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ARTICLES

RESEARCH INVOLVING CHILDREN: REGULATIONS, REVIEW BOARDS AND REFORM

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INTRODUCTION

Historical Perspectives: Past to Present

Children have been the victims of unethical clinical investigations since the earliest research trials.¹ In 1789, Edward Jenner, an English researcher trying to discover a vaccination for smallpox, initially injected his own one-year-old son with cowpox to determine whether it would offer protection against smallpox.² Then, he gave an eight-year-old child an inoculation of smallpox material to see if a prior vaccination would be effective.³ Later, in 1802, a physician for an almshouse gave the vaccine to forty-eight children who were under his care and later challenged their immunity by inoculating the children with smallpox.⁴ Although these initial vaccination trials posed obvious danger to the children who were used, they were rationalized by arguing that the possible benefits to the group outweighed the risks to the few children who were the initial subjects.

Although research on children continued, there were at least some physicians who objected to the use of children in medical experiments in which subjects were purposely injured in order to obtain scientific evidence for a disease course. In 1941, the editor of the *Journal of Experimental Medicine*, Francis Payton Rous, wrote in his rejection of a manuscript that “the inoculation of a twelve month old infant with herpes . . . was an abuse of power, an infringement on the rights of the individual, and not excusable because the illness which followed had implications

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1. Leonard H. Glantz, *Research With Children*, 24 AM. J.L. & MED. 213, 215 (1998). See also Susan E. Lederer & Michael A. Grodin, *Historical Overview: Pediatric Experimentation, in CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS AND LAW* 3 (Michael A. Grodin & Leonard H. Glantz eds., 1994).

2. Lederer & Grodin, *supra* note 1, at 4-5.

3. *Id.* at 5.

4. *Id.*

for science."⁵ His opinion, however, had little impact on the academic community and the research results were published in the *Journal of Pediatrics*.⁶

From the 1950s through the 1970s, a set of experiments were conducted at the Willowbrook State School, a New York State institution for mentally disabled children.⁷ The research was intended to help elucidate the natural course of hepatitis.⁸ Researchers systematically infected mentally disabled children with a hepatitis virus.⁹ Early subjects were given extracts of stool from infected persons, and later subjects were injected with purified virus preparations.¹⁰ The researchers justified their actions by claiming that 85% of the children in the institution would contract the disease in the first year of admission anyway, and systematic infection would allow the investigators to study the natural course of the disease.¹¹ The institution was closed to new children because of its overcrowded conditions, but the hepatitis program, with its own space in the building, was able to admit new members.¹² Therefore, in order to have a child accepted to Willowbrook, parents often had to accept their child's participation in the hepatitis program.¹³ When the Willowbrook experiments were brought to public attention in the 1970s there was a huge outcry.¹⁴ It was unimaginable to the public that innocent children had intentionally been given a serious illness and that parents, desperate to find care for their disabled children, had been coerced into permitting their participation. Furthermore, the researchers' justification that the children would have likely contracted hepatitis regardless of the intentional exposure only emphasized the terribly unsanitary conditions in which these mentally disabled children were housed. Finally, the legal authority of parents to volunteer their children for this research was questioned.¹⁵

5. *Id.* at 14.

6. *Id.*

7. *Id.* at 17.

8. *Id.*; ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 70 (2d ed. 1986).

9. Lederer & Grodin, *supra* note 1, at 17.

10. LEVINE, *supra* note 8, at 70.

11. *Id.*

12. *Id.*

13. *Id.*

14. Some results from the Willowbrook studies had been published in the *New England Journal of Medicine* in 1958 with few, if any, objections, but after the public took notice in the 1970s, "a furor attends the appearance of any Willowbrook report, even though the report may present no more than the results of continued surveillance of children infected at an earlier date." F. J. Ingelfinger, *Ethics of Experiments on Children*, 288 *NEW ENG. J. MED.* 791 (1973).

15. *E.g.*, Glantz, *supra* note 1, at 217. *But see* Ingelfinger, *supra* note 14, at 792. Ingelfinger notes that even after the public outcry some researchers believed that the risks imposed on the children were permissible given the risks of being a patient in the unsanitary conditions of Willowbrook. He states that perhaps "some broadly based system can be set up to determine under what conditions children or mentally incompetent persons can be used for experimentation not primarily designed for their benefit. This is the only reasonable way; it is also the only honest way." *Id.*

As these examples demonstrate, children have not been adequately protected from unethical clinical research. It is not enough to believe that researchers will conduct their work with adequate protection for children on their own accord. Eliot Freidson writes that the professional privilege of self-regulation has been justified on several grounds, including that the profession “may be trusted to undertake the proper regulatory action on those rare occasions when an individual does not perform his work competently or ethically.”¹⁶ Freidson is skeptical, however, that self-regulation works in medicine because the ability to observe performance is a prerequisite for regulation, and he doubts that the structure of the medical profession has an appropriate level of observation.¹⁷ Furthermore, he asserts that medical norms seem to discourage self-regulation.¹⁸ Talcott Parsons, by contrast, argues that professions are limited from perfect efficiency due to social constraints.¹⁹ The profession’s ability to function appropriately depends on an institutional structure, “the maintenance of which . . . involves a complex balance of diverse social forces.”²⁰ Certainly, institutional review boards (IRBs) are a form of self-regulation by the medical community to ensure that investigators engaged in research protect the rights and welfare of human subjects. Although many would assert that they do an admirable job, several IRBs have been accused of failing to protect human subjects adequately.²¹ Perhaps it is not that self-regulation is impossible or undesirable, but rather that the institutional structure of the regulatory system needs to be recalibrated.

Unfortunately, examples of unethical research involving children are not limited to the distant past. The truth remains that even with protections that were adopted into law in the early 1980s, there remain incidents where children have been the subjects of research deemed unethical. The existence of federal regulations does not guarantee that there will be compliance with the spirit underlying the words of the regulations or complete agreement over what constitutes ethically acceptable research. The current system relies heavily on IRBs to function appropriately and interpret the federal regulations with careful deliberation. Case examples, however, demonstrate that reasonable people can and do disagree over how the regulations should be interpreted and what types of

16. ELIOT FREIDSON, *PROFESSION OF MEDICINE: A STUDY OF THE SOCIOLOGY OF APPLIED KNOWLEDGE* 137 (2d ed. 1970).

17. *Id.* at 156-57.

18. *Id.* at 184.

19. TALCOTT PARSONS, *ESSAYS IN SOCIOLOGICAL THEORY* 34-35 (Free Press rev. ed. 1954) (1949).

20. *Id.* at 48.

21. One might argue, however, that inherent uncertainties in medical practice, knowledge, and research would lead to less than perfect outcomes *even if* IRBs functioned flawlessly. See JAY KATZ, *THE SILENT WORLD OF DOCTOR AND PATIENT* 171 (1984) (arguing that the challenge for IRBs is to be aware of, and willing to accept, uncertainty); See also LEVINE *supra* note 8, at 127-128 (stating that physicians fear acknowledging uncertainty).

research protocols are ethically permissible. Most recently, a study of housing lead abatement conducted by affiliates of Johns Hopkins University engendered differing opinions over what should be ethically acceptable.²² Additionally, a National Institute of Child Health and Human Development (NICHD) study using obese children and children of obese parents was terminated for violating the federal regulations.²³ This article will explain the special problems of involving children in research, provide a thorough understanding of some of the past and current protections for human clinical research participants (including the current federal regulations), emphasize the more controversial areas, and make recommendations on how the regulatory structure could be improved.

Part I describes why children are unique in the research world. It argues that while children are vulnerable and require additional protections when participating in research, they should not be excluded from research altogether because this is more detrimental to their well-being than permitting their participation. Rather, children should be permitted to participate in research but with additional safeguards in place that protect their vulnerability.

Part II describes the historical context of human research protections including the Nuremberg Code and the Declaration of Helsinki. It explores the ethical principles that have been used to protect humans involved in clinical research and explains how these principles of respect for persons, beneficence, and justice are applied to persons with diminished capacity, such as children. The unique characteristics of children make the application of these principles less straightforward than when applied to research involving adults, and these principles' expression in procedural and substantive norms is necessarily altered when applied to children.

The current federal regulations that govern human clinical trials involving children are scrutinized in Part III. The regulations were passed in the early 1980s, but were preceded by recommendations made by a national commission that was created several years earlier in the aftermath of the Tuskegee syphilis experiments. Although the regulations were a vast improvement over prior codes, they continue to use an array of vague language that leaves substantial room for debate in their interpretation. Several hypothetical cases and recent controversial cases will be used to exemplify how reasonable people continue to disagree over how the regulations should be interpreted and applied.

Finally, Part IV offers recommendations for change within the regulatory system. The creation of a hierarchical review board system that maintains the local IRBs but creates many regional boards and one national board analogous to the federal court structure will have a positive impact on the current regulatory system. The establishment of a more centralized system that still maintains a degree of

22. See *infra* notes 103-123 and accompanying text.

23. See *infra* notes 135-140 and accompanying text.

flexibility will divide the duties among the review boards according to their strengths, encourage greater consistency among interpreters of the regulations, provide an appeals process for individual investigators, and create one national board with the requisite case experience and knowledge of how the regional and local review boards operate to enable it to promulgate memoranda that clarify the interpretation of the federal regulations as needed.

PART I: CHILDREN IN RESEARCH

Children are distinct from other human research subjects because they do not usually have the maturity and knowledge base to make an informed decision.²⁴ They are “incapacitated” in the sense that one would not expect a five-year-old child to be able to comprehend, process, engage in abstract reasoning, or synthesize information in the same way as a twenty-five-year-old person. Children cannot be expected to make fully-informed decisions regarding their own participation in clinical trials that may or may not directly benefit them. Surely, some children will express opinions, but children can often be guided into making a decision based on the viewpoint of a parent or trusted adult. In order to ensure that a child truly understands what is being asked of him and is not being coerced or improperly informed, special protections or cautions must be used when children are research subjects.

Given the multiple examples where children have been mistreated in clinical research trials, one might argue that children should not be permitted to participate in human investigations at all. This approach, seemingly radical in the modern world, was indirectly supported by the Nuremberg Code.²⁵ Despite the desire to protect children from the possible harms that can result from their participation in research, far more detrimental effects would occur if children were prohibited from participation in human clinical investigations altogether.

If research involving children (or any group having biological differences from the “average” such as pregnant women) were disallowed, the medical progress for that population would be halted as well. Diseases such as cystic fibrosis, phenylketonuria, and Hirschprung’s disease and many congenital anomalies first manifest in childhood. If they are not treated early, the child may not ever reach adulthood.²⁶ In order to make advances in the treatment of these

24. See LEVINE, *supra* note 8, at 238-39.

25. Although the Nuremberg Code was silent with regard to children, it required legal capacity to give consent for participation, and therefore, indirectly prevented children (who cannot legally consent) from participation. See *infra* Appendix 2 for text of the Nuremberg Code.

26. For more information, see MEDLINE PLUS, MEDICAL ENCYCLOPEDIA, at <http://www.nlm.nih.gov/medlineplus/ency/article/000107.htm> (last visited June 28, 2005); NAT’L DIGESTIVE DISEASES INFORMATION CLEARINGHOUSE, WHAT I NEED TO KNOW ABOUT HIRSCHSPRUNG’S DISEASE, http://digestive.niddk.nih.gov/ddiseases/pubs/hirschsprungs_ez/ (last visited June 28, 2005).

diseases, a research study needs to enroll children who have the diseases in question. Without such research, the children become “therapeutic orphans.”²⁷ They are left behind while medicine advances for everyone else.

Furthermore, beyond research on childhood diseases, there is another category of essential research – medication use in children – that lags far behind. Presently, most medications used for children are used “off-label,” meaning that they were never formally tested on children; rather, the adult doses are modified and then given to the child. Since 1962, the FDA has required nearly all new drugs to be labeled with an “orphaning” clause such as “not recommended for use in infants and young children, since few studies have been carried out in this age group”²⁸ Nevertheless, the overwhelming majority of physicians ignore the orphaning clause on the labels and use the medications for children, albeit usually at an adjusted dose. The result of off-label usage is that it produces a *greater* risk to the child than if the child had been part of a well-designed research protocol that tested different medication doses to determine the appropriate level to be used. A child in a research study designed to test the best dose of a medication would likely have more information about the medication, frequent surveillance of side effects, and a greater likelihood of having access to medical care should an adverse reaction develop. Children given a medication off-label, however, do not have the same surveillance of side effects and risk a greater possibility of harm if an adverse reaction occurs in an uncontrolled, unmonitored setting. Robert Levine argues that the therapeutic orphan problem is a serious injustice for children. He observes that “[i]f we consider the availability of drugs proved safe and effective through the devices of modern clinical pharmacology and clinical trials a benefit, then it is unjust to deprive classes of persons, e.g., children . . . of this benefit.”²⁹

The problem with the lack of clinical pharmacology studies in children is even more concerning than the dearth of studies involving other vulnerable groups (such as prisoners or mentally disabled individuals) because children often have smaller body sizes, different physiology, and different metabolisms (for example, the newborn liver does not metabolize certain medications as efficiently as the adult liver). Therefore, improper medication doses for children could lead to grave consequences more often than with adults. Logically then, it appears that medications used in children should have more stringent testing than medications

27. Harry Shirkey, *Editorial Comment: Therapeutic Orphans*, 72 J. PEDIATRICS 119 (1968); LEVINE, *supra* note 8, at 239-41.

28. Shirkey, *supra* note 27, at 119.

29. LEVINE, *supra* note 8, at 240. Levine continues, “Parenthetically, it should be noted that most drugs proved safe and effective in adults do not produce unexpected adverse reactions in children; however, when they do, the numbers of harmed children tend to be much higher than they would be if the drugs had been studied systematically before they were introduced into the practice of medicine.” *Id.* at 240-41.

used for adults. Yet the opposite is true: medications used for children have the least amount of empirical evidence supporting their use.

