explanatory Report, Apr. 4, 1997, 36 I.L.M. 817 [hereinafter Biomedical Convention].

179. See Leuprecht, *supra* note 22, at 325 (stating that Council of Europe Convention on Human Rights and Biomedicine ("Biomedical Convention") is "the first binding legal instrument ever drafted on an international scale with a view to safeguarding human dignity and fundamental rights against any improper applications of medicine and biology").

180. See Biomedical Convention, *supra* note 178, at 827 (stating that idea for Biomedical Convention originated in European Ministers of Justice adoption of Resolution No. 3 on Bioethics). Recommendation No. 3 suggested that the Council of Europe should instruct the Steering Committee on Bioethics ("CAHBI") to formulate a framework convention to express general standards for protecting people in light of continuing biomedical developments. *Id.* CAHBI was to be instructed to "examine the possibility of preparing a framework convention 'setting out common general standards for the protection of the human person in the context of the development of the biomedical sciences.'" *Id.* In June 1991, the Parliamentary Assembly promulgated Recommendation 1160, set forth a similar recommendation for a framework convention with general provisions in its main text, and additional protocols regulating specific areas of biomedicine. *Id.*

181. *Id.* In September 1991, Mr. Vincent Tabone, chair of the Committee of Ministers, instructed the group to create a document

to prepare, in close cooperation with the Steering Committee for Human Rights (CDDH) and the European Health Committee (CDSP) . . . a framework Convention, open to non-member states, setting out common general standards for the protection of the human person in the context of the biomedical sciences and Protocols to this Convention, relating to, in a preliminary phase: organ transplants and the use of substances of human origin; [and] medical research on human beings.

*Id.* The Biomedical Convention was open to signature by both member and non-member states. *Id.*

182. See *id.* (explaining that draft Biomedical Convention was modified according to Parliamentary Assembly recommendations contained in Opinion No. 184, and reports issued by Committee on Science and Technology, Committee on Legal Affairs and Human Rights, and Social, Health and Family Affairs Committee, and adopted on

April 4, 1997.<sup>183</sup>

The Biomedical Convention is based on a variety of pre-existing international and European human rights controls<sup>184</sup> that consider respect for human dignity as their primary themes.<sup>185</sup> Each party to the Biomedical Convention must give effect to its provisions through domestic legislation.<sup>186</sup> Although the negotiating process diluted some of the provisions of the Biomedical Convention,<sup>187</sup> this document makes significant progress in unifying certain areas of biomedical regulation.<sup>188</sup> The Biomedical Convention addresses issues relevant to human research in its chapters regarding consent and research.<sup>189</sup>

The chapter on consent mandates that every person must

November 19, 1996). Belgium, Germany, and Poland abstained from the vote. Anne Lawton, *Regulating Genetic Destiny: A Comparative Study of Legal Constraints in Europe and the United States*, 11 EMORY INT'L L. REV. 365, 383, n.53 (1997).

183. See Lawton, *supra* note 182, at 383 (stating that Biomedical Convention was opened for signature on April 4, 1997).

184. See Biomedical Convention, *supra* note 178, at Preamble (stating that Biomedical Convention contains principles embodied in U.N. Universal Declaration of Human Rights, Convention for the Protection of Human Rights and Fundamental Freedoms, European Social Charter, International Covenant on Civil and Political Rights, International Covenant on Economic, Social, and Cultural Rights, Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data, and Convention on the Rights of the Child).

185. See Lawton, *supra* note 182, at 384-85 (stating that first principle is embodied in Article one of Biomedical Convention, which states, "parties to this Convention shall protect the dignity and integrity of all human beings," and second theme is represented in Article 2, which echoes Helsinki in stating that "[t]he interests and welfare of the human being shall prevail over the sole interest of society or science."); see also Eibe Riedel, *Global Responsibilities and Bioethics: Reflections on the Council of Europe's Bioethics Convention*, 5 IND. J. GLOBAL LEGAL STUD. 179, 182 (1997) (stating that Biomedical Convention used European Convention on Human Rights and Fundamental Freedoms' approach to bring "the inherent value of the human being into the bioethics debate").

186. See Biomedical Convention, *supra* note 178, art. 1.2. (stating that "[e]ach party shall take in its internal law the necessary measures to give effect to the provisions of this Convention.").

187. See Maurice A.M. de Wachter, *The European Convention on Bioethics; Includes Related Information*, HASTINGS CTR. REP., Jan.-Feb. 1997, at 13, 15 (conveying story of Parliamentary Assembly president when Assembly gave its first opinion on Biomedical Convention, stating that Biomedical Convention provisions resulted from "compromises in harmonizing the interests of the individual human being, society, and science").

188. See Riedel, *supra* note 185, at 183 (explaining Biomedical Convention's six main focal points). The main focal points of the Convention are: (1) questions of consent to interventions in the health field; (2) protection of the human genome and scientific research; (3) research on embryos; (4) transplantation medicine; (5) data protection issues; and (6) economic consequences of biogenetics. *Id.*

189. Biomedical Convention, *supra* note 178, at Chap. II & V. Chapter Two of the



give free and informed consent before undergoing any type of medical intervention.<sup>190</sup> This provision is satisfied if the patient is provided with appropriate information regarding the purpose, nature, consequences, and risks of the intervention.<sup>191</sup> The patient's consent can be written or verbal, express or implied, depending on the nature of the intervention.<sup>192</sup> A person may withdraw consent for treatment at any time.<sup>193</sup>

The Biomedical Convention also directly addresses individuals who lack the legal capacity to consent, such as children.<sup>194</sup> Although the Biomedical Convention does not explicitly define the inability to consent,<sup>195</sup> it states that a minor's opinion must be considered proportional to his or her age and maturity level.<sup>196</sup> If the patient is determined to be incompetent under

Biomedical Convention is entitled "Consent" and Chapter Five addresses "Scientific Research." *Id.*

190. *See id.* art. 5 ("[a]n intervention in the health field may only be carried out after the person concerned has given free and informed consent to it"). This provision is intended to secure the patient's autonomy in his or her relationship with the health care provider, and affirm the well-established international rule that no person should be forced to undergo a medical procedure without his or her express consent. *Id.* at Explanatory Report, para. 34.

191. *See id.* art. 5 (stating "[t]his person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks"). The information required in this paragraph, however, is not an exhaustive list; other information may be required, depending on the intervention, and must include information regarding alternative treatments. *Id.* at Explanatory Report, para. 35. Any information imparted on the patient must be clear and worded in a manner suited to the person who is to undergo the intervention, must be objective, and must be given in a way that does not exert any pressure on the patient to participate in the intervention. *Id.* at 35-36.

192. *See id.* at Explanatory Report, para. 37 (stating that express consent would be inappropriate with regard to routine medical acts). Providing the patient with sufficient information is suitable in these situations. *Id.*

193. *See id.* art. 5. ("[t]he person concerned may freely withdraw consent at any time.").

194. *See id.* art. 6 (discussing "protection of persons not able to consent").

195. *See id.* art. 6.2 (stating that "[w]here, according to law, a minor does not have capacity to consent . . ."). The Explanatory Report elaborates on this position, stating that "it is for domestic law in each country to determine, in its own way, whether or not persons are capable of consenting to an intervention and taking account of the need to deprive persons of their capacity for autonomy only where it is necessary in their best interests." *Id.* at Explanatory Report, para. 42.

196. *See id.* art. 6.2 (stating that "[t]he opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity."). The Explanatory Report states that obtaining the minor's opinion is necessary to preserve the concept of individual autonomy, in accordance with Article 12 of the Convention on the Rights of the Child. *See id.* at Explanatory Report, para. 45 (explaining that minor's opinion should be taken into account to degree that

national law, then the health care provider must obtain the consent of the patient's legal representative before performing the experiment.<sup>197</sup>

The provisions for consent are further modified in the chapter addressing scientific research.<sup>198</sup> This chapter specifies that research on incompetent individuals can only be performed if: (1) the subject will receive direct medical benefit from the protocol; (2) the research cannot be carried out on adults; (3) the subject's legal representative gives consent; and (4) the subject does not object.<sup>199</sup> Unlike the provisions for informed consent in medical treatment, consent for medical research from a legal representative must be specific and written.<sup>200</sup> This provision also requires the researcher to consider the patient's opinion on whether to participate in the protocol.<sup>201</sup> Research that does not directly benefit the research subject can only be carried out if it will contribute to a greater understanding of the individual's condition and if it will benefit patients in the subject's age group.<sup>202</sup> Although this provision would appear to exclude re-

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depends on "nature and seriousness of the intervention as well as the minor's age and ability to understand").

197. *Id.* art. 6.2.

198. *Id.* at Chap. V.

199. *Id.* art. 17 (1) (i). Article 17 (1) (i) states that research on subjects who do not have capacity to consent can only be undertaken where:

- (i) the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled [general provisions for medical research];
- (ii) the results of the research have the potential to produce real and direct benefit to his or her health;
- (iii) research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
- (iv) the necessary authorisation provided for under Article 6 has been given specifically and in writing;
- (v) the person concerned does not object.

*Id.* The Explanatory Report states that potential benefit under this Article means that "[t]he benefit must be real and follow from the potential results of the research." *Id.* Explanatory Report, para. 103. It also states with regard to objections that "the wish of the person concerned prevails and is always decisive." *Id.* para. 108.

200. *Id.* at Explanatory Report, para. 105 (explaining that Article 6 authorization must be specific and in writing, and can be withdrawn at any time).

201. *See id.* at Explanatory Report, para. 106 (stating "[t]he rule prohibiting the carrying out of research against the wish of the subject reflects concern, in research, for the autonomy and dignity of the person in all circumstances, even if the person is considered legally incapable of giving consent.").

202. *Id.* art. 17 (2) (i), (ii). Article 17 (2) states:

Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the

search in healthy children, the Biomedical Convention's Explanatory Report notes that research in healthy children under this definition is *per se* ethical, as it may eventually benefit the child.<sup>203</sup>

With regard to the level of risk exposure in a non-therapeutic trial, the Biomedical Convention imposes greater restrictions for children than those imposed for adults.<sup>204</sup> Instead of merely mandating that the benefits of the research outweigh the risks, the Biomedical Convention states that non-therapeutic research may only be conducted on children if it involves minimal risk and minimal burden to the subject.<sup>205</sup> Although the term minimal risk is not defined, the Explanatory Report further discusses this term and gives concrete examples of what constitutes minimal risk in incompetent populations.<sup>206</sup>

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health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, subparagraphs i, ii, iii, iv, and v above, and 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.

*Id.*

203. *See id.* at Explanatory Report, para. 109 (explaining that although research in healthy children is clearly for benefit of other children, "such research may well be of ultimate benefit to healthy children taking part in this research."). Paragraph 110 also states that the phrase "individual's condition" may also refer generally to aspects of normal child development, relevant to childhood abnormalities or diseases. *Id.* para. 110.

204. *See id.* art. 16 (ii) (mandating that risk may not outweigh benefits in trials involving human subjects).

205. *See id.* art. 17 (2) (ii) (stating that research is permissible if it "entails only minimal risk and minimal burden for the individual involved").

206. *Id.* at Explanatory Report, para. 113 (a). Paragraph 113 (a) of the Explanatory Report states with regard to minimal risk,

in respect of children: replacing x-ray examinations or invasive diagnostic measures for children by ultrasonic scanning; analyses of incidental blood samples from newborn infants without respiratory problems in order to establish the necessary oxygen content for premature infants; discovering the causes and improving treatment of leukaemia in children (e.g. by taking a blood sample).

*Id.* Paragraph 114 notes that non-therapeutic interventions described in paragraph 113 (a), "may be ethically acceptable if the above highly protective conditions, resulting from the combined effect of Articles 6, 7, 16, and 17, are fulfilled." *Id.* para. 114.

Due to differences in national regulations, the drafters of the Biomedical Convention faced some problems.<sup>207</sup> In particular, they encountered difficulties creating a uniform set of regulations that place a different emphasis on codified law.<sup>208</sup> General cultural and religious differences also made drafting the Biomedical Convention more difficult, as varied religious values throughout the Council of Europe created divergent views on bioethical issues.<sup>209</sup>

The Biomedical Convention's provisions regarding non-therapeutic research in subjects who are unable to give informed consent caused a significant amount of debate among the members of the Council of Europe.<sup>210</sup> This provision drew a particularly negative response from Germany, whose government refused to sign the final draft of the Biomedical Convention.<sup>211</sup> Despite these controversies, however, the Biomedical Convention is binding, as it has been signed and ratified by more than the requisite number of member states.<sup>212</sup>

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207. See Arthur Rogers, *Europe: Ethical Diversity*, 339 LANCET 861 (1992) (noting difficulties at Workshop discussions in Madrid, stating that "national approaches to bioethics [were] more divergent than had been suspected and that similarities [were] largely superficial").

208. See *id.* (stating that countries with more codified legal systems were more open to more legislation to control ethical review boards, while others, such as Canada, Germany, and United Kingdom "view legislation as too confining and difficult to interpret.").

209. See Richard H. Nicholson, *One Law for All?*, HASTINGS CTR. REP., Mar.-Apr. 1995, at 4 (explaining tendency for division in Europe on bioethical issues between predominantly Catholic South and Protestant North).

210. See Rory Watson, *European Bioethics Convention Signed*, 314 BRIT. MED. J. 1065 (1997) (quoting Dr. Peggy Norris, secretary of European Doctor's Union, stating, "[t]he basic rule should be that you cannot do research on someone without their consent").

211. See *Bioethics Convention Fails in the Council of Europe; German Opposition Decisive*, WEEK IN GERMANY, OCT. 7, 1994 (noting Germany's opposition to non-therapeutic interventions on incapacitated persons and embryonic research, and that, accordingly, prior to Council of Europe vote representatives of Germany's political parties made their opposition to Biomedical Convention unambiguously clear). It was also upon recommendation of the German Bundestag that the name of the document was changed from the "Convention on Bioethics" to the "Convention on Biomedicine." de Wachter, *supra* note 187, at 16. Germany particularly opposed the informed consent provisions, as they found that they contradicted German law, which forbids all non-therapeutic research on children. de Wachter, *supra*, at 17. This provision met with strong objections not only from the German government, but also from patient's groups, the Roman Catholic Church, the German Evangelical Church, and major German political parties. *Id.* Even after several changes were made to the Biomedical Convention to appease the German delegation, the Germans still refuse to sign on to it. *Id.*

212. See Council of Europe Website, *Convention on Human Rights and Biomedicine*,

## 5. The United Nations Convention on the Rights of the Child

The U.N. Convention on the Rights of the Child was adopted unanimously by the General Assembly of the United Nations on November 20, 1989.<sup>213</sup> Presently, all U.N. members have signed and ratified the CRC, with the exception of the United States and Somalia.<sup>214</sup> The primary value expressed by the CRC is preserving the child's dignity as a human being, defined as the child's identity, self-worth, autonomy, and development of self-realization.<sup>215</sup> The CRC working group strove to depict children in a way that illuminates their vulnerability, and as a group whose evolving capabilities must be respected, and whose rights should be granted accordingly.<sup>216</sup> Thus, the CRC promotes the view that a child should not be denied the opportunity to participate actively in matters that effect his or her life.<sup>217</sup> The CRC Committee did not, however, advocate that

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*Chart of Signatures and Ratifications* (visited Feb. 21, 2000) <<http://www.coe.fr/tablconv/164t.htm>> (on file with the *Fordham International Law Journal*) (listing states that have signed and ratified Biomedical Convention).

213. See Cynthia Price Cohen, *Introductory Note: United Nations: Convention of the Rights of the Child*, 28 I.L.M. 1448 (1998) (noting that this document is outgrowth of Declaration of the Rights of the Child, issued by United Nations in 1959). In 1979, the International Year of the Child, a working group was established to draft the Convention on the Rights of the Child ("CRC"). *Id.*

214. *Id.* at 29. See Catherine Langevin-Falcon, *Second Class Citizens?*, HUMANIST, Nov. 1, 1998, at 11 (stating that even though United States has signed CRC, it has not yet ratified it).