The Best Pharmaceuticals for Children Act of 2002³⁰ gives financial incentives to pharmaceutical companies that voluntarily decide to test their medications in children, but this law clearly has not done enough considering that as of July 2003, three-fourths of all prescription medications on the market had inadequate information regarding their safety in pediatric populations.³¹ In 1998, the Food and Drug Administration (FDA) attempted to alleviate the problem by adopting a regulation known as the Pediatric Rule.³² The Rule required pharmaceutical companies to test specific medicines in children before the drugs were marketed.³³ In October 2002, however, a judge ruled that the FDA did not have the authority to adopt the Pediatric Rule and struck it down.³⁴ Congress reacted, albeit slowly, and adopted the Pediatric Research Equity Act of 2003,³⁵ which was signed into law in December 2003.³⁶ The law gives the FDA jurisdiction to require that drugs used in pediatric patients be appropriately tested with pediatric populations prior to FDA approval.³⁷ Recognizing the importance of solving the therapeutic orphan problem, FDA Commissioner Mark McClellan stated:

Prescription drugs can do more than ever to cure diseases, including illnesses in children. But it is not good medicine to assume that children can be treated like little adults. Parents and health professionals deserve confidence that medicines used to treat children are safe and effective. FDA will use this important new law to require pediatric studies, when necessary, to give parents and doctors the confidence they deserve.³⁸

Undoubtedly, the Pediatric Research Equity Act is a step in the right direction towards alleviating the therapeutic orphan problem and decreasing off-label medication use and its associated risks. The law will lead to increased numbers of research trials involving children, and although these studies should be conducted

30. Pub. L. No. 107-109, 115 Stat. 1408 (2002).

31. David J. Schonfeld, Participation and Protection of Children in Clinical Research, Statement Before the Institute of Medicine Committee on Clinical Research Involving Children (July 9, 2003), http://www.aap.org/advocacy/washing/David_Schonfeld_testimony.htm (last visited June 28, 2005).

32. Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66, 632 (Dec. 2, 1998) (to be codified at 21 C.F.R. pts. 201, 312, 314, & 601).

33. *Id.*

34. Ass'n of Am. Physicians & Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204, 222 (D.D.C. 2002).

35. Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified as amended at 21 U.S.C.A. § 355 & 42 U.S.C.A. §§ 262 & 284m (West Supp. 2004)).

36. *Id.*

37. 21 U.S.C.A. § 355c (West Supp. 2004).

38. Press Release, U.S. Food & Drug Administration, Statement of FDA Commissioner Mark B. McClellan, M.D., Ph.D., on the Signing of the Pediatric Research Equity Act of 2003 (Dec. 3, 2003), <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00989.html> (last visited June 28, 2005).

to benefit children, additional safeguards must be in place to prevent their manipulation and exposure to unreasonable levels of possible harm. The balance between encouraging research designed to help children as a group and preventing unreasonably high levels of risk to any particular child in a study is difficult to strike. Ethical principles can serve an important role by guiding decision-makers during difficult assessments.

PART II: FOUNDATIONS OF RESEARCH ETHICS

A. Early Codes of Research Ethics

From 1945-1947, the first international warcrimes trials were held in Nuremberg, Germany in order to bring to justice the Nazis who committed terrible offenses during World War II. Many of the crimes included horrific murders and tortures conducted in the name of medical research. The three Nuremberg judges were infuriated by the atrocities, which had used science as a justification and decided to codify fundamental ethical guidelines for permissible human research "in order to satisfy moral, ethical and legal concepts."³⁹ The Nuremberg Military Tribunal's decision in *United States v. Karl Brandt*⁴⁰ included a ten-point statement that described permissible medical experiments on human subjects.⁴¹ These ten principles became known as the Nuremberg Code, which is generally regarded as the first international document to set out ethical regulations for human experimentation based on informed consent.⁴² (See Table 1.)

TABLE 1: INFLUENTIAL DOCUMENTS ON RESEARCH ETHICS⁴³

| YEAR | PUBLICATION | AUTHOR | DESCRIPTION |
|------|----------------|------------------|--|
| 1947 | Nuremberg Code | Nuremberg judges | First major international code of research conduct created after Nuremberg trials of Nazi physicians/researchers |

39. See *infra* Appendix 2, at 317-18 for text of Nuremberg Code.

40. See *infra* Appendix 2, at 317-18 for text of Nuremberg Code.

41. See *infra* Appendix 2, at 317-18 for text of Nuremberg Code.

42. Finnuala Kelleher, *The Pharmaceutical Industry's Responsibility for Protecting Human Subjects of Clinical Trials in Developing Nations*, 38 COLUM. J.L. & SOC. PROBS. 67, 72 (2004); Julie Rothstein Rosenbaum, *Educating Researchers: Ethics and the Protection of Human Research Participants*, 31 CRITICAL CARE MED. S161, S162 (2003). The Nuremberg Code, however, was not the first document to outline the obligations of researchers conducting human clinical investigations. In fact, federal law in Germany already included such obligations and prohibitions against unethical research, but these laws were ignored during the Third Reich. LEVINE, *supra* note 8, at 69.

43. Rosenbaum, *supra* note 42, at S162.

| | | | |
|------|-------------------------|--|--|
| 1964 | Declaration of Helsinki | World Medical Association | Comprehensive ethical guidelines for physicians involved with research, last updated in 2000 |
| 1979 | Belmont Report | The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research from the Department of Health, Education, and Welfare | Report that identified key principles for guiding human research protection, including respect for persons, beneficence, justice |

The first principle of the Nuremberg Code states: “The voluntary consent of the human subject is absolutely essential.”⁴⁴ The term “voluntary” is further elaborated:

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.⁴⁵

This principle, although well intentioned, is extremely overbroad because, taken literally, it would prohibit all research involving those who are unable to consent, including children and the mentally disabled. The Code makes no exceptions for proxy consent or consent for minors to be given by parents. Investigators, therefore, have largely ignored this principle of the Nuremberg Code and continue to conduct research using these populations. Even though the authors may be admired for attempting to codify basic ethical principles, the overall impact of the Nuremberg Code on actual research practices has been minimal. One scholar points out that “the very circumstances that gave the code its high moral standing – the horrors that surrounded its origins – partly account for its relative lack of influence in the postwar years: ordinary researchers found it hard to believe that the code need be applied to their own work.”⁴⁶

44. See *infra* Appendix 2, at 317-18 for text of Nuremberg Code.

45. *Id.*

46. Kendall Ann Desaulniers, Comment, Legislation to Protect the Decisionally Incapacitated Individual's Participation in Medical Research: Safety Net or Trap Door?, 13 REGENT U. L. REV. 179, 182 (2000) (quoting Jonathan D. Moreno, The Dilemmas of Experimenting on People, TECH. REV., July 1997, <http://www.technologyreview.com/articles/97/07/moreno0797.asp?p=1> (last visited June 28, 2005)).

In response to the overly restrictive Nuremberg Code, the World Medical Association adopted the Declaration of Helsinki in 1964.⁴⁷ The Declaration also emphasizes the importance of freely given informed consent by research subjects, but it parts with the Nuremberg Code in an important way:

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.⁴⁸

The Declaration of Helsinki implicitly acknowledges that research on groups who are unable to give consent is necessary to advance medical care for them and provides a method for obtaining proxy consent. It serves as a more practical guide to researchers and tries to alleviate the problem of the therapeutic orphan. Nevertheless, even after the Declaration of Helsinki was written, pediatric research was rare in the United States because the legal status of proxy consent remained uncertain.

Another important feature of the Declaration of Helsinki was its division of research into therapeutic and non-therapeutic categories. The 1975 revised Declaration divides research into “Medical Research Combined with Professional Care (Clinical Research)” and “Nontherapeutic Biomedical Research Involving Human Subjects (Nonclinical Biomedical Research).”⁴⁹ For the first category of research (therapeutic research), physicians can perform research “only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.”⁵⁰ In the non-therapeutic category, however, subjects must be “healthy persons or patients for whom the experimental design is not related to the patient’s illness.”⁵¹ The distinction between therapeutic and non-therapeutic research has the unfortunate consequence of prohibiting all placebo-controlled studies because the placebo arm is not of therapeutic value to the patient, and using healthy control subjects for the placebo arm of a trial would yield no useful information.⁵² Levine explains that the distinction between therapeutic and non-therapeutic research essentially prohibits all research in pathogenesis, pathophysiology, and epidemiology because these types of studies usually do not have therapeutic value

47. *Human Experimentation: Code of Ethics of the World Medical Association*, 2 BRIT. MED. J. 177 (1964); Declaration of Helsinki (1975), reprinted in LEVINE, *supra* note 8, 427-29. The Declaration of Helsinki has been revised several times, most recently in 2000. See *infra* Appendix 3 for full text.

48. Declaration of Helsinki, *supra* note 47, at 428.

49. *Id.*, at 429.

50. *Id.*

51. *Id.*

52. LEVINE, *supra* note 8, at 9.

for the research subjects.⁵³ Levine further argues that every clinical trial has components that are not therapeutic, but that to classify an *entire* protocol as therapeutic just because of one therapeutic component results in the “fallacy of the package deal.”⁵⁴ Non-therapeutic components of a protocol are commonly justified because the protocol includes one or more therapeutic components. Levine provides some examples:

Such erroneous justifications in the recent past have been frequent. In trials of thrombolytic therapy, repeated coronary angiograms have been performed on patients who had clinical indications for only one. Liver biopsies have been performed for no reason other than to disguise treatment assignments in a double-blind placebo-controlled trial. Repeated endoscopies have been performed in a population of patients with peptic ulcers who had clinical indications for no more than one. Placebos have been administered by way of a catheter inserted in the coronary artery. I do not want to be misunderstood as saying that any of these procedures were unethical. I am simply arguing that they should not be justified according to standards developed for “therapeutic research.”⁵⁵

The Declaration of Helsinki was most recently revised in October 2000.⁵⁶ Despite some changes adopted in this sixth version, the Declaration remains restrictive of placebo trials. In addition, although it removed the words “therapeutic” and “non-therapeutic,” it still uses the distinction to determine what research is permissible.⁵⁷

Although they were important advances in the conceptual framework for ethical research, the Nuremberg Code (1947) and the Declaration of Helsinki (1964) were never legally binding documents. As a result, these ethical codes did not halt existing research abuses such as the Tuskegee Syphilis Study and the Willowbrook School study on children.⁵⁸ The ethical canons of Nuremberg and Helsinki were not powerful enough to stop the egregious devaluing of human life

53. *Id.*; Robert J. Levine, *International Codes of Research Ethics: Current Controversies and the Future*, 35 IND. L. REV. 557, 559-60 (2002); Declaration of Helsinki, *supra* note 47, at 429.

54. Levine, *supra* note 53, at 560.

55. *Id.*

56. World Medical Ass’n Declaration of Helsinki, Doc. 17C (Oct. 2000), <http://www.wma.net/e/ethicsunit/helsinki.htm> (last visited June 26, 2005).

57. Levine, *supra* note 56, at 559.

58. The Tuskegee Syphilis experiment began in 1932 and was designed to measure the results of untreated syphilis in black males who were uneducated sharecroppers. The protocol in this trial included a placebo arm where subjects were given aspirin instead of proven treatments for syphilis. Furthermore, the researchers did not stop the trial and give subjects penicillin when it was discovered in the 1940s. The study did not receive press attention until 1972. U.S. DEP’T OF HEALTH & HUMAN SERVS., THE NAT’L CTR. FOR HIV, STD, AND TB PREVENTION, THE TUSKEGEE TIMELINE, *at* <http://www.cdc.gov/nchstp/od/tuskegee/time.htm> (last visited June 28, 2005). See *supra* notes 7-15 and accompanying text for discussion of the Willowbrook studies.

that these research studies exemplified. In the aftermath of these studies, a modern code that was legally binding was needed to govern research ethics and renew the public's trust in medical research.

B. The National Commission and Ethical Principles

The Department of Health, Education and Welfare (DHEW) published its first proposed regulations on protection of human subjects in 1973. When the atrocities of the Tuskegee experiments came to light, Congress held national hearings on human clinical research, and adopted the National Research Act of 1974,⁵⁹ which created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research [hereinafter "Commission"].⁶⁰ The Commission was to develop guidelines for ethical research involving human subjects and make recommendations to the DHEW Secretary for the application of these guidelines.⁶¹ Section 202(a)(1)(A) of the National Research Act specified that the Commission should:

- (i) conduct a comprehensive investigation and study to identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects,
- (ii) develop guidelines which should be followed in such research to assure that it is conducted in accordance with such principles, and
- (iii) make recommendations to the Secretary (I) for such administrative actions as may be appropriate to apply such guidelines to biomedical and behavioral research conducted or supported under programs administered by the Secretary⁶²

The Commission published reports on human subject research from 1975 to 1978 and presented the reports as recommendations to the DHEW Secretary as instructed.⁶³ The Commission addressed topics such as IRBs, research on the fetus and embryo, and research involving children. The Commission was disbanded in

59. Pub. L. No. 93-348, 88 Stat. 342 (1974) (originally codified at 42 U.S.C. § 2891-1 nt. (1976)), *omitted by* Health Research Extension Act of 1985, Pub. L. No. 99-158, 99 Stat. 820, 873-86 (1985).

60. Nat'l Research Act, 88 Stat. 348 (originally codified at 42 U.S.C. § 2891-1 nt. (1976)), *omitted by* Health Research Extension Act of 1985, 99 Stat. 873-86 (1985).

61. Dept. of Health, Educ., and Welfare, Office of the Sec'y, *Research Involving Children: Report and Recommendations of the Nat'l Comm'n for the Prot. of Human Subjects of Biomedical and Behavioral Research*, 43 Fed. Reg. 2084, 2084 (Jan. 13, 1978) [hereinafter *Report on Research Involving Children*].

62. National Research Act § 202(a)(1)(A), 88 Stat. at 349 (codified at 42 U.S.C. § 2891-1 nt., *omitted by* Health Research Extension Act of 1985, 99 Stat. at 873-86); LEVINE, *supra* note 8, at xi-xii.

63. Importantly, the Commission explicitly repudiated the use of therapeutic and non-therapeutic categories of research after using the distinction in its first report on research involving fetuses.

1978,⁶⁴ but during its brief years of existence it made valuable contributions to discussions on research ethics and suggested possible regulatory guidelines.

The Commission's "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects Research" (1979) described three ethical principles that should guide research involving human subjects: respect for persons, beneficence, and justice. The first of these, respect for persons, requires that individuals be treated as "autonomous agents" and also that "persons with diminished autonomy [and thus in need of protection] are entitled to such protection."⁶⁵ To treat a person as an "autonomous agent" requires that the individual be left to make his or her own decisions, even if doing so may result in harm to that person, unless he or she consents to receive help or to participate.⁶⁶ Furthermore, a person's actions should not be hindered unless they are clearly detrimental to others.⁶⁷ Certainly, not every person has the ability to act as an "autonomous agent," and it is this subset of people that require additional protections because without them, they are far more likely to have their person disrespected.⁶⁸ Because research involving children involves persons with diminished autonomy, children deserve extra protections when they participate in such research.