215. See Judith Karp, *Concepts Underlying the Implementation of the Convention on the Rights of the Child*, 4 LOY. POVERTY L.J. 113, 114 (1998) (explaining basic values underlying CRC). The 10 basic concepts underlying CRC are:

1. Respect for human dignity;
2. Rights-based orientation;
3. Holistic and integrated approach;
4. Empowerment and visibility of children;
5. Partnership and society;
6. Implementation and development as a process of empowerment;
7. Proactivity;
8. Maximization of efforts;
9. Sustainability;
10. Transparency and accountability.

*Id.*

216. See *id.* at 123-24 (explaining that CRC gives voice to movement that children should be granted rights in accordance with their developing capacities, not necessarily according to official age of majority).

217. See *id.* at 124 (explaining principle of participation and that "basic message of the Convention is that a child is not a dormant entity, devoid of all capacity until the age of eighteen.").

children should be completely independent of parental influence, but rather, that professionals should be trained to deal with children in a way that maximizes their empowerment while respecting their vulnerabilities.<sup>218</sup>

Although the CRC does not directly address pediatric medical research or medical informed consent, several articles of the CRC are relevant to this topic.<sup>219</sup> For example, the CRC entitles children with the highest standards of health and treatment facilities,<sup>220</sup> and prohibits any national health care practices that are prejudicial to children.<sup>221</sup> Parties are also encouraged to take all appropriate measures to provide necessary pediatric health care, and develop their primary care systems.<sup>222</sup> With respect to a child's participation in research decisions, the CRC states that a child should generally be able to express his or her own views according to his or her capacity, and have others respect those views in accordance with his or her age.<sup>223</sup> This provision, however, is mitigated by a provision that requires states to respect a parent's right to guide the child's decision making.<sup>224</sup>

218. See *id.* at 124 (stating that CRC advocates that decision makers should be subordinate to children, and that children's views should be listened to; this process could be facilitated by training individuals who work with children to inform them in age-appropriate manner).

219. See generally CRC, *supra* note 96.

220. *Id.* Article 24, paragraph 1 states

States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to the facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services.

*Id.*

221. See *id.* art. 24, para. 3 ("States Parties shall take all effective and appropriate measures with a view to abolishing traditional practices prejudicial to the health of children.").

222. See *id.* art. 24, para. 2 (b) ("States Parties shall pursue full implementation of this right and, in particular, shall take appropriate measures: . . . "[t]o ensure the provision of necessary medical assistance and health care to all children with emphasis on the development of primary health care.").

223. See *id.* art. 12 ("States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child.").

224. See *id.* art. 14, para. 2 (stating that all parties "shall respect the rights and duties of the parents and, when applicable, legal guardians, to provide direction to the child in the exercise of his or her right in a manner consistent with the evolving capacities of the child"). Article 5 provides that parties

shall respect the responsibilities, rights and duties of parents or, where applicable the members of the extended family or community as provided for by

Although the CRC has been ratified by 191 countries, making it the most widely adopted human rights instrument in such a short period of time, it does have its detractors, particularly the United States.<sup>225</sup> Some critics denounce the CRC as giving children too many rights, thereby separating the child from valuable familial influence and guidance.<sup>226</sup> Another criticism is that the CRC is too vague, and leaves room for certain rights to be diminished.<sup>227</sup> For all of the criticism that the CRC has received, however, even its detractors agree that the CRC symbolizes a growing movement for more autonomy, independence, and respect for children and their rights as research subjects.<sup>228</sup>

*C. Pediatric Medical Research Regulations in the United States, European Union, and Japan*

The three primary governmental entities involved in the ICH are the United States, European Union, and Japan.<sup>229</sup> Each of these entities has independent regulatory schemes governing human research issues.<sup>230</sup> These regulations, along with the international conventions discussed earlier, comprise the basis for

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local custom, legal guardians or other persons legally responsible for the child, to provide, in a manner consistent with the evolving capacities of the child, appropriate direction and guidance in the exercise by the child of the rights recognized in the present Convention.

*Id.* art. 5.

225. Robert F. Drinan, *A Global Revolution for Children*, AMERICA, Mar. 27, 1999.

226. See Bruce C. Hafen & Jonathan O. Hafen, *Abandoning Children to Their Own Autonomy: The United Nations Convention on the Rights of the Child*, 37 HARV. INT'L L. J. 449, 458, 478 (1996) (opining that Article 5 of CRC limits parental authority to that which is compatible with rights of child and that children should not necessarily be given more autonomy without data showing increased capacity to handle such responsibilities).

227. See James J. Kilpatrick, *Take a Closer Look at U.N. Children's Treaty: It Bites*, NEWS & OBSERVER, May 20, 1991 (criticizing use of phrase "highest attainable standard" as describing level of health care that children should be able to enjoy).

228. See Hafen & Hafen, *supra* note 226, at 457 (noting that CRC exemplifies international movement toward increased social and legal autonomy for children).

229. See International Conference on Harmonisation Web Site (visited Dec. 2, 1999) <<http://www.ich.org>> (on file with the *Fordham International Law Journal*) (explaining that United States, European Union, and Japan formulated idea for ICH at WHO Conference on Drug Regulatory Activities).

230. See 45 C.F.R. § 46 (1999) (including U.S. Regulations on human research); see also Guideline for Children, *supra* note 51 (including European Community guidelines on human research on children); GOOD CLINICAL PRACTICE (Japanese Ministry of Health and Welfare) effective Apr. 1998 [hereinafter NEW JAPANESE GCP] (including Japanese regulations on human research).

creating pediatric medical research guidelines in the ICH.<sup>231</sup>

### 1. U.S. Regulations on Assent and Risk

The United States has two separate sets of human research regulations.<sup>232</sup> The first set of regulations was promulgated by FDA for research on FDA-regulated products including food additives, drugs, medical devices, and biological products for human use.<sup>233</sup> The second set of regulations was agreed to by the other seventeen federal agencies that conduct human research in the United States ("Common Rule").<sup>234</sup> Although both sets of regulations are similar,<sup>235</sup> the Common Rule, unlike the FDA regulations, contains an entire set of rules devoted to pediatric research.<sup>236</sup>

The Common Rule arose from the National Research Act,<sup>237</sup> which was passed by Congress on July 12, 1974.<sup>238</sup> The

231. See Department of Health and Human Services, *International Conference on Harmonisation; Draft Guideline on Good Clinical Practice*, 60 Fed. Reg. 42948, 42498 (1995) [hereinafter Draft GCP] (explaining sources of ICH Guidelines).

232. Jeffrey Cohen, Ph.D., Associate Director of Education, Office for Protection from Research Risks, Department of Health and Human Services National Institutes of Health, Presentation at Fordham University School of Law (Feb. 16, 2000) (stating that FDA has regulations that are distinct from those adopted by all other research-oriented agencies in U.S. Government).

233. 21 C.F.R. § 50.1 (1999). Title 21, section 50.1 states that the FDA regulations apply to "all clinical investigations regulated by the Food and Drug Administration . . . that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products." *Id.*

234. See Cohen, *supra* note 232 (stating that 45 C.F.R. § 46 has been adopted to regulate human research by 17 U.S. agencies, including, among others, Departments of Agriculture, Energy, Commerce, Housing and Urban Development, Justice, Defense, Education, Veteran's Affairs, Transportation, Social Security Administration, Central Intelligence Agency, and Consumer Product Safety Commission). Title 45, section 46 of the C.F.R. is referred to as the Common Rule. *Id.*

235. See *id.* (stating that FDA regulations and Common Rule are "utterly the same").

236. See 45 C.F.R. § 46, Sub. D (1999) (addressing "Protections for Children Involved as Subjects in Research"). The FDA Regulations only state that when

[w]hen some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

21 C.F.R. § 56.111 (c) (1999).

237. 45 C.F.R. § 46 (1999).

238. *Id.*



National Research Act created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research (the "Commission").<sup>239</sup> The National Research Act empowered the Commission with the responsibility for determining how and under what circumstances research on children and other groups is appropriate.<sup>240</sup> In 1977, the Commission issued its Report and Recommendations on Research Involving Children<sup>241</sup> ("Commission Report"), which formed the basis for the Common Rule provisions regarding pediatric research.<sup>242</sup>

The Commission Report introduced several key concepts now embodied in the Common Rule.<sup>243</sup> The first concept is that research on children is necessary to promote children's health and welfare.<sup>244</sup> The Commission Report also introduced institutional review boards to evaluate each medical research study's worth and appropriateness.<sup>245</sup> The Commission further determined that the best way to achieve effective informed consent for pediatric medical research would be through a combination

239. Rules and Regulations, Department of Health and Human Services, 48 Fed. Reg. 9814, 9814 (1983) (stating that National Research Act made Commission responsible for studying "nature of research on children, the purposes of such research, the steps necessary to protect children as subjects, and the requirements for informed consent of children, their parents or guardians").

240. *Id.*

241. NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS IN BIOMEDICAL AND BEHAVIORAL RESEARCH, REPORT AND RECOMMENDATIONS ON RESEARCH INVOLVING CHILDREN (1977) [hereinafter COMMISSION REPORT].

242. See Nelson, *supra* note 44, at 52 (stating that Commission Report was foundation for current federal regulations).

243. See Leonard H. Glantz, *The Law of Human Experimentation with Children*, in CHILDREN AS RESEARCH SUBJECTS, 103, 121 (Michael A. Grodin & Leonard Glantz, eds., 1994) (noting that Commission recommendations were largely incorporated into final rules). The U.S. human research regulations apply to all federally funded pediatric medical research, except for studies employing educational tests and observations of public behavior. *Id.*; see also 45 C.F.R. § 46.401 (a) (stating that Subpart D applies to "all research involving children as subjects conducted or supported by the Department of Health and Human Services"). Section 46.402 (b) states that

[t]he exemption at §46.101 (b) (2) regarding educational tests are applicable to this subpart. However, the exemption at §46.101 (b) (2) for research involving a survey or interview procedures or observations of public behavior does not apply to research covered in this subpart, except for research involving observation of public behavior when the investigators do not participate in the activities being observed.

*Id.* § 46.402(b).

244. See Glantz, *supra* note 243, at 123-25 (describing Commission Report's influence over current regulations).

245. *Id.*

of parental permission and child assent.<sup>246</sup> The Commission Report also set forth a minimal risk standard to limit parental discretion to volunteer their children for potentially risky medical trials.<sup>247</sup> Finally, the Commission created the four risk/benefit categories that appear in the Common Rule.<sup>248</sup>

The Common Rule, like the Commission Report, does not use the term informed consent<sup>249</sup> to refer to a subject's agree-

246. See Ross, *supra* note 78, at 161 (explaining that Commission set forth minimum requirements for guidelines on pediatric research and created IRBs "to ensure that these safeguards were fulfilled").

247. Nelson, *supra* note 44, at 54.

248. See Glantz, *supra* note 243, at 120 (explaining that Commission balanced risks and benefits of research and current regulations are based on balancing these factors).

249. 45 C.F.R. § 46.116 (1999). Section 46.116 states

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

- (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
- (2) A description of any reasonably foreseeable risks or discomforts to the subject.
- (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
- (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
- (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- (7) An explanation of whom to contact for answers to pertinent

questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

- (8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
  - (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
  - (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
  - (3) Any additional costs to the subject that may result from participation in the research.
  - (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
  - (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
  - (6) The approximate number of subjects involved in the study.

*Id.* The FDA Regulation requirements for informed consent are found at 21 C.F.R. § 50.25. Title 21, section 50.25 of the Code of Federal Regulations states,

- (a) Basic elements of informed consent. In seeking informed consent, the following information shall be provided to each subject:
  - (1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
  - (2) A description of any reasonably foreseeable risks or discomforts to the subject.
  - (3) A description of any benefits to the subject or to others which may reasonably be expected from the research.
  - (4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
  - (5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
  - (6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
  - (7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and

ment to participate in pediatric studies.<sup>250</sup> Instead, the Common Rule uses the term permission<sup>251</sup> to refer to a parent's agreement to allow its child to participate in a study, and assent to refer to a legally incompetent child's express agreement to par-

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whom to contact in the event of a research-related injury to the subject.

- (8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
  - (1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
  - (2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
  - (3) Any additional costs to the subject that may result from participation in the research.
  - (4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
  - (5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
  - (6) The approximate number of subjects involved in the study.
- (c) The informed consent requirements in these regulations are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.
- (d) Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

*Id.* at § 50.25.

250. COMMISSION REPORT, *supra* note 241, at 13. The Commission Report states that "[t]he commission uses the term parental or guardian permission rather than 'consent,' in order to distinguish what a person may do autonomously (consent) from what one may do on behalf of another (grant permission)." *Id.*; see 45 C.F.R. § 46.402 (1999) (omitting definition of consent in definitions); Glantz, *supra* note 243, at 120 (stating that National Commission intentionally avoided consent in its recommendations).

251. 45 C.F.R. § 46.402 (c) (1999). Permission is defined in the Common Rule as "the agreement of parent(s) or guardian to the participation of their child or ward in research." *Id.* Although the National Commission suggested that the disclosure requirements for assent should be the same as those for consent, these components must be modified to allow the child to understand the trial. Glantz, *supra* note 243, at 144.

ticipate.<sup>252</sup> Under the Common Rule, the definition of a child may vary from one research institution to another, as it defers to the law of the jurisdiction where the research is conducted on this point.<sup>253</sup> Although the Common Rule requires that a child provide express assent to participate,<sup>254</sup> it does not include the Commission's recommendation that a child's dissent, or refusal to participate in research, should be binding.<sup>255</sup>

The Common Rule also mandates that every research institution receiving federal funding must have an IRB<sup>256</sup> to protect

252. 45 C.F.R. § 46.402 (b) (1999). The Common Rule defines assent as "a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent." *Id.* The FDA Regulations, on the other hand, only state, in their section on Exception from general requirements, that

[t]he obtaining of informed consent shall be deemed feasible unless, before the use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating the in clinical investigation certify in writing all of the following . . . (2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

21 C.F.R. § 50.25 (1999). In these cases, the subject's legally authorized representative or family member should give consent for the subject's participation in the study. 21 C.F.R. § 50.3 (l)-(m) (1999).

253. *Id.* § 46.402 (a). The Common Rule defines children as "persons who have not yet attained the legal age for consent to treatments or procedures involved in the research, under the applicable laws of the jurisdiction in which the research will be conducted." *Id.*

254. *See id.* § 46.402 (b) (stating that failure to object is not same as assent).

255. *See* Bartholome, *supra* note 13, at 347 (quoting National Commission Report, which states that "a child's objection to participation in research should be binding unless the intervention holds out a prospect of direct benefit that is important to the health or well-being of the child and is available only in the context of research").

256. 45 C.F.R. § 46.407 (1999). This section states that

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration

the health, privacy, and liberty interests of the research subject.<sup>257</sup> Each IRB is responsible for determining whether the investigator has obtained appropriate assent and permission for the applicable category of research.<sup>258</sup> Although the American Academy of Pediatrics ("AAP") has suggested that IRBs that review pediatric research must include or consult with health care professionals that are knowledgeable in pediatric medicine, psychology, and sociology, neither the Common Rule nor the FDA regulations have adopted this requirement.<sup>259</sup> Finally, IRBs must

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shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects.

- (b) Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.
- (c) Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.
- (d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.
- (e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
- (f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

*Id.* The FDA Regulations have exactly the same requirements for IRB membership. 21 C.F.R. § 56.107.

257. 45 C.F.R. § 46.103 (1999). The Common Rule states that the purpose of the IRB is to "ensure that risks are minimized, subjects are selected equitably, safety and privacy are protected, and most importantly, informed consent is obtained from subjects . . . and documented." *Id.*

258. 45 C.F.R. § 46.408 (a) (1999). The Common Rule states that, In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out 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, the assent of the children is not a necessary condition for proceeding with the research.

*Id.*

259. See Committee on Drugs, *supra* note 25, at 288 (stating that "[a]ll IRBs that

determine which children are capable of giving assent, and when the child's refusal to assent may be overridden.<sup>260</sup>

Although the Commission suggested that children should be allowed to provide assent at the age of seven,<sup>261</sup> an age that was also adopted by the AAP,<sup>262</sup> the Common Rule does not adopt a specific age requirement.<sup>263</sup> Instead, the Common Rule instructs the IRB to determine whether a child is capable of assenting based on the child's age, maturity, and psychological state, and the trial's importance to the child's health.<sup>264</sup> This instruction, however, has resulted in great variations among research institutions—as one study found that the age of assent varied from five to fifteen years of age, depending on the IRB.<sup>265</sup> Due to these discrepancies, some bioethicists have called for clearer regulations in this area.<sup>266</sup>

Under certain circumstances, the IRB may determine that parental permission is not required, such as when waiver is nec-

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review proposals for investigations in children must include or seek consultation from health care professionals who are aware of the special medical, psychological, and social needs of child research subjects.”); *see also* Weisstub, *supra* note 32, at 390 (stating that Australian Academy of Pediatrics recommended that “an ethics committee be established in all centres responsible for research in children”); Conrad & Horner, *supra* note 67, at 169 (recommending that at least one person on IRB have “solid understanding” of child development, and where this is not possible, that IRB should seek advice from child expert).

260. 45 C.F.R. § 46.408 (a)-(c) (1999) (making IRBs responsible for ensuring that “adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent”).

261. *See* Glantz, *supra* note 243, at 144 (stating that Department of Health and Human Services did not adopt National Commission recommendation that children aged seven or older should be able to provide assent).

262. Committee on Drugs, *supra* note 25, at 290.

263. *See* Bartholome, *supra* note 13, at 347 (explaining that Regulations did not adopt National Commission's recommendations regarding age requirements.)

264. *See* 45 C.F.R. § 46.408(a) (1999) (listing factors for IRBs to consider when determining which children are capable of assenting).

265. *See* Conrad & Horner, *supra* note 67, at 165 (explaining study showing that little consensus exists to determine if child is capable of assent); *see also* Weisstub, *supra* note 32, at 399-400 (noting that in one survey conducted among U.S. authorities in field of child development regarding appropriate age of consent for research participation, responses varied from age 2 to 17, with no modal agreement on age emerging).

266. *See Bioethicists Call for New Focus on Clinical Research Ethics, Sheep Get in the Way*, HEALTH LEG. & REG., May 14, 1997 (reporting that bioethicists who testified at House Governmental Reform and Oversight Human Resources Subcommittee hearing called for “statutory language to clarify rules of research involving vulnerable populations such as children and the mentally disabled,” among other suggestions).

essary for the trial's success,<sup>267</sup> when the child is neglected or abused,<sup>268</sup> or when the child can give independent informed consent.<sup>269</sup> When an IRB grants a waiver, however, trial subjects

267. 45 C.F.R. § 46.116 (c), (d) (1999). Section 46.116 (c), (d) states

- (c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
  - (1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) Public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
  - (2) The research could not practicably be carried out without the waiver or alteration.
- (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
  - (1) The research involves no more than minimal risk to the subjects;
  - (2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;
  - (3) The research could not practicably be carried out without the waiver or alteration; and
  - (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

*Id.*

268. *Id.* § 46.408 (c). Section 46.408 (c) states

In addition to the provisions for waiver contained in § 46.116 of Subpart A, if the IRB determines that a research protocol is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects (for example, neglected or abused children), it may waive the consent requirements in Subpart A of this part and paragraph (b) of this section, provided an appropriate mechanism for protecting the children who will participate as subjects in the research is substituted, and provided further that the waiver is not inconsistent with Federal, state or local law. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

*Id.* The FDA Regulations permit IRBs to waive informed consent requirements for all research when "it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context." *Id.* Where the informed consent requirement is waived, however, "the IRB may require the investigator to provide subjects with a written statement regarding the research." *Id.*

269. See Conrad & Horner, *supra* note 67, at 165 (explaining that "some adolescents may provide full informed consent without parental permission even though they



must be provided with relevant information at the study's conclusion.<sup>270</sup> Despite this provision, if the IRB incorrectly waives the parental permission requirements, then there may be serious consequences for the research institution, including the loss of federal funding.<sup>271</sup> Under these circumstances, the IRB may also be found liable in tort to the subject.<sup>272</sup>

The elements of adequate permission or assent for a particular trial depend on which of the Common Rule's four risk/benefit category are appropriate for the trial.<sup>273</sup> The first category includes research that does not involve greater than

have not yet attained full adult legal status"). The first category of minors who can make independent medical decisions are emancipated minors. *Id.* Emancipated minors live independently, are self-supporting, and are not subject to parental control. *Id.* Children in this category are comprised mainly of minors who are married or in the military. Michelle Oberman, *Minor Rights and Wrongs*, 24 J.L. MED. & ETHICS 127, 130 (1996). A minor may also give independent consent if he seeks medical treatment for a condition for which the state has passed statutes waiving the parental permission requirement for public policy reasons, such as treatment for sexually transmitted diseases, alcohol and substance abuse, and psychiatric problems. Oberman, *supra*, at 130. Finally, a mature minor may provide independent consent. *Id.*; see also Conrad & Horner, *supra*. Mature minors are "children who understand their medical condition, the alternative treatments and their associated risks and benefits, and can make an informed, voluntary decision about their medical treatments." *Id.* All minors who are not emancipated, however, are considered children for the purposes of non-therapeutic research. Glantz, *supra* note 27, at 230.

270. See 45 C.F.R. § 46.116 (c)(4) (1999) (stating that "[w]henever appropriate, the subjects will be provided with additional pertinent information after participation").

271. See *id.* § 46.122 (declaring that federal funds may not be used in any research involving human subjects that does not comply with Common Rule).

272. See Robert J. Katerberg, Note, *Institutional Review Boards, Research on Children, and Informed Consent of Parents: Walking the Tightrope Between Encouraging Vital Experimentation and Protecting Subjects' Rights*, 24 J.C. & U.L. 545, 575 (1998) (explaining that IRBs may be found tortiously liable for waiver if plaintiff shows not only that IRB incorrectly waived permission but also that IRB made waiver decision negligently).

273. See 45 C.F.R. § 46.411 (a)(4), (a)(5) (1999) (making IRBs responsible for reviewing risks and informed consent); see generally 45 C.F.R. Sub. D (holding IRBs responsible for determining level of risk and attaining appropriate assent and permission). The FDA Regulations do not have risk/benefit categories that are specific to children, but, instead, IRBs must consider

- (a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.
- (b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

minimal risk.<sup>274</sup> Research in this category requires both the

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- (c) An IRB shall require documentation of informed consent in accordance with § 50.27 of this chapter, except as follows:
    - (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or
    - (2) The IRB may, for some or all subjects, find that the requirements in § 50.24 of this chapter for an exception from informed consent for emergency research are met.
  - (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research.
  - (e) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. For investigations involving an exception to informed consent under § 50.24 of this chapter, an IRB shall promptly notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research because it does not meet the criteria in the exception provided under § 50.24(a) of this chapter or because of other relevant ethical concerns. The written notification shall include a statement of the reasons for the IRB's determination.
  - (f) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.
  - (g) An IRB shall provide in writing to the sponsor of research involving an exception to informed consent under § 50.24 of this chapter a copy of information that has been publicly disclosed under § 50.24(a)(7)(ii) and (a)(7)(iii) of this chapter. The IRB shall provide this information to the sponsor promptly so that the sponsor is aware that such disclosure has occurred. Upon receipt, the sponsor shall provide copies of the information disclosed to FDA.

21 C.F.R. § 56.109 (1999).

274. 45 C.F.R. § 46.404 (1999). The first risk/benefit category states that "HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in § 46.408." *Id.* The term minimal risk, as used 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 ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." 45 C.F.R. § 46.102 (2)(i) (1999). The FDA Regulations' definition of minimal risk is exactly the same as the Common Rule's definition. 21 C.F.R. § 50.3(k) (1999).

child's assent and the parent's permission to participate in research,<sup>275</sup> and confers no therapeutic benefit to the child.<sup>276</sup> Research in the second category includes trials that involve greater-than-minimal risk, but may directly benefit the individual subject.<sup>277</sup> Research in this category is permissible if the potential benefit of the study justifies the greater-than-minimal risk involved,<sup>278</sup> or if the trial may be as beneficial to the subject as alternative treatments.<sup>279</sup> Although this section requires that both the child's assent and the parent's permission adequately be obtained,<sup>280</sup> the IRB may waive the assent requirement where the child's participation is medically necessary.<sup>281</sup> The Common Rule's third category includes research involving greater than minimal risk that will not yield a direct benefit to the individual subject, but is likely to provide general knowledge about the subject's disorder or condition.<sup>282</sup> Research in the third category is only permissible if it represents a minor increase over minimal risk,<sup>283</sup> or involves an amount of risk that is roughly equal to that which the child would face in an ordinary medical or dental check-up.<sup>284</sup> This type of research is permissible if the study is

275. 45 C.F.R. § 46.404 (1999).

276. Conrad & Horner, *supra* note 67, at 165.

277. 45 C.F.R. § 46.405 (1999). Research in this category includes "[r]esearch involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects." *Id.*

278. *Id.* § 46.405 (a). The risk in this category must be "justified by the anticipated benefit to the subjects." *Id.*

279. *Id.* § 46.405 (b). The second category mandates that "[t]he relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches." *Id.*

280. *Id.* § 46.405 (c). This category requires that "[a]dequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408." *Id.*

281. *Id.* § 46.408 (a). This section states that "[I]f the IRB determines that . . . the intervention or procedure involved in the research holds out 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, the assent of the children is not a necessary condition for proceeding with the research." *Id.*

282. *Id.* § 46.406. Section 46.406 includes, "[r]esearch involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition." *Id.*

283. *Id.* § 46.406 (a). Research in this category is permissible if "[t]he risk represents a minor increase over minimal risk." *Id.*

284. *Id.* § 46.406 (b). This section defines a trial that involves a minor increase over minimal risk as one where "the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations." *Id.*

likely to yield general knowledge about the subject's condition,<sup>285</sup> the child assents to participation, and the child's parents give permission.<sup>286</sup> The Common Rule's final category includes trials that would not ordinarily be approved, but that present an opportunity to understand, prevent, or alleviate a serious problem affecting children's health or welfare.<sup>287</sup> These trials must undergo external review to ensure that they meet the safety and consent standards required by the Common Rule.<sup>288</sup>

Although these four categories are based on the term minimal risk, there appears to be some confusion regarding this term's definition.<sup>289</sup> In an attempt to apply this standard in a fair and ethical manner, the Common Rule instructs IRBs to apply the minimal risk standard to the particular child involved in the study.<sup>290</sup> Under this construction, however, children who are ill and often endure potentially risky interventions may be

285. *Id.* § 46.406 (c). The research in this category must be "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." *Id.*

286. *Id.* § 46.406 (d). For research in this category, IRBs must make sure that "[a]dequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408." *Id.*

287. *Id.* § 46.407. Research in this category includes "[r]esearch not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children." *Id.* Section 46.407 (a) requires that an IRB reviewing trials in this category must find "that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." *Id.* at § 46.407(a).

288. *Id.* § 46.407 (b). To ensure the ethical nature of these trials, The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: (1) That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or (2) the following:

- (i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- (ii) The research will be conducted in accordance with sound ethical principles;
- (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.

*Id.*

289. See Glantz, *supra* note 27, at 232-33 (explaining that "although the concept of minimal risk may be alluring, it is quite difficult to define and apply").

290. 45 C.F.R. § 45.102 (2)(i) (1999) (defining minimal risk as level of harm or discomfort that is commensurate with that "ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests").

subjected to studies posing a significant amount of risk.<sup>291</sup> In these situations, researchers must take care not to exceed socially acceptable limitations for levels of risk to which a child may be exposed.<sup>292</sup> To ameliorate this problem, commentators have suggested that the level of risk in studies should be commensurate with the risk involved in activities with which the child is both familiar and able to cope, rather than within the realm of the child's experience.<sup>293</sup>

Although the AAP suggests that the term minimal risk should be construed broadly,<sup>294</sup> there are several highly invasive procedures that some IRBs characterize as posing no more than minimal risk.<sup>295</sup> Additionally, aside from the physical risks that the research entails, experts believe that it is also important that researchers and IRBs consider psychological risks related to children's developmental vulnerabilities, as discussed earlier.<sup>296</sup> In the absence of a clear definition of what constitutes a minimal risk intervention, some experts fear that U.S. IRBs may underestimate the risks to which pediatric research subjects are exposed.<sup>297</sup>

## 2. European Union Regulations on Assent and Risk

Europe has led the world in harmonizing pharmaceutical

291. See Ross, *supra* note 78, at 162 (noting that concept of ordinary risk may increase vulnerability of chronically ill children).

292. See *id.* (explaining that IRBs owe fiduciary duty to patients to always look after their best interests).

293. See *id.* (citing one commentator that suggests that experimental interventions under minimal risk category should be limited to experiences with which subject is comfortable, "rather than any activity which a child may have previously experienced").

294. Committee on Drugs, *supra* note 25, at 288 (explaining that IRBs must remember that drugs and other medical interventions may pose risks that have not been exposed in earlier trials).

295. See Bartholome, *supra* note 13, at 350 (citing survey of pediatric departmental chairs and directors of pediatric research programs stating that substantial minority of those polled "regarded interventions such as arterial puncture, placement of a nasogastric tube, and tympanocentesis (aspirating fluid from the middle ear with a needle placed through the ear drum) to be minimal risk interventions.").

296. See Conrad & Horner, *supra* note 67, at 167 (explaining vulnerabilities affecting children of different ages).

297. See Ross, *supra* note 78, at 163 (noting reasons to question IRB decision-making on questions of risk). One reason why IRBs may not be reliable is that most IRBs are largely composed of members of the research community and may be biased by this affiliation. *Id.* There is also evidence that IRBs "tend to suffer from typical group mentality," which generally leads to an increase in risk taking over that of individual decision making. *Id.*

regulations.<sup>298</sup> Their efforts began in 1965, when the European Community adopted Directive 65/65,<sup>299</sup> requiring Member States to establish regulations and criteria for drug approval.<sup>300</sup> Since 1965, European countries have recognized the need to create uniform ethical guidelines for pre-market drug approval and clinical trials.<sup>301</sup> Although the European Union (or "EU") has been hesitant to become involved in ethical matters, it has also recognized the need to have some EU regulation on human research in its pharmaceutical regulatory scheme. In 1990, the Committee for Proprietary Medicinal Products<sup>302</sup> ("CPMP") promulgated the Good Clinical Practice Guideline<sup>303</sup> ("EU GCP"), which was later replaced when the ICH GCP entered into force.<sup>304</sup> With regard to pediatric medical research, the

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298. See Dan Kidd, Note, *The International Conference on Harmonization of Pharmaceutical Regulations, the European Medicines Evaluation Agency, and the FDA: Who's Zooming Who?*, 4 IND. J. GLOBAL LEGAL STUD. 183, 188 (1996) (explaining that Europe understood value of borderless pharmaceutical market before rest of world).

299. Council Directive 65/65 on the Approximation of Provisions Laid Down By Law, Regulation or Administrative Action relating to Proprietary Medicinal Products, O.J. L 22/269 (1965).

300. See Richard F. Kingham, *et al.*, *The New European Medicines Agency*, 49 FOOD & DRUG L.J. 301, 301 (1994) (stating that Directive 65/65 provided impetus for pharmaceutical regulation harmonization in EC).