The second ethical principle, beneficence, means that the researcher should maximize possible benefits and minimize possible harms.⁶⁹ It is important to recognize that this principle is more than simple non-maleficence; it also imposes a *positive* duty on the researcher to maximize benefits and minimize harms. The Belmont Report recognizes that this is not always a simple task and that researchers will need "to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the

64. LEVINE, *supra* note 8, at xii.

65. DEPT. OF HEALTH, EDUC., AND WELFARE, NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH, THE BELMONT REPORT: ETHICAL PRINCIPLES AND GUIDELINES FOR THE PROTECTION OF HUMAN SUBJECTS OF RESEARCH pt. B.1 (1979) [hereinafter BELMONT REPORT], <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm> (last visited June 28, 2005).

66. LEVINE, *supra* note 8, at 15.

67. *Id.* at 16.

68. *Id.* Levine argues:

The capacity for self-determination matures during a person's life; some lose this capacity partially or completely owing to illness or mental disability or in situations that severely restrict liberty, such as prisons. Respect for the immature or the incapacitated may require one to offer protection to them as they mature or while they are incapacitated.

Id.

69. BELMONT REPORT, *supra* note 65, at pt. B.2.

risks.”⁷⁰ The Belmont Report allows the benefit to society to be considered in the equation when balancing risks and potential benefits involved.⁷¹

Justice, the third basic principle, requires that subjects are chosen and treated fairly. Justice is essential to “insure that certain individuals or classes of individuals – such as prisoners, elderly people, or financially impoverished people – are not systematically selected or excluded, unless there are scientifically or ethically valid reasons for doing so.”⁷² This concept of justice is meant to provide an equal distribution of the benefits and burdens that accompany research. The Commission did not interpret justice in a utilitarian way to mean the greatest good for the greatest number of people because this view ignores the idea that fairness requires extra protections for vulnerable groups.⁷³ The Commission concluded:

[P]ersons having limited capacity to consent are vulnerable or disadvantaged in ways that are morally relevant to their involvement as subjects of research. Therefore, the principle of *justice* is interpreted as requiring that we facilitate activities that are designed to yield direct benefit to the subjects⁷⁴

These three principles of respect for persons, beneficence, and justice have provided the ethical framework for human clinical research, and as noted by the Commission, these principles require additional safety measures to protect vulnerable populations involved in research. The Commission’s reports and suggestions, which were later revised and adopted into the Code of Federal Regulations,⁷⁵ rely heavily on the ethical principles.

In 1980, DHEW was restructured; education became a separate department, and what remained of DHEW became the Department of Health and Human Services (DHHS).⁷⁶ Shortly thereafter, in 1981, DHHS published federal regulations on the protection of human subjects that were mostly an adoption of the Commission’s suggestions. These initial federal regulations did not include

70. *Id.*

71. *Id.* at pts. B2, C2; Desaulniers, *supra* note 46, at 202-03. *Cf.* Declaration of Helsinki, § III (4), *supra* note 47, at 429 (“In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.”).

72. NAT’L INSTS. OF HEALTH (NIH), ORIENTATION INFORMATION FOR MEMBERS OF INSTITUTIONAL REVIEW BOARDS AT THE NIH 15 (2004), http://ohsr.od.nih.gov/irb/Orientation_Guidelines_Final.pdf (last visited June 28, 2005); *see also* BELMONT REPORT, *supra* note 65, at pt. B.3.

73. LEVINE, *supra* note 8, at 18.

74. *Id.* at 236.

75. Protection of Human Subjects, 45 C.F.R. pt. 46 (2004). *See infra* Appendix 1, at 312-16 and Appendix 4, at 323-24, for pertinent parts of this regulation.

76. DEP’T. OF HEALTH & HUMAN SERVS., HISTORICAL HIGHLIGHTS, <http://www.hhs.gov/about/hhshist.html> (last visited June 28, 2005).

special regulations for children, but regulations for children were finally approved two years later in 1983.⁷⁷

Although the Code of Federal Regulations attempts to provide boundaries between acceptable and unacceptable research, there will always be research protocols that do not fall neatly into these categories. It is precisely when the regulations do not provide clear answers regarding the acceptability of a particular research protocol that the three ethical principles become even more important; they should serve as guidance when the regulations are ambiguous.

PART III: FEDERAL REGULATIONS

A. Additional Protections for Children Involved as Subjects in Research:

The Commission’s report, “Research Involving Children” (1977), made recommendations that allow children to be used in research yet still protects them adequately from harm. The recommendations served as the basis for the Code of Federal Regulations (C.F.R.) Subpart D: Additional Protections for Children Involved as Subjects in Research (1983). Unlike the Nuremberg Code and the Declaration of Helsinki, the regulations are legally binding; however, they are not without their flaws. The main purpose of Subpart D is to provide children, as members of a population considered vulnerable, with additional safeguards. The section divides research involving children into four categories, each of which has different requirements for approval. (See Table 2.) Section 46.403 further requires that IRBs only approve research that satisfies the requirements set forth in the remainder of Subpart D.⁷⁸

TABLE 2: FEDERAL REGULATIONS FOR RESEARCH INVOLVING CHILDREN⁷⁹

| FEDERAL REGULATION SECTION | RISK POSED BY THE INTERVENTION OR PROCEDURE | ADDITIONAL REQUIREMENTS FOR PROTOCOL APPROVAL (*All require IRB approval, child’s assent ⁸⁰ and permission by parent or guardian ⁸¹) |
|----------------------------|---|--|
|----------------------------|---|--|

77. Additional Prots. for Children Involved as Subjects in Research, 48 Fed. Reg. 9,818 (Mar. 8, 1983) (to be codified at 45 C.F.R. pt. 46).

78. IRB Duties, 45 C.F.R. §46.403 (2004), *infra* at 312.

79. *Id.* §§ 46.404 – 46.409, *infra* at 313-19; *see also* Jeffrey P. Burns, *Research in Children*, 31 CRITICAL CARE MED. S131, S134 (2003).

80. *Id.* § 46.408, *infra* at 315-18. The regulations state:

In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are

| | | |
|--------------------|---|---|
| 45 C.F.R. § 46.404 | No greater than minimal risk | No additional requirements |
| 45 C.F.R. § 46.405 | Greater than minimal risk with prospect of direct benefit to subject | Risk is justified by the anticipated benefit to each subject Anticipated benefit to each subject is at least as favorable as that presented by available alternative approaches |
| 45 C.F.R. § 46.406 | Greater than minimal risk with no prospect of direct benefit to subject | Risk represents a minor increase over minimal risk Intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child's actual or expected medical, dental, psychological, social or educational situations The study is likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition |
| 45 C.F.R. § 46.407 | Research not otherwise approvable | IRB finds 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 Approval of the Secretary of DHHS after consultation with a |

capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved.

Id. § 46.408(a).

81. Permission from one parent or guardian is acceptable for research covered by 45 C.F.R. §§ 46.404 or 46.405, but where research is covered by §§ 46.406 and 46.407, "both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child." *Id.* § 46.408.

| | | |
|--|--|---|
| | | panel of experts in pertinent fields, and following opportunity for public review and comment |
|--|--|---|

The drafters of the regulations, following the lead of the Commission, refrained from using the distinction between therapeutic and non-therapeutic research and thereby avoided the “fallacy of the package deal” that is created with the Declaration of Helsinki language and others who rely on such a distinction.⁸² Rather than analyzing the overall risk posed by a research protocol, the risk posed by each individual intervention or procedure in the protocol is assessed.⁸³ These risks then are weighed against possible benefits caused by those same interventions or procedures.⁸⁴ This assessment prevents the error of justifying an extremely risky intervention simply because it is part of a protocol deemed to have large overall benefits. An important caveat to the risk/benefit calculation for each study is that the benefits can only encompass the health consequences of the study’s interventions and procedures. Economic incentives such as direct payments, free medical treatment, free medications, or diagnostic tests are not included as benefits because using economic incentives in the risk/benefit analysis or including them as benefits in the informed consent is viewed as starting a slippery slope toward undue inducement.

B. Section 404: No Greater than Minimal Risk

The first category of research is that which involves interventions or procedures that pose nothing greater than minimal risk to a research subject who may be either a healthy child or a child with an illness. For this research, the criteria for approval are essentially the same as those required for all human subjects including adults or non-vulnerable populations. The only additional requirements for a pediatric population are that the child’s assent be obtained (if possible) and that a parent or guardian give permission for the child’s participation in the study.⁸⁵ Because the idea of “minimal risk” is subject to multiple interpretations, the drafters of the regulations attempted to clarify the words by defining minimal risk to mean “the probability and magnitude of harm . . . anticipated in the [proposed] research are not greater . . . than those ordinarily encountered in daily life or during the performance of routine physical or

82. See Levine, *supra* note 53, at 560 and accompanying text.

83. *Id.*

84. *Id.* at 560-61.

85. 45 C.F.R. §§ 46.402(b) & 46.402(c) (2004), *infra* at 312 (“Assent means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent [and] Permission means the agreement of parent(s) or guardian to the participation of their child or ward in research”).

psychological examinations or tests.”⁸⁶ The idea behind the minimal risk threshold is that it is a socially permissible level of risk to which parents would normally permit their children to be exposed in non-research settings. The National Commission provided some examples of interventions that easily fall within this category: “routine immunization[s], modest changes in diet or schedule, physical examination, obtaining blood and urine specimens, and developmental assessments.”⁸⁷ It is important to remember that for protocols that fall under this category, it does not make any difference whether the intervention has the potential to benefit the subject or whether the child is healthy. As long as the risk posed by the intervention is no more than minimal, there are no additional requirements for review and acceptability.

1. *Defining Minimal Risk*

There are several problems with the definition of minimal risk provided in the Code of Federal Regulations, but many of these can be reconciled by examining the Commission’s report and the principles of respects for persons, beneficence, and justice on which the regulations are based. First, the regulations do not explicitly indicate *whose* daily life should be used as a standard; certainly not all members of the research group are exposed to the same risks of harm in their daily lives. For example, a child growing up in extreme poverty may encounter a daily risk of malnourishment that is not experienced by his or her wealthier counterpart. A child growing up in a war-torn nation or a country plagued by AIDS will definitely encounter greater risks in daily life than a child growing up in a more stable environment.⁸⁸ Some argue that the “daily life” requirement should be based on the average child within that population.⁸⁹ Others argue that the acceptable risk level should be based on the daily risks encountered by healthy children in a stable environment.⁹⁰ The definition of minimal risk in the federal regulations differs in one important respect to the definition first proposed in the National Commission’s recommendations. The Commission stated: “Minimal risk is the probability and magnitude of physical or psychological harm that is normally

86. *Id.* § 46.102(i).

87. Report on Research Involving Children, *supra* note 61, at 2085.

88. *See, e.g.*, Burns, *supra* note 79, at S134. Burns asserts:

In particular, if one adopts a relative interpretation of minimal risk, then some children whose daily routine exposes them to relatively higher risks in theory could also be the subjects of research in which the risk exposure was, therefore, proportionally higher than would be approved for a child from a more protected or advantaged background.

Id.

89. Benjamin Freedman et. al., *In Loco Parentis: Minimal Risk as an Ethical Threshold for Research Upon Children*, 23 HASTINGS CTR. REP. 13, 17 (1993).

90. *E.g.*, Loretta M. Kopelman, *Children as Research Subjects: A Dilemma*, 25 J. OF MED. & PHIL. 745, 754 (2000).

encountered in the daily lives, or in the routine medical or psychological examination, of *healthy children*.⁹¹ Although the Commission's intent was to define the minimal risk threshold based on a healthy child, the federal regulations are ambiguous. The Commission also provided specific examples of procedures that it considered to be no more than minimal risk, but these specific examples were excluded from the regulations, thereby leaving the acceptability of some of these more common procedures to the individual judgment of the IRBs.

Although the federal regulations do not explicitly define minimal risk to be based on the daily risks encountered by healthy children, it is clear that the Commission's report intended it to be defined in this absolute way. Consider, for a moment, the possibility that the daily risks in the federal regulations are interpreted as being relative and not absolute. Certainly, there are children exposed to abnormally high levels of risk, but to use their daily experiences as the threshold of daily risk would unjustly subject them to higher risks than other children.⁹² This type of justification for a high risk protocol is reminiscent of the Willowbrook studies, where children who were exposed to an abnormally high risk of contracting hepatitis were then given hepatitis because it was considered to be a risk to which they were already exposed.⁹³ Undoubtedly, the federal regulations were written to prohibit this type of research, not to protect it. Therefore, daily risks, as written in the regulations, must be interpreted as risks that a healthy child in a stable environment encounters.

The National Human Research Protections Advisory Committee (NHRPAC) Children's Workgroup was formed in 2000 and charged with providing advice and recommendations on human subjects protection to the Office for Human Research Protections (OHRP).⁹⁴ NHRPAC issued a report to clarify the definitions of "minimal risk" and "minor increase over minimal risk." In the report, NHRPAC specifically denied that minimal risk should be a variable standard based on a particular child's circumstances and defined minimal risk to be the level of risk associated with the daily activities of a "normal, healthy, average child."⁹⁵ Furthermore, the report states: "Indexing the definition of minimal risk to the

91. Report on Research Involving Children, *supra* note 61, at 285 (emphasis added). It is interesting to note that the Commission offered different definitions of minimal risk in several of its reports in an effort to express their view that the threshold should be different for different populations. This subtly was lost when the drafters of the federal regulations provided a single definition of minimal risk for all human subject populations. Personal Communication with Robert J. Levine, Professor of Medicine and Lecturer in Pharmacology, Yale University School of Medicine (Jan. 2004).

92. Kopelman, *supra* note 90, at 754.

93. *Id.*

94. NAT'L HUMAN RESEARCH PROTS. ADVISORY COMM., CHILDREN'S WORKGROUP, CHILDREN'S WORKGROUP DRAFT REPORT I (Apr. 5, 2001), <http://www.hhs.gov/ohrp/nhrpac/mtg04-01/child-workgroup4-5-01.pdf> (last visited June 28, 2005).

95. NAT'L HUMAN RESEARCH PROTS. ADVISORY COMM., CHILDREN'S WORKGROUP, CLARIFYING SPECIFIC PORTION OF 45 CFR 46 SUBPART D THAT GOVERNS CHILDREN'S RESEARCH I [hereinafter WORKGROUP REPORT], <http://ctep.cancer.gov/forms/nhrpac16.pdf> (last visited June 28, 2005).

socially allowable risks to which normal, average children are exposed routinely should take into account the differing risks experienced by children of different ages.”⁹⁶

Certainly, this argument is not meant to prohibit children exposed to abnormally high risks from participating in research; it simply asserts that subjecting them to their high baseline risks cannot be classified as *minimal*. The fact that these children face abnormally high risks is not a morally relevant distinction that justifies protecting them less when they participate in human clinical trials. To use a relative standard for minimal risk would violate the principle of justice for these children. They would be subject to an unequal distribution of the burdens of research involving human participants because riskier studies could be performed with them but not with healthier children.