301. See R. Fears, *et al.* *Life Sciences, R & D, National Prosperity, and Industrial Competitiveness*, SCIENCE, May 2, 1997, at 759 (stating that "[c]oherence and consistency in science policy is essential if the full intellectual capital of Europe is to be harnessed for societal benefit.").

302. See Kingham, *supra* note 300, at 302 (stating that Commission created CPMP in 1975 to coordinate multi-state procedure for recognizing national pharmaceutical approvals). The CPMP is composed of Member State regulatory agency representatives, and coordinates multi-state procedures for accepting national drug approvals on a European level. *Id.*

303. EU GCP, *supra* note 162.

304. See Good Clinical Practice, Directive 75/328/EEC, CPMP/ICH 135/95, revised 1996, effective Jan. 1997, at Additional Notes, *available at* (visited Mar. 8, 2000) <<http://www.eudra.org/humandocs/PDFs/ICH/013595en.pdf>> (on file with the *Fordham International Law Journal*). This directive states that

This note for guidance concerns the application of Part 4, sections B and C of the Annex to Directive 75/318/EEC as amended with a view to the granting of a marketing authorisation for a medicinal product. It established the principles for standards of Good Clinical Practice both within the European Community and within the ICH regions. It replaces the previous 1990 guideline entitled *Good Clinical Practice for Trials on Medicinal Products in the European Community* (III/3976/88) adopted May 1990."). Shortly after this report was released, the standard of good clinical practice was later reinforced in an annex to a Commission directive adopted in July of 1999. See Commission Directive 91/507/EEC, O.J. L 270/32 (1999). Part four of the annex of Commission Directive 91/507/EEC on the approximation of the laws of the Member States

CPMP created a separate set of guidelines entitled the Note for Guidance on Clinical Investigation of Medicinal Products in Children<sup>305</sup> (or "Guideline for Children").<sup>306</sup>

a. The European Union Good Clinical Practice Guidelines

In July 1990, the CPMP issued the EU GCP, which set forth basic guidelines for conducting medical trials on human subjects.<sup>307</sup> The purpose of this guideline was to establish systematic procedures for protecting trial subjects' dignity while preserving the scientific integrity and reliability of trial results.<sup>308</sup> The EU GCP defined the term good clinical practice as a manner of trial design that produces credible data and protects the rights and integrity of trial subjects.<sup>309</sup>

The EU GCP adopted the general standards for ethical research set forth in the Helsinki Declarations by conferring with the Ethics Committees on issues of informed consent and risk.<sup>310</sup>

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relating to the analytical, pharmatotoxicological and clinical standards and protocols in respect of the testing of medicinal products, states that all trials shall be "designed, implemented and reported in accordance with good clinical practice."

*Id.*

305. GUIDELINE FOR CHILDREN, *supra* note 51.

306. *Id.*

307. See John Gorski, *An FDA-EEC Perspective on the International Acceptance of Foreign Clinical Data*, 21 CAL. W. INT'L L.J. 329, 550 (1991) (describing evolution of European Good Clinical Practice).

308. See *id.* at 350. The foreword of the EU GCP states that parties involved in the evaluation of medicinal products share the responsibility of accepting and working according to such standards in mutual trust and confidence. Pre-established, systematic written procedures for the organization, conduct, data collection, documentation and verification of clinical trials are necessary to ensure that the rights and integrity of the trial subjects are thoroughly protected and to establish the credibility of data and to improve the ethical, scientific and technical quality of trials. These procedures also include good statistical design as an essential prerequisite for credibility of data and moreover, it is unethical to enlist the cooperation of human subjects in trials which are not adequately designed.

*Id.*

309. EU GCP, *supra* note 162, at Glossary. The EU GCP defines Good Clinical Practice as "a standard by which clinical trials are designed, implemented and reported so that there is public assurance that the data are credible, and that the rights, integrity and confidentiality of subjects are protected." *Id.*

310. *Id.* art. 1.1, 1.2. Article 1.1 of the EU GCP states "[t]he current revision of the Declaration of Helsinki is the accepted basis for clinical trial ethics, which must be fully known and followed by all engaged in research on human beings." *Id.* art. 1.1. Article 1.2 of the EU GCP states, "[t]he personal integrity and welfare of the trial subjects is the ultimate responsibility of the investigator in relation to the trial; but in-

Some commentators, however, found fault with the EU GCP's apparently liberal wording on informed consent, which could have been construed as not requiring informed consent in inconvenient situations.<sup>311</sup> With regard to pediatric subjects, the EU GCP permitted proxy consent for legally incompetent subjects, although minors were not specifically included in this group.<sup>312</sup> This document also appeared to prohibit a child's participation in non-therapeutic trials completely, as participation in non-therapeutic studies required the subject's own signature.<sup>313</sup> In subsequent years, the original EU GCP has been replaced by the ICH GCP, which the CPMP adopted in July 1996.<sup>314</sup>

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dependent assurance that subjects are protected is provided by an Ethics Committee and freely obtained informed consent." *Id.* art. 1.2. It should be noted, however, that the EU GCP may be viewed as more permissive than Helsinki, as it allows for oral consent in situations where written consent cannot be obtained, and where there is a witness to the informed consent. Gorski, *supra* note 307, at 360 n.150. Additionally, the EU GCP states that investigators *should* consider Ethics Committee opinions, making these group's role more advisory than mandatory. Gorski, *supra*.

311. EU GCP, *supra* note 162, art. 1.8. Article 1.8 may be viewed as overly permissive, since it states that, "[t]he principles of informed consent in the current revision of the Helsinki Declaration *should* be implemented in each clinical trial. *Id.* (emphasis added).

312. *Id.* art. 1.13. Article 1.13 states that

If the subject is incapable of giving personal consent (*e.g.*, unconsciousness or severe mental illness or disability), the inclusion of such patients may be acceptable if the Ethics Committee is, in principle, in agreement and if the investigator is of the opinion that participation will promote the welfare and interest of the subject. The agreement of a legally valid representative that participation will promote the welfare and interest of the subject should be recorded by a dated signature. If neither signed informed consent nor witness signed verbal consent are possible, this fact must be documented by the investigator.

*Id.*

313. *Id.* art. 1.14. This section states that "[c]onsent must always be given by the signature of the subject in a non-therapeutic study, i.e. when there is no direct benefit to the subject." *Id.*

314. See The International Conference on Harmonisation Web Site, at Efficacy Topics, E6, Good Clinical Practice: Consolidated Guideline (visited Dec. 2, 1999) <<http://www.ich.org>> (on file with the *Fordham International Law Journal* (noting that ICH GCP was adopted by CPMP in June 1996, and was issued in CPMP report, CPMP/768/97). In the period following adoption of the ICH-GCP, numerous proposals for Parliament and Council Directives have been issued regarding the approximation of national laws to the GCP. *Id.* Most notably, these proposals suggest that the Member States must lay down laws to safeguard individuals who are incapable of providing consent. Amended Proposal for a European Parliament and Council Directive on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Tri-



b. The CPMP Note for Guidance on Clinical Investigation of Medicinal Products in Children

Although the EU GCP did not discuss pediatric research directly, the CPMP specifically addressed this issue in its Note for Guidance on Clinical Investigation of Medicinal Products in Children.<sup>315</sup> First, the Guideline for Children stresses the need to test medicinal products in pediatric subjects, even if the product will only be used in a small number of children.<sup>316</sup> It then emphasizes the fact that while adults can actively take risks with their bodies, children depend on adults to determine what risks are appropriate for them.<sup>317</sup> Consequently, informed consent must be obtained from the child's parent or guardian in accordance with national legislation.<sup>318</sup>

Along with parental consent, the Guideline for Children specifies that the child should be provided information regarding the trial in an age appropriate manner, and if able, sign and date a written informed consent form.<sup>319</sup> The child must also be informed of his or her right not to participate in the trial and, unlike U.S. regulations, the investigator must obey the child's refusal to participate.<sup>320</sup> The Guideline for Children makes no

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als on Medicinal Products for Human Use, COM/99/0193 Final-COD 97/0197, O.J. C 160/5 (1999), 3.

315. GUIDELINE FOR CHILDREN, *supra* note 51.

316. *Id.* art. 1.1. Article 1.1 states that authorities have a responsibility to ensure that

children have timely access to safe and effective medicines which have accurate, scientifically justified prescribing information. Applicants are encouraged to investigate the safety and efficacy of a product in children, if it is likely to be of therapeutic benefit in this age group, and to develop suitable formulations, even if the usage is likely to be small.

*Id.*

317. *Id.* The Guideline for Children explains that

Adults who participate in clinical trials and who understand the issues involved in giving their informed consent, accept and share the risk of injury, although in practice serious damage to trial subjects is rare. Children are legally dependent on their parents/guardians who take the legal responsibility for their welfare and safety, and fully informed consent should be obtained from the legal guardian in accordance with national legislation.

*Id.*

318. *See id.* (stating that "fully informed consent should be obtained from the legal guardian in accordance with national legislation").

319. *See id.* (mandating that "[c]hildren should be fully informed about the trial in language and terms which they are able to understand and, if able, should personally sign and date the written informed consent.").

320. *See id.* (stating that "[t]he child should be made aware of his/her rights to

distinction between therapeutic and non-therapeutic trials when conferring the right to refuse participation.<sup>321</sup>

The Guideline for Children also specifically addresses the issue of risk.<sup>322</sup> The document first delineates the physical differences between children and adults, as well as differences between children of different ages<sup>323</sup> that necessitate separate clinical trials utilizing pediatric subjects.<sup>324</sup> It thoroughly describes hazards that are specific to different age groups that may affect risk assessment.<sup>325</sup> The CPMP then suggests ways to design protocols to minimize risks to subjects.<sup>326</sup>

The Guideline for Children also provides instructions for testing medicines on children that may also be used in adults.<sup>327</sup> According to the EU GCP, medicines should first be tested in adults and then in children, unless the treatment is designed for a childhood-specific illness.<sup>328</sup> Once it is determined that the trial can be conducted in children, the Guideline for Children then describes which methods that are appropriate for pediatric trials.<sup>329</sup> As a whole, the Guideline for Children places great em-

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decline to participate. The child's wish to be withdrawn from a study *must* be respected.").

321. *Id.*

322. *See id.* arts. 1.2, 1.3, 1.4 (discussing issues including Scientific Considerations, Need to Minimise Risks, and Need to Minimise Distress).

323. *See id.* (detailing physical differences between children of different age groups).

324. *See id.* art. 1.2 (specifying pharmacokinetic, pharmacodynamic, and pathological differences between adults and children, and differences caused by process of growth and development).

325. *See id.* art. 2 (classifying children by age and maturity).

326. *See id.* art. 1.3 (explaining need to minimize risks). This article suggests that a drug should first be tested on animals, then adults, and then on older children before testing on younger children. *Id.* 1.3 (a). Article 1.3 (b) also suggests that the trial should use the minimum numbers of subjects necessary to be statistically significant. *Id.* 1.3 (b). Article 1.4 mandates that investigators should stop a trial immediately if any dangers arise in the research. *Id.* 1.4. Finally, the researchers should prepare emergency protocols in case a trial becomes dangerous. *Id.* 1.3 (d).

327. *See id.* art. 4 (explaining that medicines that treat childhood specific diseases may be tested first in children, but for other drugs, adult studies must be used to gather relevant safety and toleration information before testing in children).

328. *Id.* art. 4.1. Article 4.1 states, "[i]f a product is being developed initially for the treatment of a childhood-specific illness, the clinical development may start in children before any prior adult exposure. In other circumstances, relevant safety and toleration data from previous adult exposure is needed before proceeding with studies in children." *Id.*

329. *See id.* art. 5.1.2 (specifying that tests on small blood volumes, urinalysis, and saliva are appropriate). Protocols should be designed with four main considerations in

phasis on looking to the child's maturity level to determine the appropriate level of risk and informed consent.<sup>330</sup> Although the Guideline for Children may be helpful to investigators, as with other CPMP guidelines, it is not binding.<sup>331</sup>

### 3. Japan

As the primary non-Western participant in the ICH, Japan's cultural differences are reflected in its human research regulations.<sup>332</sup> Many of these differences result from a perspective on the doctor-patient relationship that is unique among other parties.<sup>333</sup> Commentators state that, historically, the Japanese doctor-patient relationship has been very paternalistic, making informed consent a low priority among Japanese physicians.<sup>334</sup> In recent years, however, this relationship has changed, with government officials placing a greater emphasis on informed consent.<sup>335</sup> This shift in attitudes, along with the need to produce internationally acceptable pharmaceutical exports, has played a large role in fostering Japanese acceptance of the ICH GCP provisions.<sup>336</sup>

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mind: the therapeutic class of the trial, the clinical situation, the child's maturity level, and the trial's objectives. See also *id.* art. 5.2 (stating that trial "[p]rotocols should be adapted to: (a) the therapeutic class; (b) the clinical situation; (c) the stage of maturity of the child; and (d) the proposed objectives of treatment.")

330. See *id.* art. 2 (using child's maturity to guide development of clinical study).

331. See C.A. Teijgeler, *The Role of the CPMP in the EEC, in* INTERNATIONAL MEDICINES REGULATIONS: A FORWARD LOOK TO 1992 207, 213 (S.R. Walker & J.P. Griffin, eds. 1989) (explaining that CPMP guidelines and other recommendations are not binding).

332. See generally George J. Annas & Frances H. Miller, *The Empire of Death: How Culture and Economics Affect Informed Consent in the U.S., the U.K., and Japan*, 20 AM. J.L. & MED. 357, 372-73 (1994) (describing differences between Japanese culture and Western culture that create divergent views and legislation on informed consent and other health care issues).

333. See Michael Hoffman, *Deadly Doctors*, MAINICHI DAILY NEWS, Oct. 19, 1997, at B11 (stating that doctor-patient relationships in Japan are completely different from Western doctor-patient relationships).

334. See Annas & Miller, *supra* note 332, at 373 (explaining that concept of informed consent was only introduced in Japan in 1970s, and is not yet accepted).

335. See Robert Leflar, *Informed Consent and Patients' Rights in Japan*, 33 Hous. L. REV. 1, 10 (1994) (noting results of January 1990 meeting of Japan Medical Association's Bioethics Roundtable that concluded that informed consent is necessary to trusting doctor-patient relationship).

336. See *id.* at 76 (explaining that primary motivation behind Japanese acceptance of ICH GCP was that Japan's failure to meet basic ethical standards as prescribed by Western countries impeded its pharmaceutical industry's ability to sell drugs in international markets).

a. The Emerging Concept of Informed Consent in Japanese Medicine

Even though Japan has made great strides in medical ethics in recent years, the concept of bioethics is still relatively new to Japan.<sup>337</sup> In the past, many Japanese doctors refused to disclose important information to patients regarding the severity of their medical conditions, causing some patients to ignore prescriptions for medications and skip critical follow up visits.<sup>338</sup> These physicians did not withhold information out of malice for their patients; rather, one scholar noted that this practice resulted from a widely held belief that informing a patient of serious illness would be cruel and would hinder the patient's recovery by causing him or her to give up hope.<sup>339</sup>

This failure to give patients relevant information also extended to prescription drugs.<sup>340</sup> Patients were prescribed medications routinely without receiving any explanation why they were taking the drug, what risks the medication posed, and what precautions they should take while using the medication.<sup>341</sup> Alarming, this practice was common for experimental drugs, as well as drugs that had already been approved.<sup>342</sup>

Recently, however, there has been greater support for a Western concept of informed consent in Japan.<sup>343</sup> A current

337. See (*Seimi-Rinri*)/*Bioethics*, DAILY YOMIURI/YOMIURI SHIMBUN, Feb. 20, 1997, available at 1997 WL 9499757 (explaining that concept of bioethics is new to Japan and that it has been uniquely shaped by Japan's cultural values and traditions).