The second difficulty with the definition of minimal risk is that it considers the “probability and magnitude” of possible harm, but it does not provide a framework with which to judge what are acceptable probabilities and magnitudes of harm. To decide what is an appropriately low probability or magnitude of harm is not an easy task. The evaluation requires careful balancing and normative assessments because sometimes a low probability of substantial harm might be approved, whereas a high likelihood of a more moderate harm may not.⁹⁷ Because the federal regulations do not suggest a way to judge acceptable levels of harm, the IRBs are left to make the decisions on their own. The federal regulations do not offer any examples of acceptable or unacceptable harms as a reference point for the IRBs. Perhaps local IRBs are best suited to make this assessment on a case-by-case basis, but one might also argue that leaving too much power in the hands of overburdened IRBs without adequate guidance is a recipe for inconsistency and a set up for disaster.

C. Section 405: Interventions with Prospect of Direct Benefit to Subject

The second category includes procedures or interventions that have the potential to benefit the individual subject directly. In these cases, it does not matter if the intervention poses greater than minimal risk to the subject, and the minimal risk evaluation is not needed in the analysis of these cases. Because this class of interventions must have the prospect of directly benefiting the subjects, it will generally involve a child who is *not* the average healthy child in a stable environment.⁹⁸ In such cases, the research protocol has the added requirements of

96. *Id.*

97. Kopelman, *supra* note 90, at 753.

98. *But cf.* Bruce Gordon et. al., *The Use of Normal Children as Participants in Research on Therapy*, IRB: ETHICS & HUMAN RES., May-June 1996, at 5-8. This study involved using siblings of ill children in a protocol that involved more than minimal risk procedures. The healthy siblings were viewed as gaining a direct psychological benefit from participating in the research protocol (because

showing that the risk posed to the subjects is justified by the anticipated benefit, and that the anticipated benefit is at least as favorable to the subjects as that presented by available alternatives.⁹⁹

An example of a research protocol that easily falls into this category is a study using a new chemotherapeutic agent for leukemia. The new drug may pose a significant risk to the potential subjects, but as long as the anticipated benefits are also high, and the expected benefits from the agent are at least as high as the current available alternative medication, then the trial would be appropriately approved. Importantly, any control arm of this study would need to receive the current available alternative medication and not a placebo in order for the trial to be approved.

Although it may be more controversial than the above example, there are situations when determining the high level of daily risks to which some populations are exposed and using *that* level of risk in a study is absolutely essential to examining potentially beneficial interventions for those populations. While justifying higher risks for a specific population may tread on dangerous ground, there is a moral imperative to do so because without such research, there will be fewer developments in the ways to lower those same higher risks. It would not be possible to study a particular risk factor and try to find a way to alleviate it in a practical manner unless the protocol continued to expose the population to their normal daily risks for the duration of the study. In order for the results of a study to be *practically* applicable to the population, the intervention must be tested within the population's normal environment and daily risk exposures. In these cases, the principle of justice demands that adequate research studies are carried out with these populations in order to help lower the risks to which they are exposed.

A real-life case example is provided by the placebo-controlled trials of the "short-duration" AZT therapy in preventing perinatal transmission of HIV in developing countries. Some opponents of the research argued that the research subjects were unjustly treated in that they received a sub-standard level of care during that trial. True, the subjects did not receive the best proven therapeutic method available in industrialized countries (076 regimen), but the interventions they did receive had the possibility of benefiting their specific situation. To ride an ethical high horse about why research that is not acceptable for a child in America should also not be acceptable for a child in a disease-torn country does a disservice to the child who is subjected to the increased risks already. *That* child has the potential to benefit from the research far more than the child in America, and the risk/benefit analysis needs to take this into account in the determination of what is

they could potentially help keep their ill sibling alive) and therefore, were able to participate under 45 C.F.R. § 46.405.

99. 45 C.F.R. § 46.405 (2004), *infra* at 313-14.

acceptable research. Levine argues that to use the 076 regimen in these countries would have required an almost impossible revision of their perinatal customs including requiring women to seek prenatal care much earlier than they are accustomed, using intravenous medications, and finding a safe alternative to breast feeding for babies of HIV-infected mothers in countries with no infant formula and contaminated water supplies.¹⁰⁰ Levine asserts:

In summary, it is clear that the 076 regimen of AZT cannot be made available to most HIV-infected pregnant women in the resource poor countries now or in the foreseeable future. This is the main reason that it is essential to find methods to reduce the rate of perinatal transmission of HIV that are within the financial reach of the resource poor countries. Finding these methods was the primary justification for conducting the clinical trials of the short duration regimen of AZT. The cost of the AZT in this regimen was about ten percent of that of the 076 regimen. Moreover, there was no need for intravenous therapy or administration of the drug to the babies. At the time the trials began, it seemed likely that two of the countries could afford to provide the short duration regimen if it proved effective; there was also a commitment from international agencies to assist the other resource poor countries in securing and providing the drug.¹⁰¹

Another example provides additional clarity: If a child is already exposed to a contaminated water supply and there are no resources to improve the supply, a study to see if partially purified water alleviates some disease that is usually caused by the impure water should be acceptable.¹⁰² Such a study submits the children to a higher level of risk than an average healthy child, but it has the potential to benefit the subjects in a way that healthy children would not benefit. To expose the children to improperly cooked meat or another type of risk to which they are not already exposed would not be permissible, even though it poses a similar *level* of risk as the impure water, because the risk is not something already experienced by the child. Furthermore, taking a child with a healthy water supply and submitting her to impure water for the purpose of the research would also not be permissible under section 405 because she does not gain any direct benefit from the intervention. Although this scenario may seem far-fetched because pure water

100. Levine, *supra* note 53, at 563.

101. *Id.*; see also COUNCIL FOR INT'L ORGS. OF MED. SCIS., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2002), http://www.fhi.org/fr/topicsf/ethicsf/curriculum/pdf_files/cioms.pdf (last visited June 28, 2005).

102. One might argue that in each of these cases the children are not truly exposed to a risky intervention but instead something of potential benefit is withheld from them. The withheld benefit is something to which they did not previously have access and will likely not have access to in the future. True, the regulations do not specifically address this issue. But, in this hypothetical, one can imagine a scenario where the method of partially purifying water exposes the children to an *additional* degree of risk.

is taken for granted in an industrialized country like America, the hypothetical is analogous to a recent study involving lead abatement interventions to reduce lead poisoning in children.

1. Grimes v. Kennedy Krieger Institute: Section 405 Gone Awry?

In 1993, the Environmental Protection Agency awarded a research grant to the Kennedy Krieger Institute (KKI), a research institution affiliated with Johns Hopkins University, entitled: "Evaluation of Efficacy of Residential Lead Based Paint Repair and Maintenance Interventions."¹⁰³ The study was designed to compare comprehensive lead paint abatement with less-comprehensive repair and maintenance interventions that would possibly be more cost effective.¹⁰⁴ There were five arms to the study, three of which were interventions with different levels of lead abatement and two of which were controls.¹⁰⁵ Researchers used houses that were built before 1941 or had documented lead-based paint present for the intervention groups.¹⁰⁶ Each of these three groups received a different amount of money in either grants or loans for different levels of repairs and maintenance aimed at reducing lead within the house.¹⁰⁷ Groups four and five consisted of houses that were already lead abated or houses that were built after 1980 when lead paint was no longer used.¹⁰⁸

The subjects enrolled in the study were the children of the families that rented the homes. Some of the children were already living in the homes included in the study, but importantly, some of the families moved to the houses during the study because participation in the study allowed the properties to enter the rental market.¹⁰⁹ Investigators recruited families with young children to occupy the homes. Parents permitted their children to participate in the study and agreed to submit them to as many as eight or nine blood tests within the following two years, to allow their homes to be tested for lead periodically over that time period and to answer questionnaires.¹¹⁰

The Johns Hopkins University Joint Committee on Clinical Investigations, the institution's IRB, initially questioned whether the use of healthy control subjects in non lead-paint homes was permissible under the federal regulations

103. *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 819 (Md. 2001). See also Hazel Glenn Beh, *The Role of Institutional Review Boards in Protecting Human Subjects: Are We Really Ready to Fix a Broken System?*, 26 LAW & PSYCHOL. REV. 1, 4 (2002).

104. Beh, *supra* note 103, at 4.

105. *Id.* at 5-6.

106. *Id.* at 5.

107. *Id.*

108. *Id.* at 5-6.

109. *Id.* Landlords participating in the study attempted to rent to families with young children and in return, KKI helped the landlords apply for grants for lead abatement. *Id.* at 7.

110. *Id.* at 7.

given that there was no real therapeutic benefit to these control subjects (and therefore, the intervention could not be categorized under section 405).¹¹¹ The IRB therefore suggested that the consent form be changed to identify some additional benefits that all subjects would receive by participating in the study.¹¹² The IRB also wanted the consent form to indicate that the control group was being studied to determine the amount of lead exposure these children would have outside the house, and therefore, these children would also receive some benefit from the study interventions.¹¹³

Two of the families in the study later sued KKI when their children were found to have increased levels of lead.¹¹⁴ The families alleged that KKI discovered lead hazards in their respective homes and, despite having a duty to notify them, failed to warn in a timely manner or otherwise act to prevent the children's exposure to the known presence of lead.¹¹⁵ Additionally, they alleged that they were not fully informed of the risks of the research.¹¹⁶ The trial court in Baltimore granted summary judgment in favor of KKI on the ground that KKI did not owe a legal duty to the plaintiffs to warn them of the presence of lead dust but the appellate court vacated the lower court's ruling and remanded for a trial.¹¹⁷ Although the appellate court determined that KKI may have owed a legal duty to the plaintiffs and that therefore summary judgment was improper, the appellate court overstepped the limited question presented by the case and made several statements in its opinion that are not in accordance with a reasonable interpretation of the federal regulations.

From the facts available to the appellate court, it does appear that KKI's protocol violated several of the federal regulations as well as basic ethical norms. Some of the more egregious errors included: (1) enticing healthy controls to move into lead-exposed housing (violation of section 404 because lead exposure is more than minimal risk);¹¹⁸ (2) rephrasing the protocol (at the IRB's suggestion) so that healthy controls in groups four and five were supposed to obtain some benefit from the interventions even though it seemed unlikely that they were being exposed to

111. The IRB failed to appreciate that the control arms (houses without lead) did not pose greater than minimal risk to the subjects and therefore was justifiable under § 404. Furthermore, if all the children are viewed as being "at-risk" for lead exposure, then the subjects in the control arms, having been removed from lead risks in the home, did benefit from the intervention. See Lainie Friedman Ross, *In Defense of the Hopkins Lead Abatement Studies*, 30 J.L. MED & ETHICS 50, 52 (2002).

112. Beh, *supra* note 103, at 8.

113. *Id.*

114. *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 818 (Md. 2001).

115. *Id.*

116. *Id.*

117. *Id.* at 818, 858.

118. *Id.* at 849. Even if being "at-risk" of lead poisoning qualifies as a "condition or disorder," § 45.406 may have been violated because the risk of living in lead contaminated housing may be more than minor increase over minimal risk.

lead outside the home (this was simply a disingenuous representation of the study); (3) inadequate consent forms (violation of requirements for informed consent in section 46.116); and (4) a several month delay in reporting the lead levels to the families (violation of a promise made by KKI to the subjects). Although these violations of the federal regulations and unethical acts can hardly be excused, it is important to note that the *Grimes* Court also erred in several respects.¹¹⁹

The Court made the pervasive mistake of classifying the research into “therapeutic” and “non-therapeutic” categories and deeming the research study to be “non-therapeutic.” By adopting the “package deal” the court denied that any of the interventions could have a direct benefit to any of the subjects. This in fact was not the case. The children who were already living in the houses with high lead levels did receive direct benefit by obtaining a degree of lead abatement in their houses.¹²⁰ The Court stated: “We hold that in Maryland, a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or studies in which there is any risk of injury or damage to the health of the subject.”¹²¹ The Court later explained this statement by insisting that it meant “minimal risk” when it stated “any risk,”¹²² but even given this clarification, the Court seemed to permit only section 404 research and completely deny section 405 research, primarily because it rejected the entire protocol instead of weighing the interventions’ potential benefits against the risks. The Court disregarded the permissibility of approving non-beneficial procedures according to section 405.

In other words, if the protocol had included only houses that *already* had children living in them, every child in the three intervention groups would have received some benefit from being part of the trial because their lead exposure was likely to decrease, and therefore, the trial should have been deemed acceptable under section 405. Furthermore, the children in groups four and five would not be subjected to the risk of lead and only required to have periodic venipunctures, an intervention that, while not directly beneficial, poses only minimal risk and falls

119. *Id.* at 860 (Raker, J., concurring in result only). Judge Raker stated:

I cannot join in the majority’s sweeping factual determinations that . . . Institutional Review Boards are not sufficiently objective to regulate the ethics of experimental research; that it is never in the best interest of any child to be placed in a nontherapeutic research study that might be hazardous to the child’s health; that there was no therapeutic value in the research for the child subjects involved; that the research did not comply with applicable regulations; or that there was more than a minimal risk involved in this study.

Id.

120. In fact, the partial lead abatement interventions were so effective that the program has been replicated in 13 other cities. Robert M. Nelson, *Nontherapeutic Research, Minimal Risk, and the Kennedy Krieger Lead Abatement Study*, IRB: ETHICS & HUM. RES., Nov.-Dec. 2001, at 7.

121. *Grimes*, 782 A.2d at 858.

122. Ross, *supra* note 111, at 51.

under the category of procedures that are approvable under section 404. From the statements made by the *Grimes* Court, however, it appears that the Court would not accept even this limited study because the continued exposure to some lead for the intervention groups was more than a minimal risk. One might object to this more limited study because the children in the intervention groups are not receiving fully lead abated houses, but similar to the short-course AZT trials, this population of children does not have realistic access to fully lead abated houses, so certainly to help them a little is better than not to help at all. Unfortunately, the *Grimes* Court overstepped the limited question presented to it, and its opinion, taken to its fullest, would not permit even this hypothetical study where no children are actively recruited to live in lead contaminated houses.¹²³

The *Grimes* opinion should raise warning bells. If the federal regulations are not explicated further, either in the federal regulations themselves, or by an authoritative governmental body, mistakes in interpretation will lead to results not intended by the National Commission or the drafters of the regulations.

D. Section 406: Interventions with No Prospect of Direct Benefit to Subject

The third category involves interventions or procedures with no prospect of direct benefit to the subject. For these types of studies, the intervention must present only a minor increase over minimal risk to the subject, and the study must be likely to yield knowledge about the child's disorder or condition that is of vital importance for understanding or ameliorating the disorder or condition. Furthermore, the intervention or procedure must present experiences to the subjects that are reasonably commensurate with those experiences inherent to their actual or expected medical, dental, psychological, social, or educational situations.¹²⁴ The commensurability requirement exists because children who have had a particular intervention previously are better able to understand what is being asked of them, and therefore, their assent to participate in the study will be better informed.¹²⁵ The questions of what constitutes a "minor increase" above minimal risk, and what is meant by "disorder or condition" and "reasonably commensurate" have produced considerable disagreement and serve as another source of differing interpretations of the regulations.

A research protocol that might fall within this category is a trial that takes a child with leukemia and subjects him or her to one additional bone marrow

123. This is an important distinction that sets this study apart from the Willowbrook studies. Even if the prevalence of lead-tainted houses in the Baltimore area were 85%, it would not be permissible to actively rent previously empty houses in the study to families with children. This is analogous to the situation in Willowbrook where the children living in the house had an 85% risk of contracting hepatitis. The high baseline risk does not give the researchers the right to turn a high risk into a definite risk (either living in a lead contaminated house or contracting hepatitis) for a particular child.

124. 45 C.F.R. § 46.406 (2004), *infra* at 314.

125. LEVINE, *supra* note 8, at 248.

aspirate in order to obtain information about the disease course, but the information is not intended to benefit this particular child. It is imaginable that the child with leukemia has already had a bone marrow aspirate and that another aspirate would be reasonably commensurate with her actual experience so that if she assents to participate, her assent is more informed than a child who has never experienced a bone marrow aspirate. Furthermore, it is imaginable that such a research study could be designed to yield generalizable knowledge about leukemia that is of vital importance for its amelioration, and, therefore, such a trial would fulfill the requirements set by section 406. In this hypothetical case, one additional bone marrow aspirate is viewed as only a minor increase over minimal risk, but what if the protocol called for two? Three? Ten? When does the protocol exceed the threshold? Some might argue that it is not possible to set a threshold – that it is an instinctual “gut feeling” that causes reviewers to know when the limit has been exceeded. But surely this type of “I know it when I see it” standard that the Supreme Court has used for recognizing pornography cannot be invoked when errors in judgment potentially expose children to real danger.¹²⁶ IRBs would be hard pressed to find a public willing to accept such a subjective interpretation of section 406.

1. Defining Minor Increase

The *NHRPAC Children's Workgroup Report* provided some insight into the definition of "minor increase over minimal risk." The group concluded that minimal risk itself should be an absolute standard but that minor increase over minimal risk is a relative standard. It acknowledged that the concept of commensurability is crucial to allow the child and parents to have a point of reference from which to make their decision about participation. The Workgroup report included lists of specific interventions and how they thought those interventions should be classified. (See Tables 3 and 4) Nevertheless, these recommendations are not universally agreed upon and local IRBs will differ on their decisions of whether a particular research protocol is acceptable or not. Some examples of what has been approved by Yale's IRB as presenting minor increases above minimal risk include bone marrow aspirations in children with leukemia, single additional spinal taps in adolescents who have already had at least one for a neurological disorder, and administration of yohimbine in order to gain information about the pathogenesis of a neurological disorder. This IRB rejected a proposal to do left heart catheterizations on children at risk for the development of cardiac hemosiderosis.¹²⁷

126. *Jacobellis v. Ohio*, 378 U.S. 184, 197 (1964) (Stewart, J., concurring).

127. LEVINE, *supra* note 8, at 249.

TABLE 3: COMMON PROCEDURES AND CATEGORY OF RISK¹²⁸

| PROCEDURE* | MINIMAL RISK | MINOR INCREASE OVER MINIMAL | MORE THAN A MINOR INCREASE OVER MINIMAL |
|--|--------------|-----------------------------|---|
| Routine history taking | X | | |
| Venipuncture/fingerstick/heelstick | X | | |
| Urine collection via bag | X | | |
| Urine collection via catheter | | X | |
| Urine collection via suprapubic tap | | | X |
| Chest xray | X | | |
| Bone density test | X | | |
| Wrist xray for bone age | X | | |
| Lumbar puncture | | X | |
| Collection of saliva | X | | |
| Collection of small sample of hair | X | | |
| Vision testing | X | | |
| Hearing testing | X | | |
| Complete neurological exam | X | | |
| Oral glucose tolerance test | X | | |
| Skin punch biopsy w/topical pain relief | | X | |
| Bone marrow aspirate w/topical pain relief | | X | |
| Organ biopsy | | | X |
| Standard psychological tests | X | | |
| Classroom observation | X | | |

* The category of risk is for a single procedure. Multiple or repetitive procedures are likely to affect the level of risk.

128. WORKGROUP REPORT, *supra* note 95, at 5-6.

TABLE 4: INTERPRETING LEVEL OF RISK IN COMMON PROCEDURES¹²⁹

| PROCEDURE | DETERMINANTS OF LEVEL OF RISK |
|---|--|
| Indwelling heparin lock catheter | The level of risk may range from minimal to more than a minor increase over minimal depending on: age of the child, length of time catheter will be in place, number and volume of samples, and setting of the research |
| Single SC or IM injection | The level of risk of a single injection may range from minimal to more than a minor increase over minimal depending on the substance injected |
| Nasogastric tube insertion | Generally minor increase over minimal risk but should be commensurate with prior experience of the child in order to provide adequate assent and permission |
| Small amount of additional tissue obtained at surgery | Generally minor increase over minimal risk but must take into account any increased operative time, the specific organ or tissue, and the likelihood of bleeding and infection |
| MRI | If no sedation – generally minimal If procedural sedation – generally minor increase over minimal. Intubation in the appropriate setting may decrease potential risks for certain children and its possible use should be considered on a case by case and proposal by proposal basis |
| Psychological test /survey/interview/ observation | Generally minimal if performed under standardized conditions but the level of risk may increase depending on the sensitive nature of questions, the possibility to trigger unpleasant memories or emotions, and the length of the instrument or observation |

One of the problems with the section 406 requirements is that it is very difficult, if not impossible, to generate any control data with healthy children for these types of studies. In the leukemia example above, it would not be permissible to subject a healthy child to a bone marrow aspirate because it is a procedure that is not reasonably commensurate with the child's actual or expected situation. Furthermore, section 406 presupposes a clear line between a child with a disease and a child who is healthy. As was demonstrated through the examples for section 405 research, the line is not always well demarcated because the more "at-risk" a

129. *Id.* at 7.

population is, the more it may be considered unhealthy. In fact, the NHRPAC Workgroup defined the concept of “disorder or condition” rather broadly:

We interpret the concept of disorder or condition as relating to a specific characteristic which describes a group of children, a physical, social, psychological, or neuro-developmental condition affecting children, or the risk of certain children developing a disease in the future based on diagnostic testing or physical examination. Thus, for example, prematurity, infancy, adolescence, poverty, living in a compromised physical environment, institutionalization, or having a genetic predisposition to future illness are some of the disorders or conditions of children that can, under the appropriate circumstances, warrant permissible research that presents levels of risks that are a minor increase over minimal without the prospect of direct benefit.¹³⁰

The NHRPAC definition, therefore, seems to classify the *risk of developing* a disease as a disorder and consequently widely broadens this category of research. One might wonder, then, if the NHRPAC Workgroup would permit children in the lead abatement study who have normal lead levels, but are *at risk* for developing lead poisoning simply because they lived in an area of Baltimore where the prevalence of living in a lead-tainted home is very high, to be enrolled in a lead abatement study that presented a minor increase over minimal risk without any intervention that could provide direct benefit to the subjects (i.e. the recruitment of children from the area to move into the homes participating in the study).

The Workgroup provided an example of children who have a predisposition to diabetes because of obesity being enrolled in a study that used various procedures to assess insulin resistance.¹³¹ Although the risks posed by the interventions would not be minimal because they are greater than those risks normal, healthy children encounter, the study could be approved under section 406 because the interventions posed only a minor increase over minimal risk, the study would be likely to yield generalizable knowledge of vital importance about the development of diabetes or pathophysiology of obesity, the interventions performed were commensurate with the expected experience of the subjects, and the site for the study and skill of the investigator were appropriate. The NHRPAC Workgroup meant to define disorder or condition more concretely, but their example reveals how the line between healthy children and children with disorders or conditions is very difficult to draw. For example, are children with a body mass index in the ninety-fourth percentile at risk for diabetes and therefore qualify as having a “condition”?¹³² What definition of obesity should be used? When do

130. *Id.* at 3.

131. *Id.* at 7. *But cf. infra* notes 133-34 and accompanying text.

132. The current definition for obesity in children is being above the ninety-fifth percentile of body mass index. A body mass index that is between the eighty-fifth and ninety-fifth percentile is considered

healthy populations become “at-risk”? The NHRPAC Workgroup’s expansive definition of condition or disorder will definitely engender debate, but certainly such a definition does allow access to more control data, as the “at-risk” children can serve as “control” subjects in many studies. It is important to recognize that as the NHRPAC Workgroup’s definition makes research using “control” subjects easier, it does so at the expense of the commensurability safeguard, because these children are less likely to fully understand whether the intervention in the protocol is similar to an actual or expected situation.

Stephanie Amiel, a Yale pediatric endocrinologist studying diabetes, completed a study in which “normal controls” were admitted for a 48-hour hospital stay in order to allow a 24-hour blood hormone level profile through an intravenous cannula, plus a 4-hour hormone sensitivity test through an additional intravenous cannula.¹³³ This study could not be justified as presenting no more than minimal risk because the psychological effects of a two-day hospital stay were unknown.¹³⁴ The “normal controls” were actually siblings of diabetic children and were judged to have a “condition or disorder,” thereby permitting review under section 406. The Yale IRB approved the study under section 406 because it presented only a minor increase above minimal risk. In retrospect, the only harm actually suffered by the control subjects seems to have been uncomfortable IV sites and boredom, so perhaps the study could have in fact been approved under section 404 as causing no more than minimal risk. However, at the time approval was sought the risks could not have been so easily calculated.

In contrast, the National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH), began a study to determine population differences in insulin sensitivity, resting energy expenditure, and body composition of obese children and children of obese parents in 1996, which was subsequently terminated by the OHRP in 2000.¹³⁵ The trial had enrolled over 190 children aged six to ten before it was terminated.¹³⁶ The investigators had planned to follow the children for fifteen years and collect blood samples, radiographs, and magnetic resonance imaging scans, all of which were considered to be minimal risk by the original review board that approved the study.¹³⁷ Four years later, however, the OHRP stated that the interventions posed

overweight.. For more information, see WEBMD, HEALTH GUIDE A-Z, OBESITY: TOPIC OVERVIEW (2005), at http://my.webmd.com/hw/weight_control/hw252867.asp (last visited June 28, 2005).

133. Stephanie A. Amiel, *Pediatric Research on Diabetes: The Problem of Hospitalizing Youthful Subjects*, IRB: A REV. OF HUM. SUBJECTS RES., Jan.-Feb. 1985, at 4.

134. LEVINE, *supra* note 8, at 249.

135. Letter from Michael A. Carome, Director, Div. of Compliance Oversight, U.S. Dep’t of Health and Human Servs., to Michael M. Gottesman, Deputy Director for Intramural Research, Nat’l Insts. of Health (Nov. 3, 2000), http://www.hhs.gov/ohrp/detrm_lets/nov00a.pdf (last visited June 28, 2005).

136. Eliot Marshall, *Enforcers Halt NIH Study Called Less Risky Than Outdoor Play*, 290 SCIENCE 1281, 1281 (2000).

137. *Id.*

more than minimal risk,¹³⁸ did not present the prospect of direct benefit to the subjects, and therefore could not be approved under section 404 or section 405, respectively. Furthermore, it concluded that “these [non-obese healthy children] do not have a disorder or condition,” many of the interventions and procedures were not reasonably commensurate with those inherent in their actual or expected situations, and the risks exceeded a minor increase over minimal risk; therefore the study also could not be approved under section 406.¹³⁹ The OHRP recommended that section 407 approval be sought and later terminated the trial.¹⁴⁰

The differences between the Amiel study and NICHD study seem slight, yet the outcomes are quite dissimilar. Why do the siblings of diabetic children qualify as having a “disease or condition” (and therefore obtain section 406 review) but the non-obese children of obese parents do not? The siblings of the diabetic patients have a higher risk of developing diabetes than the general population, but the same could be argued for the non-obese children. Did the Yale IRB or the OHRP look at empirical evidence to determine how “at-risk” these children were in their determination of what qualifies as a “condition or disorder”? It seems unlikely given that it is questionable whether such data exists. Neither the Yale IRB nor the OHRP elucidated the definition of “disease or condition” on which they relied, yet the difference in the outcomes hinges on these words.¹⁴¹ Once again, it is obvious that reasonable people can and do interpret the federal regulations differently and create drastically different end results.

E. Section 407: Research Not Otherwise Approvable

Finally, the last category outlined in Subpart D involves research that would not be approvable under any of the aforementioned categories. In such cases, if the IRB finds that the research presents a “reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children,” then the Secretary of the DHHS may consult with a panel of experts, provide an opportunity for public review and comment, and then possibly approve the research.¹⁴² The Secretary can find the protocol acceptable by finding either that the research actually does satisfy the conditions of sections 404, 405, or 406, or that the research (1) presents a reasonable opportunity to

138. *Id.* The specific intervention that posed more than minimal risk was a “clamp” study that required an overnight stay in the hospital with the insertion of two intravenous catheters so that insulin and sugar could be infused while taking blood samples. The study would manipulate each child’s blood sugar between 80-200 mg/dL and measure the child’s response. *Id.*

139. Letter from Michael A. Carome, *supra* note 135, at 5.

140. *Id.* at 6.

141. Although one could argue that even if the non-obese children were said to have a “condition or disorder” the interventions posed more than a minor increase over minimal risk and still would not meet the requirements of section 406. 45 C.F.R. § 46.406(a) (2004), *infra* at 314.