338. See Derek Kroft, *Informed Consent: A Comparative Analysis*, 6 J. INT'L L & PRAC. 457, 473 (1997) (explaining facts of leading informed consent case in Japan, *Makino v. The Red Cross Hospital*, 1325 Hanji 203, 31 WAHBURN 455 (1992)). In *Makino*, the doctor never informed his patient that he suspected that she had cholecystic cancer. *Id.* The patient subsequently cancelled follow up appointments with the doctor, unaware of the severity of her condition, and died several months later. *Id.*

339. See Leflar, *supra* note 335, at 21, 22 (stating that many doctors believe that disclosing this type of information to patients would be medically and ethically irresponsible, and contrary to their obligation to preserve patients' lives).

340. See *id.* at 27 (noting that another example of cultural paternalism in Japanese medicine occurs in prescribing drugs).

341. See *id.* (explaining that often doctors neglected to explain drugs' purpose, risks, or cautions for use).

342. See *id.* (stating that physicians withhold information with experimental as well as standard drugs).

343. See Kroft, *supra* note 338, at 474-75 (mentioning that although doctors have discretion in determining how much information to give patients, pressure is mounting to make Japanese standards of informed consent more closely conform to those of United States); see also Kyoko Imamura, *A Critical Look at Health Research in Japan*, LAN-

poll conducted by a Japanese newspaper revealed a significant increase in the number of respondents who wished to be fully informed in medical situations.<sup>344</sup> The numbers favoring disclosure were even higher among respondents between the ages of twenty and thirty.<sup>345</sup>

Public opinion, economic pressure, and several embarrassing and fatal drug approvals<sup>346</sup> influenced the Japanese government to implement major changes in human research regulations.<sup>347</sup> To facilitate this process, the Japanese Ministry of Health and Welfare ("MHW") appointed an advisory committee to formulate recommendations for revising clinical trial regulations.<sup>348</sup> In 1985, the advisory committee issued its report.<sup>349</sup> Japan adopted its first Good Clinical Practice standards ("Japanese

CET, July 31, 1993, at 281 (explaining that even though many Japanese "appreciate the stabilising influence of a powerful figure such as a physician . . . people are now willing to shed some of this dependence on medical authority, as shown by increasing pressure for informed consent.").

344. See *Survey: 80% Favor Law on Medical Disclosure*, YOMIURI SHIMBUN/DAILY YOMIURI, July 4, 1999, available at 1999 WL 17755311 (stating that 82% represents highest approval rating since this survey was first conducted in 1987).

345. See *id.* (reporting that 87% of respondents in their 20s wanted to be informed if they had cancer, as opposed to 72% in 1995).

346. See Michelle D. Miller, *The Informed Consent Policy of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Knowledge Is the Best Medicine*, 30 CORNELL INT'L L.J. 203 222 (1997) (describing Sorivudine scandal). Sorivudine was an anti-viral drug that was released in the Japanese market despite being rejected in Europe for causing death in chemotherapy patients, and despite three patients and many animals that died in clinical trials. *Id.* Sixteen people died when this drug was released on the market and many others were injured. *Id.*

347. See generally, *Anticancer Drugs: Primarily Led by Increase in Metabolic Protagonists*, PHARMA JAPAN, Nov. 13, 1995, available at 1995 WL 10665757 (indicating that Sorivudine scandal sparked greater efforts to obtain informed consent).

348. See Leflar, *supra* note 335, at 76 (explaining that Japanese Ministry of Health and Welfare ("MHW") appointed prestigious committee to study clinical trial revision in Japan).

349. See K. Uchida, *Future Perspectives of Regulations in Japan*, in INTERNATIONAL MEDICINES REGULATIONS: A FORWARD LOOK TO 1992 173, 179 (S.R. Walker & J.P. Griffin, eds., 1989) (explaining that MHW issued GCP proposal relating to investigational drug trials, including: requiring that ethical aspects be considered when conducting clinical trials; requiring contracts between investigators and institutions; requiring that institutions be properly equipped to deal with trial and any emergencies that may arise; that IRBs review trials in all institutions; that proper records must be kept; and that investigators must "explain the details of a clinical trial to each subject and obtain consent based on the subject's free will."). The report also defines the sponsor's responsibilities, including the duty to monitor the trial, the investigator's responsibilities, and the MHW's right to inspect and verify all trial results. *Id.*

GCP"), based on the MHW advisory committee's recommendations, in 1989.<sup>350</sup>

Even after these regulations were adopted, many Japanese physicians appeared to be unaware that the Japanese GCP even existed,<sup>351</sup> and many IRBs continued to approve trials blindly.<sup>352</sup> Some surveys, however, indicate that Japanese researchers have begun to require written informed consent from their test subjects.<sup>353</sup> The growing awareness of the importance of informed consent, along with continued abuses, led to criticisms of the first Japanese GCP,<sup>354</sup> and its revision in accordance with the ICH GCP.<sup>355</sup>

### b. The New Japanese GCP

To remedy the old Japanese GCP's deficiencies and address the growing concerns of the Japanese public, the MHW released a revised version of the Japanese Good Clinical Practice Guidelines in April of 1997<sup>356</sup> ("New Japanese GCP").<sup>357</sup> Unlike the original Japanese GCP, the New Japanese GCP mandates that investigators obtain written informed consent<sup>358</sup> from their pa-

350. See Leflar, *supra* note 335, at 76 (explaining that MHW waited for resistance expressed by non-exporting Japanese drug manufacturers to settle down before issuing original GCP in October 1989).

351. See *id.* at 80 (citing Nagoya Bar Association survey conducted in 1992-93, suggesting that 23% of Japan's physicians were unaware that GCP existed and another 24% had not read them).

352. See *id.* at 80 (stating that serious IRB examination of research trials "appears to be the exception rather than the rule").

353. See *Necessity of Written Informed Consent Deemed High by Investigators*, PHARMA JAPAN, June 24, 1996, available at 1996 WL 10082891 (discussing results of one study indicating that 72.9% of investigators wanted written informed consent, compared with 60.5% of IRB members in 1994 and 48.9% of investigators in 1995).

354. See *Ministry To Tighten Drug-Testing Policies*, DAILY YOMIURI/YOMIURI SHIMBUN, Mar. 21, 1997, available at 1997 WL 10099146 (explaining that continued abuses led MHW to believe that Japanese GCP is too ambiguous).

355. See *GCP Guidelines Agreed on*, JAPAN CHEM. WK., May 22, 1996, available at 1996 WL 8148615 (stating that after new ICH-GCP Guidelines were adopted, Japanese authorities took steps to conform Japanese GCP to ICH-GCP).

356. See JAPAN'S NEW GCP AND OTHER RULES ON CLINICAL TRIALS, PART III 2 (Review Assessing Group, *et al.* eds., 1999) [hereinafter JAPAN'S NEW GCP AND OTHER RULES] (explaining that Japanese GCP was introduced in April 1997 and became effective in 1998).

357. *Id.*

358. See *id.* art. 52 (explaining informed consent requirements). Article 52 paragraph 3 states that if the subject cannot read, the subject can give verbal consent in the presence of a witness who is not affiliated with the researchers. *Id.* art. 52.3.

tients.<sup>359</sup> Another major change in the New Japanese GCP is that each research facility should have an IRB that includes members who are not affiliated with the research institution.<sup>360</sup> Generally, the New Japanese GCP, like the EU GCP, is based on the principles outlined in the Helsinki Declarations.<sup>361</sup>

Under the New Japanese GCP, almost every research institution is required to have an IRB.<sup>362</sup> The IRB is charged with con-

359. See JAPAN'S NEW GCP AND OTHER RULES, *supra* note 356, at 2 (listing primary objections to written informed consent as being: "(1) that the notion of a contract was foreign to most Japanese, (2) that the act of signing (or sealing), which is rarely performed in daily life, would cause prospective subjects unnecessary anxiety"). Many investigators also opposed the notion of written consent, stating that most patients would take time to seek their relative's consent, and then return to tell the investigator that they will not participate. *Id.*

360. See *id.* art 28 (describing IRB composition). According to Article 28 of New Japanese GCP, the IRB must meet the following qualifications:

- (1) Being capable of fully reviewing the proposed clinical trial from the ethical and scientific viewpoints;
- (2) Being comprised of at least five members;
- (3) Having, as its member(s), a person or persons other than, and besides, those who have an expert knowledge in medicine, dentistry, pharmacy, health care, or clinical trials [besides the member(s) described in (4)];
- (4) Having, as its member(s), among others, a person or persons disinterested in the medical institution.

*Id.* The Pharmaceutical Affairs Bureau ("PAB") Notification, On Application of Guideline for Good Clinical Practice, also notes, however, that "[t]he IRB may invite non-members with expertise in relevant special areas for assistance." See On Application of Guideline for Good Clinical Practice (PAB/PCD Notification No. 445; PAB/SD Notification No. 8), May 29, 1997, art. 28 [Explanation] para. 6 [hereinafter On Application].

361. On Application, *supra* note 360, at chap. 1 para. 2(1). Chapter 1, paragraph 2, section 1 states, "[c]linical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and the standards for the conduct of clinical trials on drugs established under the Ordinance (hereinafter referred to as "the GCP")." *Id.*

362. NEW JAPANESE GCP, *supra* note 230, art. 27. Article 27 states,

The heads of medical institutions shall organize an institutional review board for each institution to have the board review and deliberate on whether it is appropriate to conduct a clinical trial and on other matters relevant to the clinical trial. When it is impracticable to organize an institutional review board because the medical institution is small in scale or of any other reason, however, the relevant institutional review board may be substituted by any of the following alternatives.

- (1) A joint institutional review board organized by the head of the medical institution in collaboration with heads of other medical institutions.
- (2) An institutional review board organized by a juridical person pursuant to Article 34 of the Civil Law (Law No. 89, 1896).

ducting both preliminary and continuing ethical and scientific review of the protocol,<sup>363</sup> paying special attention to vulnerable subjects.<sup>364</sup> Although the IRB must review the ethical and scientific validity of the trial, the New Japanese GCP does not specifically make them responsible for monitoring whether appropriate informed consent has been obtained.<sup>365</sup> The Pharmaceutical Affairs Bureau ("PAB") Notification on Application, however,

(3) An institutional review board organized by an academic organization composed of health care professionals.

(4) An institutional review board organized by the heads of other medical institutions (excluding cases specified in Item 1).

*Id.*

363. *Id.* art. 32. Article 32 states that

the institutional review board shall review the ethical and scientific appropriateness of the clinical trial and state its opinion in writing as to whether it is appropriate to conduct the clinical trial at the medical institution on the basis of the following documents.

(1) The documents specified in the items of Article 10.

(2) Documents concerning subject recruitment procedures.

(3) Documents describing information specified under Article 7, Paragraph 5, and other information important for the proper conduct of the clinical trial.

(4) Current *curriculum vitae* of each prospective investigator, etc.

(5) Other documents the institutional review board considers necessary.

*Id.*; see On Application, *supra* note 360, art. 32 ¶ 2 (C), (D) (stating that IRB must also examine sample informed consent forms and written information sheets).

364. See On Application, *supra* note 360, art. 32, para. 1 (stating that "[t]he IRB should safeguard the rights, safety, and well-being of all subjects. Special attention should be paid to clinical trials that may include vulnerable subjects"). Paragraph 7 states that

[w]hen a non-therapeutic trial without anticipated direct clinical benefit to the subject carried out with the consent of the subject's proxy consentor [(see Article 7, Paragraph 2) (7-2-3)] is proposed, the IRB should ensure that the submitted protocol and other documents adequately address relevant ethical concerns and comply with Article 7, Paragraph 2 (7-2-3) (4-2-8). The documented approval of the IRB should specifically state that the IRB approves that such subject is to be enrolled in the trial

*Id.* at para. 7. The term "vulnerable subjects" is defined in the Central Pharmaceutical Affairs Bureau ("CPAC") GCP under Advice Made to the Minister by the CPAC, as

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are . . . minors and those incapable of giving consent.

Advice Made to the Minister by CPAC, CPAC Notification No. 40, dated Mar. 13, 1997, arts. 2-14.

365. NEW JAPANESE GCP, *supra* note 230, art. 32. The PAB Notification On Application, however, places some responsibility for ensuring that all subjects have consented in writing on the sponsor. On Application, *supra* note 360, art. 21, para. 4.



states that the IRB may request that more information be added to the subject informed consent form when necessary to protect the patient's rights.<sup>366</sup>

Section four of the New Japanese GCP discusses informed consent requirements.<sup>367</sup> This section outlines the requirements surrounding subjects who are incapable of giving legal consent.<sup>368</sup> Although section four does not allow for any type of de-

366. See *On Application*, *supra* note 360, art. 32, para. 6 (explaining that "[t]he IRB may request more information than is required to be included in the written information [see Article 51 (7-3)] be given to the subjects when, in the judgment of the IRB, the additional information should add meaningfully to the protection of the human rights, safety and/or well-being of the subjects").

367. NEW JAPANESE GCP, *supra* note 230, art. 51. The specific requirements for the informed consent form are enumerated in article 51. The requirements under this paragraph include explanation of the following items:

- (1) That the clinical trial involves research
  - (2) Objectives of the clinical trial
  - (3) The name, title and address of the investigator to contact
  - (4) Trial procedures
  - (5) Anticipated benefits of the investigational products and anticipated disadvantages to the subject
  - (6) Matters concerning other therapeutic measures
  - (7) Duration of participation in the clinical trial
  - (8) That the subject may withdraw from the trial at any time
  - (9) That subject's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her
  - (10) That the monitors, the auditors, and the institutional review board are given access to the relevant source documents on condition that confidentiality of the subject is fully secured
  - (11) That privacy of the subject is kept
  - (12) The office of the medical institution to contact in the event of trial-related injury
  - (13) That necessary treatment is available to the subject in the event of trial-related injury
  - (14) Matters regarding compensation in the event of any trial-related injury
  - (15) Other necessary matters concerning the clinical trial.
2. The written information shall not include any language which causes the prospective subject to waive or to appear to waive any legal rights, or any language which releases or lightens or appears to release or lighten the sponsor, the medical institution or the investigators etc. from their liabilities.
  3. Wording and expressions in the written information should be as plain as possible.

*Id.*

368. *Id.* art. 50. Article 50 states that

1. Investigators etc. shall beforehand explain the content of the clinical trial and other trial-related matters utilizing appropriate written information to each prospective subject to obtain his or her informed consent in writing to participate in the trial.

cision-making by the child or any other incompetent subjects,<sup>369</sup> a PAB Notification to the Department of Health<sup>370</sup> ("Notification on Enforcement"), provides that incompetent subjects can participate in the decision-making process.<sup>371</sup> The Notification on Enforcement states that investigators should obtain the incompetent subject's written consent to the extent permitted by the subject's cognitive abilities.<sup>372</sup> The Notification on Enforcement also states that investigators should not enroll any subject in a trial who cannot give informed consent unless the trial will benefit the subject.<sup>373</sup> There is, however, an exception to this general rule, as subjects who cannot give consent can be used in a trial if their participation is deemed necessary.<sup>374</sup> Article seven elaborates on this exception, stating that persons who cannot give legal consent can be enrolled in a non-therapeutic clinical trial if the investigator submits documentation that these subjects are needed for the trial's success,<sup>375</sup> and that the risk is min-

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2. A subject incapable of giving consent may be enrolled in a trial on the consent of a person to act as a proxy consentor on behalf of the subject, notwithstanding the provisions of the preceding paragraph.
  3. When a proxy consentor's consent is obtained pursuant to the preceding paragraph, the investigators etc. shall prepare a record of the consent and the relation of the proxy consentor to the subject.

*Id.*

369. *See id.* (stating that researchers only have to obtain proxy consent for subjects who are incapable of giving informed consent).

370. On Enforcement of MHW Ordinance on Good Clinical Practice, PAB Notification No. 430, Mar. 27, 1997 [hereinafter Notification on Enforcement].

371. *See id.* para. 34(B) (stating that "[e]ven when the subject is enrolled in the clinical trial on the consent of a person to act as the proxy consentor on behalf of the subject pursuant to Paragraph 2, the investigator shall explain the clinical trial to the subject dependent on his or her ability to understanding (sic.), and, whenever possible, obtain his or her informed consent in writing").

372. *Id.*

373. *See id.* para. 4 (stating that "[t]he investigators etc. shall not enroll any subject incapable of giving consent to participation in a clinical trial in which no clinical benefits of the investigational products can be anticipated in the subject, notwithstanding the provisions of Paragraph 2, excluding cases stated under Article 7, Paragraph 2").

374. *See* NEW JAPANESE GCP, *supra* note 230, art. 44.2 (stating, in pertinent part, that "[i]nvestigators etc. shall select a prospective trial subject respecting the following principles . . . (2) Any subject incapable of giving consent shall not be selected unless it is inevitable to enroll him or her as a subject in the clinical trial").

375. *See id.* art. 7.2.1 (stating that where investigator wishes to use subjects who are not able to give competent consent, investigator must include in protocol "[e]xplanation on reasons why subjects whose consent pursuant to Article 50, Paragraph 1 is expected to be difficult to obtain, have to be enrolled in the clinical trial").

imal or non-existent.<sup>376</sup> Although the term minimal risk is not defined in Article 7, or in the New Japanese GCP's glossary,<sup>377</sup> it is briefly discussed in the Notification on Enforcement, which states that minimal risk occurs when the negative mental and physical impact on the subject is low, and that researchers should try to avoid such risks.<sup>378</sup>

## II. THE INTERNATIONAL CONFERENCE ON HARMONISATION

The ICH was created to deal with specific problems caused by the globalization of the pharmaceutical industry and the domestic nature of existing pharmaceutical regulations and licensing.<sup>379</sup> In furtherance of obtaining these goals, the ICH adopted the ICH Guidelines for Good Clinical Practice on May 1, 1996, to address practical and ethical concerns surrounding human re-

376. *Id.* art. 7.2.2. The investigator must also provide an "[e]xplanation on how the potential risk incurred to the subject, if at all, is minimal." *Id.*

377. *Id.* art. 7, 2.

378. See Notification on Enforcement, *supra* note 370, at chap. 2, para. 5. This chapter states that "[t]he phrase 'how the potential risk incurred to the subject, if at all, is minimal' used in Item 2 of the same paragraph means that 'the potential risks in the subject are low and that an (sic.) negative impact physically and mentally on him or her is minimal by efforts made to avoid them.'" *Id.* The requirements are further explained in On Application, at Article 7, paragraph 2. On Application, *supra* note 360, art. 7, para. 2. This document explains that

Non-therapeutic trials may be conducted in subjects whose consent is difficult to obtain, with consent of their proxy consenters provided the following conditions 1) to 4) are fulfilled. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. The investigator or the subinvestigator should particularly closely monitor the subjects in these trials and withdraw them if they appear to be unduly distressed.

- (1) The objectives of the clinical trial can not be achieved through a trial in subjects who can give consent personally.
- (2) The foreseeable risks to the subjects are low.
- (3) The negative impact on the subject's well-being is minimized and low.
- (4) The approval of the IRB is sought expressly on the inclusion of such subjects based on the consents of their proxy consenters, and the documented approval should expressly indicate the IRB's approval on the inclusion.

*Id.*

379. See *A Brief History of ICH* (visited Feb. 8, 2000) <<http://www.ifpma.org/ich8.html>> (on file with the *Fordham International Law Journal*) (explaining that pharmaceutical regulation remained national, while pharmaceutical industry had international scope).

search.<sup>380</sup> Recently, one of the ICH Expert Working Groups ("EWGs") developed the Draft Consensus Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population,<sup>381</sup> to deal with the unique issues that are raised when conducting research on children.<sup>382</sup>

### A. History of the ICH

In the past, differences between domestic pharmaceutical regulations forced pharmaceutical companies to engage in expensive, time-consuming, and repetitive experimental trials to gain international market acceptance.<sup>383</sup> This repetition resulted in increased research and development costs, as well as an overall increase in the cost of health care, and delays in marketing life saving treatments around the world.<sup>384</sup> The ICH's primary goal is to ensure that high quality, safe, and effective medicines were developed and registered in the most cost-effective manner.<sup>385</sup> Its members aim to diminish clinical trial duplication without compromising consumer safety.<sup>386</sup>

The need to harmonize pharmaceutical regulations was first recognized by the European Community.<sup>387</sup> Simultaneous ef-

380. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline for Good Clinical Practice, (updated May 1, 1996) <<http://www.ich.org>> (on file with the *Fordham International Law Journal*) [hereinafter GCP]. "Good Clinical Practice" is defined in the Glossary of the ICH GCP as "[a] standard for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected." *Id.* art. 1.24.

381. See DRAFT GUIDELINE ON PEDIATRIC TRIALS, *supra* note 19 (explaining that goals of this document include safe, timely, efficient, and ethical pediatric trials).

382. *Id.*

383. See *A Brief History of ICH*, *supra* note 379 (explaining that varying national regulations caused repetition of costly and time-consuming testing procedures).

384. *Id.*

385. See *Statement by the ICH Steering Committee Tokyo, October 1990*, (visited Feb. 8, 2000) <<http://www.ifpma.org/ich7.html>> (on file with the *Fordham International Law Journal*) (stating that parties at this meeting "reaffirmed their commitment to increased international harmonisation, aimed at ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner.").

386. See *id.* (stating that harmonization efforts "are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and too minimise the use of animal testing without compromising the regulatory obligations of safety and effectiveness").

387. See *Initiation of ICH* (visited Feb. 8, 2000) <<http://www.ifpma.org/ich8.html>>

forts at harmonization led the United States, Japan, and Europe to form the ICH at the WHO Conference on Drug Regulatory Activities ("ICDRA") in Paris, in 1989.<sup>388</sup> The International Federation of Pharmaceutical Manufacturers Association ("IFPMA") also participated in the ICH in order to work with the pharmaceutical industry to create a set of common guidelines.<sup>389</sup> Today, the six sponsors of the ICH include the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese MHW, the Japanese Pharmaceutical Manufacturers Association, the U.S. FDA, and the U.S. Pharmaceutical Research Manufacturers of America.<sup>390</sup> These entities participated in the first ICH Conference in Brussels in April 1990.<sup>391</sup>

At the Brussels conference, the parties to the ICH decided that the three criteria to be considered for drug approval should be safety, quality, and efficacy.<sup>392</sup> Topics based on these criteria would be examined by separate EWGs.<sup>393</sup> These topics were eventually subdivided into narrower categories of review.<sup>394</sup> As a result, new topics considered for regulation are subjected to a structured, multi-levelled process for developing new guidelines.<sup>395</sup>

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(on file with the *Fordham International Law Journal*) (stating that European Community pioneered movement toward harmonization in 1980s).

388. See *id.* (stating that after bilateral negotiations, United States, European Union, and Japan began to lay groundwork for ICH at ICH and WHO Conference on Drug Regulatory Activities in Paris in 1989 ("ICDRA")).

389. See *id.* (explaining that International Federation of Pharmaceuticals Manufacturers Association ("IFPMA") was asked to join ICH to discuss "joint regulatory-industry initiative on international harmonisation").

390. See International Conference on Harmonisation; Draft Documents on Essential Documents for the Conduct of a Clinical Study, 60 Fed. Reg. 42948 (1995) (listing parties involved in ICH).

391. See *Initiation of ICH*, *supra* note 387 (noting that first meeting was hosted by European Federation of Pharmaceutical Industry Associations in Brussels in 1990).

392. See *The Early Meetings* (visited Feb. 8, 2000) <<http://www.ifpma.org/ich8.html>> (on file with the *Fordham International Law Journal*) (stating that new topics for consideration "would be divided into *Safety, Quality and Efficacy* to reflect the three criteria which are the basis for approving and authorising new medicinal products").

393. See *ICH Expert Working Groups*, (visited Nov. 5, 1999) <<http://www.ich.org/ich3.html>> (on file with the *Fordham International Law Journal*) (explaining that EWG has representatives from each entities, and meet at same time as Steering Committee to report on EWG's progress).

394. See *ICH Topics and Guidelines* (visited Feb. 9, 2000) <<http://www.ifpma.org/ich5.html>> (on file with the *Fordham International Law Journal*) (listing narrower categories of review including stability testing, carcinogenicity, good clinical practice, medical terminology, and genotoxicity).

395. See *The ICH Process for Harmonisation of Guidelines* (visited Feb. 8, 2000) <<http://>

B. *Guidelines for Good Clinical Practice*

The Draft Guidelines for Good Clinical Practice, prepared by the Efficacy EWG, were first made available for public comment on May 9, 1995.<sup>396</sup> The standards embodied in this document reflected the standards enunciated in Helsinki IV, as well as the regulations of the three regulatory entities, and Australia, Canada, the Nordic Countries, and the WHO.<sup>397</sup> The ICH GCP's sought to coordinate standards for designing, recording, and reporting information from pharmaceutical trials involving human subjects, and to protect the rights and safety of trial subjects.<sup>398</sup> It was the ICH's hope that this document would influence not only the countries that are direct participants in the ICH, but also the standards of Australia, Canada, the Nordic countries, and the WHO<sup>399</sup> in formulating standards for all types of human research.<sup>400</sup>

The finalized ICH GCP was approved by the Steering Committee on May 1, 1996.<sup>401</sup> Like the Helsinki Declarations, the ICH GCP states that the anticipated benefits of a trial should

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/www.ifpma.org/ich4.html> (on file with the *Fordham International Law Journal*) (explaining ICH procedure). New topics considered for harmonization are selected by the Steering Committee based on Concept Papers that are submitted to it by the entities. *Id.* Once the Steering Committee chooses a topic, they select an EWG to formulate a draft guideline on that topic. *Id.* These draft guidelines are then returned to the Steering Committee, who distributes the draft to the three regulatory agencies for consultation in accordance with those countries' individual processes. *Id.* These comments are then returned to the Regulatory Rapporteur, who, in consultation with regulatory experts, incorporates any necessary changes. *Id.* If changes are significant, then the draft may be recirculated for another round of consultation. *Id.* The Rapporteur then prepares a final draft of the document that must first be approved by the EWG, and then by the Steering Committee. *Id.* After the final draft is discussed and approved by the three regulatory parties, the process is complete when the countries adopt the regulations into national law or regulations. *Id.*

396. See International Conference on Harmonisation; Draft Documents on Essential Documents for the Conduct of a Clinical Study, 60 Fed. Reg. 42948 (1995) (noting that Steering Committee agreed to release Draft ICH GCP on May 9, 1995 for public comment).

397. *Id.* at 42498.

398. See *id.* (stating that ICH GCP was designed to "provide a unified standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.").

399. See *id.* (stating that the guidelines are to influence regulations of Australia, Canada, EU, Japan, Nordic Countries, United States, and WHO).

400. *Id.* at Introduction. The Introduction to the Draft GCP states that "[t]he principles established in this Guideline should also be applied to other investigations that involve therapeutic intervention in, or observation of, human subjects." *Id.*

401. ICH GCP, *supra* note 12.

justify its risks.<sup>402</sup> Similarly, the ICH GCP states that preserving the research subject's rights and safety should prevail over the interests of society,<sup>403</sup> and that all pharmaceutical trials should be supported by prior laboratory testing.<sup>404</sup>

Also, as with the Helsinki Declarations, the ICH GCP states that all trials must be supervised by an IRB, or an Independent Ethics Committee ("IEC").<sup>405</sup> The ICH GCP recommends that the IRB/IEC be composed of at least five members, and that one member is primarily interested in a non-scientific field, one member is not affiliated with the institution, and that only members who are not associated with the trial investigator may vote.<sup>406</sup> The IRB/IEC may, at its election, invite outsiders with

402. Compare *id.* art. 2.2 (stating that "[b]efore a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks."), with *HELSINKI V*, *supra* note 157, at art. 1.4 (stating "[b]iomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.").

403. ICH GCP, *supra* note 12, art. 2.3. Article 2, paragraph 3 states, "[t]he rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over the interests of society." *Id.*

404. *Id.* art. 2.4. Although this section does depart from the past requirements of the Code and Helsinki Declarations that state that animal testing should be carried out prior to human trials, Article 2.4 does require that "[a]vailable nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial." *Id.*

405. Compare *id.* art. 2.6 (stating that "[a trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion"), with *HELSINKI V*, *supra* note 157, art. 1.2. Helsinki V mandated that

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee in conformity with the laws and regulations of the country in which the research experiment is performed

*HELSINKI V*, *supra* note 157, art. 1.2.

406. ICH GCP, *supra* note 12, at 3.2.1. Article 3.2.1 states that the IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

- (1) At least five members.
  - (2) At least one member whose primary area of interest is in a non-scientific area.
  - (3) At least one member who is independent of the institution/trial site.
- Only those IRB/IEC members who are independent of the investiga-

specialized expertise to assist in its evaluations.<sup>407</sup>

The IRB/IEC's primary responsibility is to ensure that the trial subjects' rights and safety are protected.<sup>408</sup> It is also incumbent on the IRB/IEC to ensure that the investigator is qualified,<sup>409</sup> and to conduct ongoing review of the trial.<sup>410</sup> The IRB/IEC must also supervise obtaining informed consent from subjects,<sup>411</sup> and ensure that there is no coercion involved in subject solicitation.<sup>412</sup>

Under the ICH GCP, informed consent should be obtained from subjects in accordance with the Helsinki Declarations, applicable regulations of the jurisdiction where the trial is being conducted, and the ICH GCP.<sup>413</sup> The ICH GCP places primary responsibility for compliance with these guidelines on the IRB/IEC.<sup>414</sup> The informed consent form must be submitted to the IRB/IEC for approval prior to use and it must be updated if new,

tor and the sponsor of the trial should vote/provide opinion on a trial-related matter.

*Id.*

407. *See id.* art. 3.2.6 (stating that "[a]n IRB/IEC *may* invite nonmembers with expertise in special areas for assistance") (emphasis added).

408. *See id.* art. 3.1.1 (stating that "[a]n IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.").

409. *See id.* art. 3.1.3 (directing that "[t]he IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.").

410. *See id.* art. 3.1.4 (providing that "[t]he IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.").

411. *See id.* art. 3.1.5 (stating that IRB may "request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.").

412. *See id.* art. 3.1.8 (stating that "[t]he IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.").

413. *Id.* art. 4.8.1. Section 4.8.1. states

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to the GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

*Id.*

414. *See id.* (describing IRB/IEC's responsibilities for reviewing informed consent forms).



relevant information pertaining to the trial is discovered.<sup>415</sup> The informed consent form's wording is also regulated; it cannot contain any statements that would operate to waive any legal claims that the subject may have against the investigator, institution, or sponsor.<sup>416</sup> The informed consent form must be written in layman's terms, and in a manner that is relatively comprehensible to the subject or the subject's representative.<sup>417</sup> Approved informed consent forms must be signed and dated by the subject or its legal representative.<sup>418</sup> Prior to signing, however, the subject must be afforded the opportunity to question the investigator regarding the details of the trial and freely decide whether to participate.<sup>419</sup> Although Article Four states that trials should be conducted on subjects who are capable of providing legal con-

415. *Id.* art. 4.8.2. Article 4, paragraph 8.2 states,

The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

*Id.*

416. *Id.* art. 4.8.4. Article 4, paragraph 8.4 states that

[n]one of the oral and written information concerning the trial, including the informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

*Id.*

417. *See id.* art. 4.8.6 (stating that "[t]he language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.").

418. *See id.* art. 4.8.8 (explaining that "[p]rior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.").