142. 45 C.F.R. § 46.407, *infra* at 314-15.

further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (2) will be conducted in accordance with sound ethical principles; and (3) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in section 46.407.¹⁴³ Although this category has been used to permit research with children infrequently, the OHRP lists six protocols as currently under section 407 review.¹⁴⁴

In 1989, Prentice et al. published a description of a case that could not be approved under sections 404, 405, and 406, and which also was not suitable for section 407.¹⁴⁵ The protocol was designed, in part, to determine whether a biosynthetic growth hormone could promote linear growth in children suffering from Turner Syndrome.¹⁴⁶ The control arm of the study was to receive placebo injections three times per week, plus routine blood and urine exams, and radiographs of the hands and wrists every six months to measure bone age.¹⁴⁷ The multiple injections each week and the radiological examinations were judged to present more than minimal risk to the subjects, so the protocol could not meet section 404 approval.¹⁴⁸ Furthermore, there was no firm evidence to support the possibility that the placebo group would receive direct benefit from the injections under the hypothesis that stress induces the release of natural growth hormone, so the protocol could not satisfy section 405. The protocol did not meet section 406 approval because the placebo group would miss the opportunity to be treated with available alternatives, such as different types of biosynthetic growth hormone, estrogens, or androgens, posed *more than* a minor increase over minimal risk. The multiple injections over eighteen months was not commensurate with the actual or expected medical treatment of a patient with Turner syndrome; and, the research would not yield generalizable knowledge about Turner syndrome of vital importance for developing methods of treatment because there was no evidence to show that the drug being tested would be any better than another biosynthetic drug already being studied for the same purpose.¹⁴⁹ Finally, the IRB decided that the protocol did not even qualify for section 407 review because they did not think short stature was a "serious" enough condition to warrant attempting to get section

143. *Id.*

144. U.S. DEP'T HEALTH & HUMAN SERVS., OFFICE FOR HUMAN RESEARCH PROTS. (OHRP), SPECIAL PROTECTIONS FOR CHILDREN AS RESEARCH PARTICIPANTS (2004), <http://www.hhs.gov/ohrp/children/> (last visited June 28, 2005).

145. Ernest D. Prentice et al., *Can Children Be Enrolled in a Placebo-Controlled Randomized Clinical Trial of Synthetic Growth Hormone?*, IRB: A REV. OF HUM. SUBJECTS RES., Jan.-Feb. 1989, at 6-9.

146. *Id.* at 6. Turner Syndrome is an anomaly of the chromosomes whose characteristics include short stature, webbed neck, infantile sexual development, and amenorrhea. The vast majority of children with Turner Syndrome become significantly short adults. *Id.*

147. *Id.*

148. *Id.* at 7.

149. *Id.* at 8-9.

407 approval.¹⁵⁰ Interestingly, several years later, similar studies involving the use of growth hormone in children with Turner syndrome or idiopathic short stature were presented to an expert panel for section 407 review.¹⁵¹ The studies were designed as a double-blind randomized control with half the children receiving human growth hormone (hGH) and the other half receiving placebo injections three times per week for four to seven years.¹⁵² Although the nine-member panel disagreed about the risks involved with the study, in the end there was only one member of the panel who thought the study could not be justified.¹⁵³ The differences in the study described by Prentice and these more recent studies seem slight, yet the latter was permitted under section 407 review and the earlier one was not even able to receive section 407 review. There may have been evolving thought over what constitutes a “serious” problem, but the evidence once again points to the fact that reasonable people serving on different IRBs, facing similar protocols, can reach very different results.¹⁵⁴

An example of a study recently approved under section 407 was a protocol entitled, “Precursors to Diabetes in Japanese American Youth.”¹⁵⁵ Three hundred children of Japanese ancestry and 150 Caucasian children would undergo several routine examinations plus have blood drawn by venipuncture, intravenous glucose tolerance tests, measurement of body composition by Dual X-ray Absorptiometry (DEXA), and intra-abdominal fat determination by Magnetic Resonance Imaging (MRI).¹⁵⁶ None of the interventions had the prospect of direct benefit to the children, and several of these interventions were thought to involve more than minimal risk. Nevertheless, the majority of the reviewing experts found that the study could be approved under section 407 with the condition that the protocol and consent forms be modified to further reduce the risks to the subjects.¹⁵⁷ The experts found that the study could be approved because it presented a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health and welfare of children.¹⁵⁸

150. *Id.* at 9.

151. Kopelman, *supra* note 90, at 755. Importantly, hGH was already the standard of care for Turner Syndrome. *Id.*

152. *Id.*

153. *Id.* Kopelman served as one of the co-chairs of the review panel and was the only dissenting member.

154. For an interesting discussion of whether a similar trial is ethically permissible involving children with very short stature and not Turner’s Syndrome, see Carol A. Tauer, *The NIH Trials of Growth Hormone for Short Stature*, IRB: A REV. OF HUM. SUBJECTS RES., May-June 1994, at 1-9.

155. Report on Expert Panel Review Under Subpart D of 45 CFR 46: *Precursors to Diabetes in Japanese American Youth*, <http://www.hhs.gov/ohrp/pdjay/expert.htm> (last visited June 28, 2005).

156. *Id.* at 2-3.

157. *Id.* at 3-4.

158. *See id.* at 4. This reasoning implies that the NICHD study would have received section 46.407 approval as well. *See supra* notes 135-40 and accompanying text.

Some argue that this last category of research should be proscribed altogether. Lainie Friedman Ross asserts that research in this category is entirely immoral and that “the decision to balance the well-being of a particular child against the possibility of significant societal benefit is a utilitarian calculus which fails to respect the developing personhood of the individual child.”¹⁵⁹ Ross, however, is too quick to equate a utilitarian analysis with evil when, in fact, most research ethics entail justification according to a utilitarian analysis. It is equally possible to imagine a child who wants to participate in a research trial that has no component which is physically beneficial to him, but one where his psychological well-being is increased because his participation in a study may help alleviate a serious problem affecting children.¹⁶⁰ To prevent such a child from participating in a trial may just as easily fail to respect that child’s developing personhood. The onus is on the researcher to carefully assess whether the benefits to the child outweigh the risks, but the lack of physical benefits should not preclude this analysis. For example, a trial that involves multiple daily painful procedures for the healthy control group but has the potential benefit of alleviating a severe illness for the children in the intervention arms may be considered by a healthy child to be a worthwhile sacrifice to make for the benefit of others. A utilitarian calculus can just as easily take this into account and conclude that section 407 offers reasonable safeguards for the welfare of children in these studies.

By devising four categories of risk, the federal regulations sought to provide a level of protection for children proportionate to the level of risk to which they are exposed. Nevertheless, although the regulations seek to provide guidance to IRBs about the acceptability of research protocols, the language used in the regulations, including “minor increase,” “reasonably commensurate,” “disorder or condition,” and “serious problem,” are sufficiently vague so as to create a battleground over how to define these terms. Even the relatively well-defined term of “minimal risk” lends itself to multiple interpretations. Although some of these words have reached consensus meanings eventually, not all have done so. The definitional ambiguities leave an incredible amount of power in the hands of the IRBs. How can we ensure IRBs will apply consistent interpretations of the definitions and generate results that reflect the commitment to the principles of respect for persons, beneficence and justice? How can courts be better informed when facing cases involving children as research subjects so that they do not commit the same mistakes the *Grimes* Court made and produce large discrepancies between IRB decisions and court decisions? One possible mechanism for improvement is to restructure the IRB system.

159. 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, 167 (1997).

160. This very argument has been used to permit children to donate kidneys to their siblings or undergo bone marrow transplant. Lederer & Grodin, *supra* note 1, at 106-9.

PART IV: RECOMMENDATIONS FOR CHANGE

Disagreements over which interventions pose minimal risk or minor increase over minimal risk exist among experts in the field and among members of IRBs. In 1981, empirical work by Janofsky and Starfield found significant differences among pediatric experts about how to assess the risks of a venous blood draw, arterial puncture, and gastric and intestinal intubation.¹⁶¹ They concluded that the variability in risk assessment by those surveyed suggested that their judgments were based on an inadequate body of knowledge.¹⁶² In 1982, Goldman and Katz published a controversial study of IRBs that concluded that there were significant inconsistencies in both the application of the federal regulations among many IRBs and in the application of ethical, methodological, and informed-consent standards within individual IRBs.¹⁶³ The researchers gave three imperfect protocols to different IRBs to determine whether the boards would identify the ethical, methodological, and consent form flaws and how they would address these defects.¹⁶⁴ Goldman and Katz reported that IRBs neglected to make the appropriate objections to the protocols and that there were internal inconsistencies that indicated failures of the individual IRBs.¹⁶⁵ Levine responded to the study by explaining why the Goldman-Katz protocols may have received substandard review compared to most of the protocols presented to the Yale IRB.¹⁶⁶ He reported that the Goldman-Katz protocols did not make proper use of the primary reviewer system upon which Yale's system relies.¹⁶⁷ Furthermore, the protocols did not go through a second review after initial revisions were recommended, thereby eliminating the opportunity to identify additional problems with the protocols. Additionally, Goldman and Katz did not recognize some of the ethical objections made by the Yale IRB and report them correctly.¹⁶⁸ Given Levine's critique, one could assume that similar types of problems may have occurred with the other IRBs that Goldman and Katz investigated.

Although the Goldman and Katz study definitely had flaws, there is no denying that different IRBs do not always come to the same conclusion about the

161. Jeffrey Janofsky & Barbara Starfield, *Assessment of Risk in Research on Children*, 98 J. PEDIATRICS 842, 844-45 (1981).

162. *Id.* at 845.

163. Jerry Goldman & Martin D. Katz, *Inconsistency and Institutional Review Boards*, 248 JAMA 197, 200 (1982).

164. *Id.* at 197.

165. *Id.* at 198-201.

166. Robert J. Levine, *Inconsistency and IRBs: Flaws in the Goldman-Katz Study*, IRB: A REV. OF HUM. SUBJECTS RES., Jan.-Feb. 1984, 4-8.

167. *Id.* at 4.

168. *Id.* at 5; see also Gregory J. Hayes et al., *A Survey of University Institutional Review Boards: Characteristics, Policies, and Procedures*, IRB: A REV. OF HUM. SUBJECTS RES., May-June 1995, at 4. Hayes points to several problems with IRBs including lack of membership diversity, inadequate expertise, observer drift, lack of an evaluation process and groupthink. *Id.* at 4-5.

acceptability of a study.¹⁶⁹ Furthermore, as the discussion of terms such as "minimal risk," "minor increase over minimal risk," and "disease or condition" in Part III reflects, IRBs continue to interpret these concepts differently because they are difficult concepts to grasp from the outset. Even though the federal regulations attempt to divide research protocols into four categories of risk and require additional protections for children as the risks increase, the regulations obviously have not created a simple framework that will always consistently be applied among different IRBs and within any particular IRB. While perfect consistency may be an unattainable goal, given the importance of protecting human subjects equally, it is certainly a defensible goal.

The NHRPAC's Children's Working Group recognized several problems with the interpretation of the current regulations governing clinical research involving children. The group, however, concluded that the regulations do not need revision but require clarification. The group is currently soliciting members of research institutions to submit examples of research protocol that would be approved under sections 404, 405, and 406.¹⁷⁰ They plan to make the report widely available to other advisory committees currently considering the issue of protection for children in research.¹⁷¹ Although the Working Group efforts should be applauded, their report is unlikely to provide long-term solutions to the problems of variable interpretation of words and inconsistent application of the regulations because it is difficult to anticipate the ethical problems that future protocols will pose.

The current system relies heavily on IRBs to perform efficiently and appropriately. IRBs are required to review fundable federal grant proposals involving human subjects, and all FDA regulated research, as well as most other research involving human subjects to the extent specified in their institutions' Federal Wide Assurances.¹⁷² Additionally, IRBs must determine adequacy of consent forms and conduct at least annual review of ongoing studies.¹⁷³ Some have argued that the increasing number and complexity of multicentered randomized clinical trials overtax IRBs.¹⁷⁴ Others have argued that the real problem is that IRBs are weighed down with tedious, low-yield, time-consuming

169. See *supra* text accompanying notes 133-141.

170. Andrew Kessler, *Behavioral Science Working Group Looks at IRB Regulations*, APS OBSERVER (Am. Psychological Society), Dec., 2001, <http://www.psychologicalscience.org/observer/1201/irb.html> (last visited June 28, 2005).

171. *Id.*

172. See generally *Assuring Compliance with this Policy – Research Conducted or Supported by any Federal Department or Agency*, 45 C.F.R. § 46.103 (2004), *infra* 323-25 (discussion of requirements for assurances).

173. IRB Review of Research, 45 C.F.R. § 46.109 (2004), *infra* 326-27.

174. See William J. Burman et al., *Breaking the Camel's Back: Multicenter Clinical Trials and Local Institutional Review Boards*, 134 ANN. INTERNAL MED. 152, 154-55 (2001) (arguing that involvement of local IRBs in all aspects of multicenter clinical trials may overload the system).

tasks.¹⁷⁵ Further criticism of the entire system is that the dependence on IRBs yields inconsistent results.

Mashaw wrote that if an IRB is to “do its core job well, we must live with its inevitable incompetence at other tasks. Moreover, we must also live with the rather vague regulatory standards and with the continuing inability of the Federal funding agencies to know for sure whether IRBs are functioning effectively.”¹⁷⁶ True, maybe the current scheme imposes too many demands on the local IRBs, but instead of accepting the weaknesses in the system, perhaps a different system is needed.

One way to establish clarification of the current regulations *and* create a system that will encourage greater consistency while maintaining some flexibility is to change the review board system. A restructured system that distributes duties within a regulatory hierarchy will help solve the current problems and, perhaps more importantly, provide a long-term solution by establishing a *permanent process* by which to address new issues as they arise. Although the proposal that follows discusses only the federal regulations involving children, one might imagine a system where all protocols involving human subjects are able to use the restructured review board system.

A. A Proposal to Restructure the Review Board System:

A new review board system will preserve the local IRBs and create twelve Regional Review Boards (RRBs) and one National Review Board (NRB). The system will use a hierarchical structure that is similar to the federal court system. (See Figure 1.) The structure will include local IRBs with their current membership, but their duties will be slightly different. The local IRBs will continue to review protocols as required by section 46.108 and section 46.109, except that under certain circumstances, they will have the discretion or the requirement of forwarding protocols to their RRB. Although minimal risk protocols are generally easy to spot, those protocols that do not clearly fall under section 404 review can be forwarded, at the discretion of the local IRB, for regional review. Furthermore, protocols that are reviewed under section 405 or section 406 and are contentious with regard to what level of risk exists must be forwarded to the RRB. Those that are contentious will include protocols where there is disagreement between IRB members over how to classify the risks of the interventions and procedures, and where no precedent exists for approving or

175. See Robert J. Levine, Editorial, *Institutional Review Boards: A Crisis in Confidence*, 134 ANN. INTERNAL MED. 161 (2001) (discussing effectiveness of IRBs).