419. *Id.* art. 4.8.7. Article 4.8.7 states that

Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

*Id.*

sent,<sup>420</sup> it does list exceptions under which research may be conducted in legally incompetent subjects.<sup>421</sup>

Although there is no article or section of the ICH GCP devoted exclusively to pediatric research subjects, the ICH GCP does allude to children in various places in the document.<sup>422</sup> Even though there are no distinct definitions of the words child or minor in the ICH GCP Glossary, children are still classified as a vulnerable population in the ICH GCP.<sup>423</sup> When outlining the IRB/IEC's responsibilities, the ICH GCP specifies that the IRB/IEC should give special consideration to trials involving vulnerable populations.<sup>424</sup> Specifically, the IRB/IEC must ensure that trial protocols recognize special ethical concerns involved in these trials and to ensure compliance with local regulations.<sup>425</sup>

Minors receive the most attention in the article of the ICH GCP that discusses informed consent.<sup>426</sup> This article first provides proxy consent for all individuals who cannot give informed

420. See *id.* art. 4.8.13 (stating that except under specific circumstances, "a non-therapeutic trial (*i.e.*, a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form").

421. See *id.* art. 4.8.14 (explaining circumstances under which non-therapeutic trials can be conducted in subjects who require consent of legally acceptable representatives).

422. *Id.*

423. *Id.* art. 1.61. Article 1.61 defines vulnerable subjects as

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, *minors* and those incapable of giving consent.

*Id.* (emphasis added)

424. See *id.* at 3.1.1 (stating that "[s]pecial attention should be paid to trials that may include vulnerable subjects").

425. See *id.* at 3.1.6 (stating that "[w]hen a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.").

426. See *id.* art. 4.8 (discussing informed consent of trial subjects).

consent.<sup>427</sup> Despite this general rule, however, the ICH GCP does provide that the subject must be informed to the extent that he is able to understand.<sup>428</sup> The subject should personally sign and date the written informed consent form, if he or she is able to do so.<sup>429</sup>

Although the ICH GCP includes the general proposition that subjects who cannot give informed consent should not be involved in non-therapeutic trials,<sup>430</sup> it also specifies some situations where participation is permissible.<sup>431</sup> Subjects who are incapable of providing informed consent may participate in non-therapeutic trials under certain specific conditions.<sup>432</sup> These conditions include: (1) if a legal representative gives informed consent, (2) if the risks and effect on the subject's well-being are low, (3) if the trial complies with applicable law, and (4) if the IRB/IEC specifically has approved including this group in the trial.<sup>433</sup> Under the ICH GCP, these trials should be closely moni-

427. *See id.* art. 4.8.5 (explaining that "[t]he investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.").

428. *See id.* art. 4.8.5 (explaining requirements for obtaining consent from both subject's representative and subject).

429. *Id.* art. 4.8.12. Article 4, section 8.12 states,

When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

*Id.*

430. *See id.* art. 4.8.13 (explaining that non-therapeutic trials should be conducted in subjects who are capable of providing informed consent).

431. *See id.* art. 4.8.14 (describing when minors can be used in non-therapeutic trials).

432. *See id.* (describing conditions under which non-therapeutic research on children may be conducted).

433. *Id.* Article 4, section 8.14 states that

Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

- (a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
- (b) The foreseeable risks to the subjects are low.
- (c) The negative impact on the subject's well-being is minimized and low.
- (d) The trial is not prohibited by law.
- (e) The approval/favourable opinion of the IRB/IEC is expressly sought

tored for signs of distress among research subjects, so that subjects may be withdrawn if they demonstrate signs of undue distress.<sup>434</sup>

C. *Draft Consensus Guideline on Clinical Investigation of Medicinal Products in the Pediatric Population*

In 1998, the Steering Committee appointed a new EWG to deal with clinical investigation of medicinal products in children ("EWG on Pediatric Trials").<sup>435</sup> This EWG is charged with developing pediatric testing methods that will make it easier for pharmaceutical companies to produce safer treatments for children, and encourages clinical trials on pediatric groups.<sup>436</sup> On October 7, 1999, the EWG on Pediatric Trials released its Draft Guideline on Pediatric Trials for consultation and commentary by ICH members.<sup>437</sup> The goals of this document are to facilitate timely, safe, efficient, and ethical studies of medicinal products for use in pediatric populations and to increase the number of medications that are licensed specifically for pediatric use.<sup>438</sup> Although the Draft Guideline on Pediatric Trials is not intended to be a comprehensive and exclusive document on pediatric studies, it succeeds in covering a wide variety of topics, including

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on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

*Id.*

434. See *id.* art. 4.8.14 (stating that subjects should be closely monitored and withdrawn if they show signs of undue distress).

435. See ICH Web site, *supra* note 314, at Efficacy Topics (explaining that this EWG's goal was to facilitate development of safe and effective medicinal products and to help eliminate current difficulties encountered by companies that operate internationally).

436. *Id.* at Efficacy Topics, E11, Clinical Investigation of Medicinal Products in Children.

437. DRAFT GUIDELINE ON PEDIATRIC TRIALS, *supra* note 19.

438. *Id.* art. 1.1. Article 1.1 states

The number of medicinal products currently labeled for pediatric use is limited. It is the goal of this guideline to encourage and facilitate timely pediatric medicinal product development internationally. This guideline provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.

*Id.*

general considerations for investigators when starting a pediatric trial, timing, types of studies to be conducted, age categories, and ethics.<sup>439</sup>

The Draft Guideline on Pediatric Trials begins by stating general principles, including the idea that medicines be tested in children of different ages before they may be prescribed generally.<sup>440</sup> The general principles also state that drug studies for a particular medicinal product should include pediatric groups when the product is being developed for use in adults and will have an anticipated use in children.<sup>441</sup> Finally, the general principles state that great emphasis should be placed on the pediatric trial subject's safety.<sup>442</sup>

The Draft Guideline on Pediatric Trials also addresses the timing of pediatric trials.<sup>443</sup> Article two, paragraph one provides a list of factors to consider when determining whether to test drugs on children.<sup>444</sup> The most important of these factors is whether the treatment to be tested will be used for a serious dis-

439. *Id.* art. 1.3. Article 1.3 states that specific clinical studies issues addressed include: considerations when initiating a pediatric program for a medicinal product; timing of initiation of pediatric studies during medicinal product development; types of studies (pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD), efficacy, safety); age categories for studies; ethics of pediatric clinical investigation. This guideline is not intended to be comprehensive; other ICH guidelines as well as documents from regional regulatory authorities and pediatric societies provide additional detail.

*Id.*

440. *Id.* art. 1.4. Article 1.4 explains that Pediatric patients should be given medicines that have been appropriately evaluated for their use. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages, and often of pediatric formulations of those products. Major advances in formulation chemistry and in pediatric study design ensure that this goal can be achieved.

*Id.*

441. *See id.* (stating that "[d]rug development programs should include the pediatric patient population when a product is being developed for a disease/condition in adults and it is anticipated the product will be used in the pediatric population.").

442. *See id.* (stating that "[t]he ethical imperative to obtain knowledge of the effects of medicinal products in pediatric patients has to be balanced against the ethical imperative to protect each pediatric patient in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.").

443. *See id.* art. 2.1 (discussing "issues when initiating a pediatric medicinal product development program").

444. *See id.* art. 2.1 (stating that investigators should consider:

ease that currently does not have an effective therapy.<sup>445</sup> In situations where a medicinal product will not be used on pediatric patients, the product does not have to be tested on children.<sup>446</sup>

Conversely, where a drug is being developed specifically for a condition that is unique to children, the drug need not be tested on adults if the results of such testing would be completely irrelevant to pediatric populations, or if the study would expose adults to inappropriate risk.<sup>447</sup> Wherever possible, however, initial safety information should be obtained in studies on adult subjects.<sup>448</sup> Where a medicinal product is intended to treat a life threatening illness occurring in both children and adults, testing in children should occur simultaneously with adult studies, but only after initial safety testing in adults.<sup>449</sup> Where pediatric testing is feasible in a particular situation, but none is conducted, the sponsor must provide a detailed explanation of why there are no pediatric trial results for that product.<sup>450</sup> For drugs used

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- the prevalence of the condition to be treated in the pediatric population;
  - the seriousness of the condition to be treated;
  - the availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy of those treatments, and the adverse event profile (including any unique pediatric safety issues);
  - whether the medicinal product is novel or one of a class of compounds with known properties;
  - whether there are unique pediatric indications for the medicinal product;
  - the age ranges of patients likely to be treated with the medicinal product;
  - unique pediatric (developmental) safety concerns about the medicinal product, including any non-clinical safety issues; and
  - potential need for pediatric formulation development.

*Id.*

445. *See id.* (explaining that “[o]f these factors, the most important is the presence of a serious disease without good current therapy. This situation suggests relatively urgent and early initiation of pediatric studies.”).

446. *See id.* (explaining that trials do not have to be conducted on children if using product on children is clearly inappropriate).

447. *See id.* art. 2.3.1 (stating that some trials on medicinal products that treat diseases that occur predominantly or exclusively in pediatric patients, must be initially tested only in children, even in initial phases).

448. *See id.* art. 2.3.1 (explaining that “the entire development program will be conducted in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults”).

449. *Id.*

450. *See id.* art. 2.3.2 (stating that where medicine treats serious or life threatening illness in both adults and children, studies on children should commence early, after

to treat less serious conditions, testing on pediatric populations may begin later, or even after the drug is on the market for adults, if there are safety concerns.<sup>451</sup> If, however, the drug will represent a major advance in treating pediatric patients, then testing should begin in the earlier stages of product development.<sup>452</sup>

The next several sections of the Draft Guideline on Pediatric Trials outline technical considerations, indicating how much information may be extrapolated from adult studies, and that certain types of trials should only be conducted in pediatric patients that are suffering from the disease that the medicine is designed to cure.<sup>453</sup> Next, the Draft Guideline on Pediatric Trials explains that trials conducted on children may require unique elements of trial design to measure factors such as pain and other physical responses to treatment adequately.<sup>454</sup> As with the CPMP Guideline for Children, the Draft Guideline on Pediatric Trials then divides children into five different age categories in order to address properly the biological and pharmacological factors that investigators must consider when planning research trials.<sup>455</sup>

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initial trials on safety and efficacy, and where pediatric testing is impossible, "lack of data should be justified in detail").

451. *See id.* art. 2.3.3 (explaining that where drug is used to treat non-life-threatening illness, companies may wait longer to commence testing, but they must have plan for how and when pediatric testing will be conducted).

452. *See id.* (stating that "[e]ven for a non-serious disease, if the medicinal product represents a major therapeutic advance for the pediatric population, studies should begin as early in development as possible, and the submission of pediatric data would be expected in the application.").

453. *See id.* art. 2.4.1 (discussing pharmacokinetics and practical considerations for conducting pharmacokinetic trials).

454. *See id.* art. 2.4.2 (stating that "[t]he principles in study design, statistical considerations and choice of control groups detailed in ICH 6,9, and 10 in general apply to pediatric efficacy studies," but that researchers also have to be aware that certain elements must be adapted specifically for pediatric trials, like "[m]easurements of subjective symptoms such as pain").

455. *See id.* art. 2.5. (explaining that breaking pediatric population down into five categories may help develop effective trial designs for each age group). This paragraph separates children into five groups: pre-term newborn infants, term newborn infants, infants and toddlers (28 days to 23 months), children (2-11 years), and adolescents (12 up to 16-18 years, depending on region where trial is conducted). *Id.* This paragraph also discusses circumstances where division by age group is unnecessary, such as in longer-term studies, where patients may move from one age group to another within course of study. *Id.* In discussing adolescent age group, EWG placed particular emphasis on possible external factors that might effect the study, such as non-compliance, particularly when trial may effect appearance, and subject's recreational use of non-

The remainder of the Draft Guideline on Pediatric Trials concerns ethical issues.<sup>456</sup> Article two, paragraph six describes pediatric populations as a vulnerable group requiring special rights and safety protections.<sup>457</sup> Here, the Draft Guideline on Pediatric Trials states that every child subject should reap some direct or indirect benefit from the trial, except as described in the ICH GCP.<sup>458</sup>

The Draft Guideline on Pediatric Trials then discusses the role of the IRB/IEC, stating that their responsibilities have been set forth in the ICH GCP.<sup>459</sup> The Draft Guideline on Pediatric Trials does, however, state that all IRB/IECs that review pediatric trials should include or consult with people who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.<sup>460</sup> Furthermore, while subjects may be reimbursed for recruitment expenses, researchers cannot offer coercive inducements, either to the child or to the child's parents.<sup>461</sup> Additionally, the group selected for the study should represent the demographics of the region or the disease being studied unless a good reason exists for restricting the group of subjects.<sup>462</sup>

The Draft Guideline on Pediatric Trials also discusses consent.<sup>463</sup> The Draft Guideline on Pediatric Trials requires that researchers must always obtain full, informed consent from the subject's parents in accordance with national or regional regula-

prescribed drugs. *Id.*; see also GUIDELINE FOR CHILDREN, *supra* note 51 (referring to classification by age and maturity level).

456. DRAFT GUIDELINES ON PEDIATRIC TRIALS, *supra* note 19, art. 2.6. Article 2.6 is entitled "Ethical Issues in Pediatric Studies." *Id.*

457. See *id.* ("[t]he pediatric population represents a vulnerable subgroup. Special measures are therefore needed to protect their rights and to shield them from undue risk.").

458. See *id.* ("participants in clinical studies are expected obtain [sic] some direct or indirect benefit from the clinical study except under very special circumstances as discussed in ICH E-6 (GCP; section 4.8.14)).

459. See *id.* art. 2.6.1 ("[t]he roles and responsibilities of IRB/IECs as detailed in ICH E-6 are critical to the protection of study participants").

460. See *id.* ("[w]hen protocols involving the pediatric population are reviewed, there should be IRB/IEC members, or experts consulted by the IRB/IEC, who are knowledgeable in pediatric ethical, clinical, and psychosocial issues").

461. See *id.* art. 2.6.2 (explaining that subjects may be paid for reimbursement and subsistence costs, but may not receive coercive financial or other inducements).

462. *Id.* Article 2.6.2 states that "[w]hen studies are conducted in the pediatric population, an attempt should be made to include individuals representing the demographics of the region and disease being studied, unless there is a valid reason for restricting enrollment." *Id.*

463. *Id.* art. 2.6.3. Article 2.6.3 is entitled Consent. *Id.*



tions.<sup>464</sup> Additionally, the subjects themselves must be informed about the study in a comprehensible manner.<sup>465</sup> The EWG specified that a child who is considered capable of providing assent should be allowed to do so, and, if able, sign and date an informed consent form.<sup>466</sup> The child subject must also be informed of his or her right to withdraw or refuse to participate in the trial, and the child's wish not to participate must be respected, unless participation is necessary for the child's well-being.<sup>467</sup> This section concludes by stating that, wherever possible, trials should be conducted in populations that are more competent to give consent, than those that are less capable.<sup>468</sup>

Finally, the Draft Guideline on Pediatric Trials divides risk into two separate categories, Minimizing Risk<sup>469</sup> and Minimizing Distress.<sup>470</sup> The section on minimizing risk states that researchers must take every precaution to anticipate and reduce the risk of physical injury resulting from participation.<sup>471</sup> Researchers must understand the level of toxicity of the drug studied, and maintain a staff that is sufficiently trained and knowledgeable in studying and treating pediatric patients.<sup>472</sup> The trial should in-

464. *See id.* (explaining that because children are legally dependent on their parents, "fully informed consent should be obtained from a legal guardian in accordance with regional laws or regulations."). Researchers, however, do not have to obtain parental consent for children who are classified as mature minors or emancipated minors. *Id.* Indeed, "[e]mancipated or mature minors (defined by local laws) may be capable of giving autonomous consent." *Id.*

465. *See id.* (stating that "[a]ll participants should be fully informed about the study in language and terms they are able to understand").

466. *Id.* Article 2.6.3 states that "[p]articipants should assent to enroll in a study (age of assent to be determined by IRB/IECs). Participants of appropriate intellectual maturity should personally sign and date either a separately designed written assent form or the written informed consent." *Id.*

467. *Id.* Subjects must be made aware of their right to decline to participate in a study or to withdraw at any time. *Id.* The right to withdraw must be respected, unless "in the opinion of the investigator, parents, and IRB/IEC the welfare of the pediatric patient would be jeopardized by their failing to participate in the study; the patient's agreement or assent may be waived under such circumstances." *Id.*

468. *See id.* (stating that "[i]nformation that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one unable to provide individual consent").

469. *Id.* art. 2.6.4.

470. *Id.* art. 2.6.5.

471. *See id.* art. 2.6.4 (stating that "[e]very effort should be made to anticipate and reduce known hazards").

472. *Id.* This provision requires that

Investigators should be fully aware before the start of a clinical study of all relevant pre-clinical and clinical toxicity of the medicinal product. Minimiz-

clude the minimum number of participants and interventions possible, and should be able to be stopped immediately should an adverse reaction or hazard arise.<sup>473</sup>

The section of the Draft Guideline on Pediatric Trials entitled Minimizing Distress recognizes pediatric subjects' emotional and psychological vulnerabilities.<sup>474</sup> Article two, paragraph six, section five states that to minimize subjects' distress level, all persons involved in conducting the study should be experienced in treating pediatric patients, and if a trial protocol was originally used for a study on adult subjects, it should be redesigned for use with children.<sup>475</sup> This section then makes specific suggestions designed to comfort children in the research environment, such as using age-appropriate furniture, activities, and food, minimizing the number of venipunctures and other invasive procedures, and always respecting the child's right to decline to participate.<sup>476</sup>

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ing risk in pediatric clinical studies requires that those conducting the study be properly trained and experienced in studying the pediatric population, including the evaluation and management of potential pediatric adverse events.

*Id.*

473. *See id.* (expressing that "every attempt should be made to minimize the number of participants, consistent with good study design, and the number of procedures. Mechanisms must be in place to assure that a study can be rapidly terminated should an unexpected hazard be noted").

474. *See id.* art. 2.6.5 (recognizing that "[r]epeated invasive procedures may be painful or frightening").

475. *See id.* (suggesting that to reduce stress, "[d]iscomfort can be minimized if the studies are designed and conducted by investigators experienced in the treatment of pediatric patients," and that "[p]rotocols and investigations should be specifically designed for the pediatric population, (not simply re-worked from adult protocols and approved by a competent and experienced IRB/IEC)").

476. *Id.* Article 2.6.5 states,

Practical considerations to ensure that participants' experiences in clinical studies are positive, and to minimize discomfort and distress include:

- personnel knowledgeable and skilled in dealing with the pediatric population and its age-appropriate needs, including skill in performing pediatric procedures;
- a physical setting with furniture, play equipment, activities, and food, appropriate for age;
- conducting studies in a familiar environment such as the hospital or clinic where they normally receive their care;
- use of approaches to minimizing discomfort of procedures, e.g. topical anesthesia to place IV catheters;
- in-dwelling catheters rather than repeated venipunctures for blood sampling;
- collection of some blood samples when routine clinical samples are ob-

III. *THE PARTIES TO THE ICH AND THE ICH STEERING  
COMMITTEE SHOULD ADOPT THE PROTECTIONS SET  
FORTH IN THE DRAFT GUIDELINE ON PEDIATRIC TRIALS  
WITH SOME MODIFICATIONS*

The Draft Guideline on Pediatric Trials takes definite steps toward clarifying the ICH GCP in areas that address the unique requirements of working with children. Although specific guidelines for pediatric research should eventually be adopted at a broader international level, the ICH's limited membership and partnership with non-governmental entities makes it an appropriate place to start refining the current international regulatory scheme.<sup>477</sup> Eventually, the parties to the ICH and the ICH Secretariat should adopt the Draft Guideline on Pediatric Trials, with some modifications, because it will provide necessary clarification on issues arising in pediatric research.

A. *The ICH Is a Good Place To Start Improving Pediatric  
Medical Research Regulations*

The ICH provides a good forum to begin refining pediatric medical research regulations. Unlike some of the other international organizations that have addressed this topic,<sup>478</sup> the ICH has a limited number of participants, making it easier for the parties to agree on issues of greater specificity.<sup>479</sup> Moreover, current regulations in the United States, Europe, and Japan do not differ from each another dramatically: all three entities currently have regulations limiting the level of risk in pediatric trials to low or minimal,<sup>480</sup> and all allow for the child subject's involvement in research participation decisions.<sup>481</sup> Due to these similarities on fundamental issues, none of the participants would

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tained . . . [t]he participant's right to refuse further investigational procedures must be respected.

*Id.*

477. See *supra* note 169 and accompanying text (describing consultation process for CIOMS/WHO Guidelines).

478. *Id.*

479. See *supra* note 97 and accompanying text (describing cultural differences impeding international human research regulation).

480. See *supra* notes 290-97, 322-26, 376-78 and accompanying text (describing U.S. regulations on risk, CPMP Guideline for Children on risk, and New Japanese GCP on risk).

481. See *supra* text accompanying notes 249-72, 319-20 367-75 (describing U.S., CPMP Guideline for Children, and Japanese GCP regulations on assent).

need to incorporate new standards that are completely foreign to their current regulations.

Additionally, because the pharmaceutical industry is an active participant in the ICH, the ICH GCP and other ICH documents have great potential to effect research positively, in a way that national regulations and current international documents have not. Although past international guidelines have included input from the medical community,<sup>482</sup> many national regulations, such as those in the United States, do not apply to privately funded research.<sup>483</sup> Because the pharmaceutical industry sponsors the majority of privately funded research on human subjects,<sup>484</sup> its participation in creating guidelines that it would agree to follow, is crucial.

Finally, the ICH's overriding goal is creating and marketing safe, effective medications, in the most efficient manner possible.<sup>485</sup> In this process, however, the ICH must not only focus on the physical needs of patients, but also on the research subjects' psychological state and liberty interests, a point that has been reiterated throughout international human research guidelines.<sup>486</sup> The ICH must defend these basic principles with respect to pediatric subjects.

*B. Despite Some Weaknesses, the Draft Guideline on Pediatric Trials Takes Significant Steps To Improve the Standards for Pediatric Research Set Forth in the ICH GCP*

The ICH GCP was insufficient to protect the safety and liberty interests of pediatric patients adequately. Specifically, its provisions on informed consent and level of risk are too vague and are in need of clarification. Additionally, the ICH GCP does not contain special requirements for IRBs that review pediatric trials. Doing so would improve local input into research proto-

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482. See *supra* note 127, 169 and accompanying text (explaining medical community's movement for new guidelines resulting in Helsinki Declarations), and CIOMS/WHO inclusion of medical schools' opinions).

483. See *supra* note 243 and accompanying text (stating that U.S. regulations do not apply to privately funded research).

484. See *supra* note 16 and accompanying text (indicating that pharmaceutical research accounts for most research using human subjects).

485. See *supra* note 385 and accompanying text (explaining ICH goals).

486. See *supra* note 149 and accompanying text (explaining Helsinki II's provision on subject's psychological state).

cols by including IRB members that are competent and knowledgeable on children's issues.

With regard to the child's involvement in research participation decisions, although the ICH GCP specified that the child subject should be informed about the trial and give his consent to the extent that he is able, it did not provide any guidance on how to implement this requirement.<sup>487</sup> It neither explained which factors the IRB or IEC should review when determining a subject's capacity to provide consent or assent,<sup>488</sup> nor did it discuss what type of information should be conferred upon the subject.<sup>489</sup> It is important to clarify these guidelines, as ambiguity in this area can result in many subjects being deprived of their right to be included in the research participation decision. Significantly, allowing a child to participate in making this decision may contribute to a trial's success, as it may enhance the child's willingness to cooperate in the study, as well as improving the child's self esteem.<sup>490</sup> In contrast, depriving a child of this input may have significant negative implications for the child's future opinion and trust of the medical community.<sup>491</sup> Most importantly, involving the child in the research participation decision is the best way to promote rights for pediatric subjects that are already granted to all other research subjects in every international guideline since the Nuremberg Code. The importance of granting these rights to children has been affirmed by the international community's overwhelming support for the CRC, which specifically grants children the right to participate in decisions that effect their lives.<sup>492</sup>

The EWG on Pediatric Research took some steps to clarify the ICH GCP's stance on informed consent in the Draft Guideline on Pediatric Trial's paragraph on consent. First, this paragraph, like the U.S. regulations, uses the term assent, rather

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487. See *supra* notes 426-29 and accompanying text (explaining ICH GCP's regulations on assent).

488. *Id.*

489. *Id.*

490. See *supra* note 80 and accompanying text (explaining benefits of allowing child subjects to contribute to research participation decision-making).

491. See *supra* note 82 and accompanying text (explaining opinions suggesting that ignoring child's decision may result in future distrust of medical community and parents).

492. See *supra* note 225 and accompanying text (stating that 191 countries ratified CRC).

than consent, to refer to the child's agreement to participate in a trial.<sup>493</sup> Using the term assent rather than consent will give the ICH and the EWG on Pediatric Trials a specific term to define and refer to that is distinct from the term used for competent adults.<sup>494</sup> Additionally, the EWG on Pediatric Trials adopted the CPMP's provision stating that a child's refusal to participate in a study should be binding on the researcher,<sup>495</sup> unless participation is necessary for the child's health or survival. This provision shows respect for the child's liberty interests and autonomy, as called for in the CRC, while protecting his health and safety.

Although the consent paragraph in the Draft Guideline for Pediatric Trials helps to clarify some issues, there is still room for improvement during the consultation period. Although the EWG was correct in not adopting a strict age requirement for assent<sup>496</sup> that may infringe on national sovereignty, the EWG should provide more specific guidelines to help IRBs determine which children are capable of providing assent. Like the provisions for informed consent for adults, the Draft Guideline on Pediatric Trials should be revised to include a list of the type of information that should be provided to the pediatric participant, subject to IRB review and revision, to enable him or her to give adequate assent. Supplementing the text of the Draft Guidelines on Pediatric Trials with these provisions would make them more practical and comprehensible for local IRBs and IECs.

The parties to the ICH would be also likely to accept these new assent provisions. In the United States, multiple commentators have suggested that the provisions in the Common Rule regarding assent are too vague, allowing for vast differentiation between research institutions.<sup>497</sup> Furthermore, clearer guidelines on this subject may help to ameliorate some of the human rights concerns expressed by some European countries, particularly

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493. See *supra* notes 251-52 and accompanying text (explaining the difference between assent, permission, and consent in U.S. regulations).

494. See *supra* notes 463-67 and accompanying text (referring to consent provisions of Draft Guideline on Pediatric Trials).

495. See *supra* note 320 and accompanying text (discussing CPMP's provision that child's refusal to participate must be respected).

496. See *supra* note 84 and accompanying text (describing AAP suggestion that children should be able to provide assent at age seven).

497. See *supra* notes 291-97 and accompanying text (describing critic's views of U.S. regulations).

Germany.<sup>498</sup> Finally, although Japan has been historically hesitant to address the issue of informed consent at all, recent surveys<sup>499</sup> and the New Japanese GCP and Notes on Enforcement,<sup>500</sup> indicate that this country is ready for more progressive guidelines in this area.

The ICH GCP also inadequately described the level of risk to which children can be exposed in research trials. Although the ICH GCP permits children to be involved in low risk non-therapeutic research, unlike the U.S. Common Rule or the Biomedical Convention, the term low risk not defined.<sup>501</sup> This deficiency is potentially very dangerous, as even in the United States, which has defined the term minimal risk, there is great disparity in how this phrase is interpreted.<sup>502</sup> By not defining the term minimal risk at all, the ICH GCP left its interpretation completely in the hands of local IRBs, which may be dangerous.<sup>503</sup>

The EWG on Pediatric Trials takes significant steps to define this term more completely, similar to the CPMP Guideline for Children. The Draft Guideline on Pediatric Trials thoroughly explains special physical risks for children of different age groups and details means of minimizing both physical *and* psychological strain on subjects.<sup>504</sup> As with the CPMP Guideline for Children, as well as the Biomedical Convention, the Draft Guideline on Pediatric Trials also gives concrete examples of which trial methods are safe and which are unsafe for various age groups.<sup>505</sup> These provisions represent a significant improvement over both the ICH GCP and other international docu-

498. See *supra* note 211 and accompanying text (describing German criticisms of Biomedical Convention).

499. See *supra* note 344 and accompanying text (citing polls indicating new Japanese attitudes toward informed consent).

500. See *supra* note 371 and accompanying text (explaining that New Japanese GCP allows children to participate in research decisions).

501. See *supra* note 432 and accompanying text (citing ICH GCP's provision for risk in nontherapeutic trials).

502. See *supra* note 295 and accompanying text (describing different interpretations of minimal risk).

503. See *supra* notes 1-9, 297 and accompanying text (describing problems of group think and IRB members that are sympathetic to medical community)

504. See *supra* note 325 and accompanying text (citing Guideline for Children provisions on risk).

505. See *supra* note 326, 204-06 and accompanying text (describing minimal risk provisions in Guideline for Children and Biomedical Convention).

ments for protecting pediatric subjects' physical and emotional well-being.<sup>506</sup>

Even if the Draft Guideline on Pediatric Trials is accepted with the changes proposed above, a great deal of discretion still lies in the hands of the local IRBs who ultimately decide which trials are acceptable and which are not. For this reason, the EWG on Pediatric Trials was correct in adopting the AAP's suggestion that IRBs who regularly review children's research protocols should include or consult with pediatric experts.<sup>507</sup> To ameliorate logistical problems that may arise in small institutions, the ICH GCP may adopt a provision similar to that of the New Japanese GCP,<sup>508</sup> which allows for one specialized IRB that would provide opinions for protocols at several small institutions. Finally, the EWG on Pediatric Trials should require that IRBs reviewing protocols that will be conducted in developing countries should include an anthropological or sociological expert to evaluate local customs and opinions on informed consent.<sup>509</sup> This scheme would help to further improve issues of ethnic diversity addressed in the CIOMS/WHO Guidelines.<sup>510</sup> Because IRBs are crucial in determining which trials can be carried out on children, it is of utmost importance that IRB members are experienced and knowledgeable in issues that are unique to pediatric research and in local traditions.

### CONCLUSION

The Draft Guideline on Pediatric Trials makes significant progress in providing practical, comprehensive guidelines for institutions conducting research on children. Specifically, the EWG on Pediatric Trials has made great progress in identifying

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506. See *supra* note 68-70 and accompanying text (describing importance of considering psychological risks along with physical risks).

507. See *supra* note 259 and accompanying text (describing AAP's suggestion to include pediatric experts on IRBs).

508. See *supra* note 362 and accompanying text (citing Japanese GCP provision that states that small institutions can have shared IRBs).

509. See *supra* notes 97, 168 and accompanying text (describing cultural differences in concepts of informed consent and CIOMS/WHO requirement that IRBs reviewing trials in developing countries should include member familiar with local customs and traditions).

510. See *supra* note 97 and accompanying text (explaining that CIOMS/WHO Guidelines addressed issues regarding trials in developing countries and that cultural differences effect attitudes on informed consent).



and describing special physical and psychological risks for investigators and IRBs to consider when reviewing pediatric studies. The Draft Guideline on Pediatric Trials could, however, be improved in the areas of informed consent and IRB membership. With regard to informed consent, the EWG should provide clearer guidelines for determining which children are capable of providing assent as well as what information should be provided to these children. The EWG should also mandate, instead of merely suggest, that IRBs that review pediatric protocols should include pediatric specialists. By implementing these provisions, along with the existing draft guidelines on risk, the ICH will be able to end some of the injustices that have plagued pediatric research, protect pediatric subjects' rights in the future, and meet their goal of producing safe, effective medications in the most efficient manner possible.