176. See LEVINE *supra* note 8, at 327 (quoting Jerry L. Mashaw, *Thinking About Institutional Review Boards*, in THE PRESIDENTIAL COMM'N FOR THE STUDY OF ETHICAL PROBLEMS IN MED. AND BIOMEDICAL RES.: WHISTLEBLOWING IN BIOMEDICAL RESEARCH: POLICIES AND PROCEDURES FOR RESPONDING TO REPORTS OF MISCONDUCT 22 (1982)).

rejecting such a protocol. The precedent may exist from a protocol reviewed by that same local IRB, the appropriate RRB, or the NRB. These rules regarding what may be submitted for regional review should appropriately limit the number of cases that are sent to the RRB, but still allow a sufficient number to pass to the RRB so that it gains experience addressing these more difficult cases.

Finally, protocols that are determined to fall under section 407 review and previously required the assembly of an expert panel will now receive automatic NRB review. Section 407 will be amended to reflect that instead of asking the Secretary to consult with a panel of experts, the IRB will ask the Secretary to consult with the NRB to make a decision based on the remaining requirements of section 407. The NRB will function as the expert panel in these cases.

FIGURE 1: ANALOGOUS STRUCTURE OF FEDERAL COURTS AND PROPOSED REVIEW BOARDS



The intention behind enabling local IRBs to forward protocols to the RRBs is to: 1) remove the responsibility of defining ambiguous terms from the IRBs who have minimal time to devote to any one protocol; 2) encourage greater consistency between local IRBs in their applications of federal regulations by mandating that they look to precedents (including precedents from the regional and national levels) when making decisions; 3) reduce the likelihood of conflicts of interest and/or bias that can exist when local IRBs review their colleagues' proposals; and 4) decrease some of the time that local IRB members devote to reviewing difficult protocols. Accusations have been made that local IRB members often do not fully understand the nuances of the regulations, and therefore do not appropriately apply them.¹⁷⁷ This new regulatory structure removes the more sophisticated analyses

177. See Bette-Jane Crigger, *What Does It Mean to "Review" a Protocol?* *Johns Hopkins & OHRP, IRB: A REV. OF HUM. SUBJECTS RESEARCH*, July-Aug. 2001, at 13-15. During the OHRP investigation of the IRB system at Johns Hopkins University, the OHRP concluded that Hopkins failed to protect human subjects appropriately after the death of a healthy twenty-four year old woman in research

from the purview of local IRB members, who, despite a genuine interest in research ethics, may not have the time or desire for appropriate training or education in the field, and places them in the hands of a more qualified body.

In addition, investigators whose applications are denied at the local level will be permitted to appeal their protocols to the RRB for reconsideration. Because the RRB will meet less frequently than the local IRB, and thus there will likely be a delay before a decision is made, most investigators will be dissuaded from appealing their protocol unless they truly think it deserves another review. Given the current lack of the need for an appeals process at some institutions, it seems unlikely that this appellate function of the RRBs will be used very often, but its existence is still valuable.¹⁷⁸ Finally, the local IRBs should continue to work closely with local investigators, remain familiar with the local institutions, and educate themselves and others regarding research ethics. The local IRBs' unmatched experience with reviewing a large volume of protocols will enable them to best identify ambiguities in the regulations and problems with their application best and send protocols exemplifying these problems to the RRB level.

The RRBs will be organized and tailored to fit their charge. There will be twelve regional RRBs, each one serving a specific geographic jurisdiction, analogous to the federal Circuit Courts, and they should meet at least once a month. Membership of an RRB should consist of representatives from its local IRB constituents, but given the large number of local IRBs, a revolving membership is needed to ensure adequate representation, but manageable meetings and discussions. Each IRB may nominate one member to serve on the RRB. The RRB Chair will review all those nominated and assemble a board of twenty to thirty members that best reflect the constituents and meets the requirements of section 46.107. Furthermore, no more than one member from any local IRB may serve on the RRB. Membership should not exceed three years, and a revolving membership should create a system that allows different local IRBs to have a turn serving on the RRB. Large academic institutions with large numbers of research studies under review, however, may end up serving on their RRB continually, but a different representative from the institution should serve as the RRB member.

In addition, there should be at least one member of the RRB with full-time duties. This member will be responsible for writing a synopsis of the discussion and conclusion reached for the cases presented. The intention is that this will include a more detailed summary than just minutes of the meeting. It will be a sufficiently detailed synopsis that can serve as a precedent to which local IRBs can turn for future guidance on similar issues. These case summaries should be

designed to study asthma physiology. *Id.* at 13. OHRP concluded that the large volume of research overburdened IRB members and chairs and that members did not sufficiently understand the federal regulations. *Id.* at 15.

178. See LEVINE, *supra* note 8, at 341 (reporting that an appeals process at Yale ceased to exist because there were no requests for an appeal for over 15 years).

published and catalogued in a searchable database for easy access by IRBs, the NRB, and members of the public.

The RRB members will assume a higher degree of responsibility in understanding the federal regulations and research ethics. To that end, members will be required to undergo a well-structured, high-quality educational course. This is not to say that the local IRB members are absolved of the duty to be well-informed of the federal regulations and research ethics, but rather that a high-quality, time-consuming educational system will be easier to initiate with a smaller number of self-selected individuals who have a veritable interest in research ethics.¹⁷⁹ Perhaps such an education system could later be extended to local IRB members.

The charge to the RRBs will be to not only review the protocols sent by the local IRBs, but to clearly summarize the way in which they choose to define certain terms in the regulations. In other words, if the RRB decides that the child of obese parents qualifies as having a "condition," the RRB must identify how they reached that conclusion. If they relied on specific data to make a conclusion, that should be identified as well. Furthermore, they must be bound by their own precedents and those set by the NRB. This will ensure that their decisions are internally consistent and, ideally, promote consistency among the various IRBs within their jurisdiction. Because the members of the RRB will have a greater understanding of research ethics and the regulatory guidelines due to their education on the subjects, they will be in a better position to review these more difficult protocols. Furthermore, because they will not oversee the expedited review protocols or the minimal risk protocols, they should, ideally, have more time to dedicate to each of the protocols that comes before them for review. Finally, when the RRB members are unable to reach a consensus decision on a particular protocol, they will be permitted to send up to twenty percent of their protocols to the NRB.

Structurally, the benefit of having the RRBs follow the geographical boundaries of the federal circuit courts is that if there are legal suits filed against the investigators in any of these RRB-approved cases later, the district and circuit courts will be able to look at the RRB approval summary statement to gain a better understanding of why the protocol was approved. (See Table 5). Undoubtedly, the RRB opinion will not be binding on the court, but it can serve as expert opinion and evidence of what happened in the protocol review process. For example, under this new review board system the recruitment of children who were "at risk" of lead poisoning to live in partially lead-abated houses in the KKI protocol would have flagged the case to go to an RRB review because it would be debatable

179. *Cf. Levine, supra* note 175, at 162-63. Levine calls for an education system for all IRB staff and members. *Id.* at 162. He further reflects on adding an accreditation system for IRBs and a certification system for IRB staff. *Id.*

whether these children had a “condition or disorder.” If an RRB had granted approval, the *Grimes* Court could have used the RRB written report to help understand why the protocol was approved. One of the goals of creating a regional review system is that it may prevent the development of a discrepancy between the courts’ legally binding opinions and the institutional review board decisions. By providing the court system with a comprehensible, detailed summary of the discussion that occurred during review, the court will be better able to understand the issues at bar and hopefully will be less likely to overstep its bounds without regard to the consequences, as did the *Grimes* court.

TABLE 5: CIRCUIT COURT JURISDICTION¹⁸⁰

| Circuit Court | Geographical Jurisdiction |
|------------------------------|--|
| 1 st Circuit | Maine, Massachusetts, New Hampshire, Puerto Rico and Rhode Island |
| 2 nd Circuit | Connecticut, New York and Vermont |
| 3 rd Circuit | Delaware, New Jersey, Pennsylvania and Virgin Islands |
| 4 th Circuit | Maryland, North Carolina, South Carolina, Virginia and West Virginia |
| 5 th Circuit | District of the Canal Zone, Louisiana, Mississippi and Texas |
| 6 th Circuit | Kentucky, Michigan, Ohio and Tennessee |
| 7 th Circuit | Illinois, Indiana and Wisconsin |
| 8 th Circuit | Arkansas, Iowa, Minnesota, Missouri, Nebraska, North Dakota and South Dakota |
| 9 th Circuit | Alaska, Arizona, California, Guam, Hawaii, Idaho, Montana, Nevada, Oregon and Washington |
| 10 th Circuit | Colorado, Kansas, New Mexico, Oklahoma, Utah and Wyoming |
| 11 th Circuit | Alabama, Florida and Georgia |
| District of Columbia Circuit | District of Columbia |

Because members of the RRB will be drawn from several local IRBs and the proposals before them will be from a wide geographical area, the chances for a conflict of interest between a member of the RRB and a researcher asking for approval is significantly reduced. The RRB members will not be placed in the

180. See 28 U.S.C.A. § 41 (West 1993 & Supp. 2004) (defining the thirteen judicial circuits). There is also a Federal Circuit which has nationwide jurisdiction to hear appeals in patent law cases and cases decided by the Court of International Trade and the Court of Federal Claims. See 28 U.S.C.A. § 1295 (West 1993 & Supp. 2004) (defining the Federal Circuit).

position of having to reject the research of their colleagues while at the same time being fully aware that their own research needs IRB approval soon. A regional review system creates distance between the researcher and the approval process that removes local pressures and allows for a better, non-biased application of the federal regulations.¹⁸¹ Furthermore, because members would be from different IRBs, they will be encouraged to share information about the structure and effectiveness of their own IRB so that they may learn from one another.

Criticism launched against local IRBs has included the inability to police themselves appropriately. By having a second board review contentious protocols, the chances that the same biases or improper review processes will occur diminishes, and respect for the local IRB system should improve.¹⁸² Local IRBs that have received bad press in recent years will be better able to regain the trust of their local community if the community knows that an additional regional review may occur when the protocols involve procedures or interventions whose risks are not easily classified.

The National Review Board will consist of one member of each RRB and should meet at least four times a year. Additional members should include experts in different disciplines and segments of society, as is required by section 46.107, but total membership should not exceed twenty. Membership may be derived from large and small institutions, policymakers, ethicists, lawyers, patients, and advocates for vulnerable populations. Members will serve a maximum of five years in order to create an evolving board that keeps up with developing ethical understandings, changes in law, and advances in types of medical research. It will also prevent the members from becoming complacent in their duties. All members will be required to undergo extensive educational training on research ethics and the federal regulations similar to the RRB requirements for membership. NRB members should also have a thorough understanding of the OHRP, the history and reports of the various committees that have been formed to address human research issues (the National Commission, NHRPAC Workgroup, etc.), and why or why not these committees have been successful in carrying out their charges. The NRB should aspire to be the most successful of any of these bodies and draw upon the experiences of these prior committees.

The NRB's duties will be to review those protocols that the RRBs ask it to review, grant appellate review when an investigator has been denied at the IRB and

181. The *Grimes* Court claimed that such pressures were present in the Hopkins's IRB and contributed to the protocol being miscast as having beneficial components for the control groups. *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807, 817 (Md. 2001).

182. Note that the local IRBs are not entirely bypassed by this new system. They remain the initial reviewers and are able to decide when to send a protocol for RRB review. Cf. Robert J. Levine & Louis Lasagna, *Demystifying Central Review Boards: Current Options and Future Directions*, IRB: A REV. OF HUM. SUBJECTS RES., Nov.-Dec. 2000, at 1-2. In his discussion of Central Review Boards, Levine asserts that academically oriented IRBs are unlikely to delegate the entirety of their responsibilities to an off-site review board. *Id.*

RRB level (exceedingly rare),¹⁸³ and most importantly, draft memoranda that will clarify the language in the federal regulations.

In its case-review duties, the NRB will have access to the summary opinions from all twelve of the RRBs, plus a member from each RRB present at the meetings, and will be in the best position to apply consistent applications of the regulations. Because the NRB will have a substantially smaller caseload than the RRBs, it should have more than adequate time to spend on each case that it is asked to review. The NRB should strive to reach consensus opinions, but if this is not possible, at least a two-thirds majority should be required before a protocol can be approved. This condition admittedly will and should protect human subjects at the expense of limiting some important research. Similar to the RRB system, the NRB should write a clear summary opinion as to how and why it reached its conclusion. The NRB Chair will appoint a member of the NRB to write the opinion for a particular case, and members may write additional concurring or dissenting opinions if they wish.

The NRB will also serve as the “expert panel” for section 407 review. Because it will have representation from all around the country and members who are experts in the field, there should be no need to assemble a separate expert panel. Furthermore, the NRB will be knowledgeable about national practices and will ensure that the opinion is not out of line with current RRB and IRB decisions. Moreover, by requiring the NRB to address the most problematic protocols that raise the most difficult ethical issues, the NRB will begin to understand where the real sources of conflict lie and how to best address them. The remainder of section 407 will be unchanged and the opportunity to consult with additional experts and for public review and comment will still exist.

The most important function of the NRB will be to draft memoranda to clarify the current federal regulations and make suggestions to Congress regarding amendments to the regulations as needed. Through their case decisions, the NRB members will gain experience in defining terms such as “minimal risk,” “minor increase,” “reasonably commensurate,” and “disorder or condition.” Because they will have actual experience with cases that they examine during their case-review duties, they will be in a much better position to issue these memoranda than the NHRPAC Working Group, National Bioethics Advisory Committee, or any of the various other governmental bodies that have called for explication of the regulations. Much like a court that hears cases, the NRB will be able to see the practical effects of their decisions and therefore prevent interpretative mistakes that are made when one deals only with the theoretical application of the regulations.

Case-based ethical reasoning rather than purely theoretical reasoning will be far superior in balancing the advancement of medical research with the protection

183. Given that appeals to the NRB are likely to be rare, there should be no need for a certiorari process analogous to the United States Supreme Court.

of the rights and welfare of human subjects. The NRB actions will create nationwide impact, and therefore, if their decisions are viewed as gravely wrong, researchers will demand changes in the federal regulations. The NRB members can consult national experts and use their experience to suggest appropriate revisions to Congress. (See Table 6.)

TABLE 6: MEMBERSHIP AND DUTIES OF NEW REVIEW BOARD SYSTEM

| BOARD | MEMBERSHIP | FUNCTIONS/EXPERTISE |
|---|---|---|
| Local Institutional Review Board (IRBs) | As currently defined by 45 C.F.R § 46.107 (at least five members, diversity of backgrounds, at least one member with expertise in a scientific area and on member with expertise in a nonscientific area, one member not affiliated with the institution) | <ul style="list-style-type: none"> • review research as currently conducted under § 46.108 and § 46.109 <i>except</i>: <ul style="list-style-type: none"> - protocols that involve interventions or procedures that are not clearly minimal risk or less may be forwarded to the appropriate RRB for review accompanied by a statement for why review is requested - protocols falling under §405 and §406 that are contentious due to reliance on ambiguous regulatory language and have no prior precedent for approval must be forwarded to the appropriate RRB for review - protocols seeking §407 review must be forwarded to the NRB for review • review protocols as currently conducted under § 46.110 (expedited review) • maintain familiarity with local institution conditions and investigators • continue to work closely with investigators to assure human subject protection • educate investigators, board members and community members regarding research ethics • where not otherwise stated, the current IRB functions will continue <p><u>Specific Advantages:</u></p> <ul style="list-style-type: none"> • experience with reviewing large number of protocols best enables them to identify ambiguities in the regulations and problems with their application and send |

| | | |
|--------------------------------------|--|--|
| | | <p>protocols exemplifying these problems to the RRB level</p> |
| <p>Regional Review Boards (RRBs)</p> | <ul style="list-style-type: none"> • no more than one member from each local IRB • revolving membership so that each RRB has no more than 30 members and over years, local IRBs have the opportunity to have a representative serve as a member of their RRB • membership not to exceed 3 years | <ul style="list-style-type: none"> • review all protocols forwarded by IRBs • appellate function for investigators denied at local level • send protocols for review to NRB at RRB's discretion, but no more than 20% of all protocols may be sent • draft case summaries after making a decision and circulate that decision to the NRB and the local IRB who conducted the initial review • maintain familiarity with local IRBs' decisions <p><i>Specific Advantages:</i></p> <ul style="list-style-type: none"> • information sharing between members from different institutions at regional meetings • time available to discuss areas of regulations that are ambiguous such as "minor increase" "disease or condition" "vital importance" etc. and make decisions accordingly |
| <p>National Review Board (NRB)</p> | <ul style="list-style-type: none"> • 12 members (one from each RRB) • additional members, not to exceed 8, drawn from areas not otherwise represented by the RRB representatives; these may be investigators, lawyers, ethicists etc. • membership not to exceed 5 years | <ul style="list-style-type: none"> • review all protocols forwarded by RRBs • review all § 46.407 protocols • appellate function for investigators denied at regional level • draft memoranda to clarify federal regulations as needed • maintain familiarity with state and federal court cases involving human subjects research and research ethics • recommend changes to Congress as needed • maintain familiarity with research studies nationwide and RRB review decisions <p><i>Specific Advantages:</i></p> <ul style="list-style-type: none"> • ability to spend time drafting memoranda to clarify federal regulations drawing upon their knowledge of the |

| | | |
|--|--|---|
| | | entire review board system and their experience as a reviewing body |
|--|--|---|

Indeed, one might argue that a hierarchical review board system will be unwieldy and approval of research protocols will take too long, but that is all the more reason to design the system to function *efficiently*. With appropriate parsing of duties between the local, regional and national review boards, each group can function more efficiently and, ideally, with a lesser workload. A more centralized review organization encourages greater consistency, but maintaining the local IRBs and including twelve RRBs still allows for flexibility within the system. Local IRBs also reserve their autonomy as they are the ones that decide which protocols to send to the RRB. It may be that local IRBs will not handle this responsibility appropriately or refuse to send protocols to their RRB. Although it is beyond the scope of this paper, such malfunctioning within the local IRBs possibly could be dealt with by the accreditation systems that are in place and beginning to function.¹⁸⁴ Above the local level, the regional review system and its requirement of creating a database of written summary opinions are designed to produce information sharing between IRBs. There is incredible value to knowing how other local IRBs operate. It seems clear that the Yale system, which uses a primary reviewer process, is believed to work well,¹⁸⁵ but certainly it is not the only method being used.¹⁸⁶ Local IRBs would benefit from learning about each others' processes to help increase efficiency and awareness of difficult protocol decisions that are made. A hierarchical IRB system creates the opportunity for each review board level to foster and develop specific strengths that will ultimately afford greater protections for human subjects in clinical research.

CONCLUSION

Unethical research involving children has occurred throughout history. Only in recent years have federal regulations been created in the United States to help prevent further violations of human rights. The federal regulations are grounded in the principles of respect for persons, beneficence, and justice. They create a valuable risk-based assessment system for evaluating research protocols, but the regulations are fraught with imprecise language that often leads to their inconsistent application and incongruous results. The KKI lead abatement study,

184. For information on accreditation programs, see ASS'N FOR THE ACCREDITATION OF HUMAN RESEARCH PROT. PROGS., INC., ACCREDITATION STEP-BY-STEP (2005) at <http://www.aahrpp.org/www.aspx?PageID=95> (last visited June 28, 2005).

185. See LEVINE, *supra* note 8, at 328-341 (providing an in-depth look at Yale's IRB system).

186. For a comparison of the primary review system with Johns Hopkins executive committee system see David A. Blake, *An Executive Committee System for IRBs*, IRB: A REV. OF HUMAN SUBJECTS RESEARCH, Nov. 1982, at 8-9.

the Amiel and NICHD studies of children who were at risk for diabetes and obesity respectively, and the human growth hormone studies are just a few examples of protocols that, however well-intended, received widely differing views of their acceptability, and ultimately had diverse outcomes. The definitions of “minor increase,” “reasonably commensurate,” and “disorder or condition” continue to plague those who are charged with interpreting the regulations.

The ambiguities in the federal regulations make them inherently difficult to apply and, because IRBs are charged with their application but not their revision, the IRBs are often blamed for inconsistent and ineffective applications. Amidst the confusion over how to interpret words in the regulations, it is not surprising that despite their best efforts, individual IRBs have been criticized for inappropriately accepting or denying research protocols. Clarification of the regulations protecting children are inevitably needed, but the substantive changes to the regulations will not be realized without first making procedural changes. The IRBs cannot take on the additional duties of interpreting and possibly revising the regulations when they provide inadequate guidance.

A new review board system, modeled after the federal court system, will redistribute some of these responsibilities and create boards that are better able to carry out their specific mandates. Local IRBs will continue to oversee minimal risk research, but will not be solely responsible for interpreting the more ambiguous definitions in the regulations. Regional review boards, with members who are well educated on research ethics and federal regulations, will assume some of these duties. Finally, a national review board, which has some case-review duties, will be best able to use case-based ethical reasoning and carry out the mandate of drafting memoranda that clarify the federal regulations and recommending changes to Congress as needed. An overhaul of the review board system seems like a rather drastic proposal, but it may serve as the best way to efficiently and effectively ensure the protection of human subjects, including children, according to the principles of respect for persons, beneficence and justice.

APPENDIX 1**DEPARTMENT OF HEALTH AND HUMAN SERVICES,
45 CODE OF FEDERAL REGULATIONS 46, SUBPART D****TITLE 45—PUBLIC WELFARE
SUBTITLE A—DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL ADMINISTRATION
PART 46—PROTECTION OF HUMAN SUBJECTS
SUBPART D—ADDITIONAL PROTECTIONS FOR CHILDREN INVOLVED
AS SUBJECTS IN RESEARCH****§ 46.401 To what do these regulations apply?**

(a) This subpart applies to all research involving children as subjects, conducted or supported by the Department of Health and Human Services.

(1) This includes research conducted by Department employees, except that each head of an Operating Division of the Department may adopt such nonsubstantive, procedural modifications as may be appropriate from an administrative standpoint.

(2) It also includes research conducted or supported by the Department of Health and Human Services outside the United States, but in appropriate circumstances, the Secretary may, under paragraph (e) of § 46.101 of Subpart A, waive the applicability of some or all of the requirements of these regulations for research of this type.

(b) Exemptions at § 46.101(b)(1) and (b)(3) through (b)(6) are applicable to this subpart. The exemption at § 46.101(b)(2) regarding educational tests is also applicable to this subpart. However, the exemption at § 46.101(b)(2) for research involving survey or interview procedures or observations of public behavior does not apply to research covered by this subpart, except for research involving observation of public behavior when the investigator(s) do not participate in the activities being observed.

(c) The exceptions, additions, and provisions for waiver as they appear in paragraphs (c) through (i) of § 46.101 of Subpart A are applicable to this subpart.

§ 46.402 Definitions.

The definitions in § 46.102 of Subpart A shall be applicable to this subpart as well.

In addition, as used in this subpart:

- (a) “Children” are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.
- (b) “Assent” means a child’s affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
- (c) “Permission” means the agreement of parent(s) or guardian to the participation of their child or ward in research.
- (d) “Parent” means a child’s biological or adoptive parent.
- (e) “Guardian” means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.

§ 46.403 IRB duties.

In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only research which satisfies the conditions of all applicable sections of this subpart.

§ 46.404 Research not involving greater than minimal risk.

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.

§ 46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being, only if the IRB finds that:

- (a) The risk is justified by the anticipated benefit to the subjects;
- (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.406 Research 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.

HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:

- (a) The risk represents a minor increase over minimal risk;
- (b) 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;
- (c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
- (d) Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

§ 46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:

- (a) The IRB finds 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; and
- (b) 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.

§ 46.408 Requirements for permission by parents or guardians and for assent by children.

(a) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine 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. 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. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with § 46.116 of Subpart A.

(b) In addition to the determinations required under other applicable sections of this subpart, the IRB shall determine, in accordance with and to the extent that consent is required by § 46.116 of Subpart A, that adequate provisions are made for soliciting the permission of each child's parents or guardian. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research to be conducted under § 46.404 or § 46.405. Where research is covered by §§ 46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(c) 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.

(d) Permission by parents or guardians shall be documented in accordance with and to the extent required by § 46.117 of Subpart A.

(e) When the IRB determines that assent is required, it shall also determine whether and how assent must be documented.

§ 46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under § 46.406 or § 46.407 only if such research is:

- (1) Related to their status as wards; or
- (2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in, the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

APPENDIX 2

THE NUREMBERG CODE

Permissible Medical Experiments

The great weight of the evidence before us to effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts:

1. 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, overreaching, 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.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No 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.
6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9. During 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 seemed to him to be impossible.
10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

APPENDIX 3

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

*Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964
and amended by the 29th World Medical Assembly Tokyo, Japan, October 1975
35th World Medical Assembly Venice, Italy, October 1983
and the 41st World Medical Assembly Hong Kong, September 1989*

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care, which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures, and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research, in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that, the standards, as

drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles, and should be based on adequately performed laboratory and animal experimentation, and on a thorough knowledge of the scientific literature.
2. 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 independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country, in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons, and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person, and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical 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.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks, in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every 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.
7. Physicians should abstain from engaging in research projects involving human subjects, unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation, if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation, not in accordance with the principles laid down in this Declaration, should not be accepted for publication.
9. 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 a 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 physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. 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.

11. 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.

12. The research protocol should always contain a statement of the ethical considerations involved, and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH CLINICAL CARE (*CLINICAL RESEARCH*)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if, in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I. 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS
(NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person, on whom biomedical research is being carried out.
2. The subjects should be volunteers—either healthy persons, or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.

APPENDIX 4**DEPARTMENT OF HEALTH AND HUMAN SERVICES,
45 CODE OF FEDERAL REGULATIONS 46,
SELECTED SECTIONS RELATING TO INSTITUTIONAL
REVIEW BOARDS****TITLE 45—PUBLIC WELFARE
SUBTITLE A—DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER A—GENERAL ADMINISTRATION
PART 46—PROTECTION OF HUMAN SUBJECTS
SUBPART A—BASIC HHS POLICY FOR PROTECTION OF HUMAN
RESEARCH SUBJECTS****§ 46.103 Assuring compliance with this policy—research conducted or supported by any Federal Department or Agency.**

(a) Each institution engaged in research which is covered by this policy and which is conducted or supported by a federal department or agency shall provide written assurance satisfactory to the department or agency head that it will comply with the requirements set forth in this policy. In lieu of requiring submission of an assurance, individual department or agency heads shall accept the existence of a current assurance, appropriate for the research in question, on file with the Office for Protection from Research Risks, HHS, and approved for federalwide use by that office. When the existence of an HHS-approved assurance is accepted in lieu of requiring submission of an assurance, reports (except certification) required by this policy to be made to department and agency heads shall also be made to the Office for Protection from Research Risks, HHS.

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the department or agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(1) A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human subjects of research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles, or a statement formulated by the

institution itself. This requirement does not preempt provisions of this policy applicable to department- or agency-supported or regulated research and need not be applicable to any research exempted or waived under § 46.101 (b) or (i).

(2) Designation of one or more IRBs established in accordance with the requirements of this policy, and for which provisions are made for meeting space and sufficient staff to support the IRB's review and recordkeeping duties.

(3) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant. Changes in IRB membership shall be reported to the department or agency head, unless in accord with § 46.103(a) of this policy, the existence of an HHS-approved assurance is accepted. In this case, change in IRB membership shall be reported to the Office for Protection from Research Risks, HHS.

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

(c) The assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this policy and shall be filed in such form and manner as the department or agency head prescribes.

(d) The department or agency head will evaluate all assurances submitted in accordance with this policy through such officers and employees of the department or agency and such experts or consultants engaged for this purpose as the department or agency head determines to be appropriate. The department or agency head's evaluation will take into consideration the adequacy of the proposed

IRB in light of the anticipated scope of the institution's research activities and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and the size and complexity of the institution.

(e) On the basis of this evaluation, the department or agency head may approve or disapprove the assurance, or enter into negotiations to develop an approvable one. The department or agency head may limit the period during which any particular approved assurance or class of approved assurances shall remain effective or otherwise condition or restrict approval.

(f) Certification is required when the research is supported by a federal department or agency and not otherwise exempted or waived under § 46.101 (b) or (i). An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by § 46.103 of this Policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal or by such later date as may be prescribed by the department or agency to which the application or proposal is submitted. Under no condition shall research covered by § 46.103 of the Policy be supported prior to receipt of the certification that the research has been reviewed and approved by the IRB. Institutions without an approved assurance covering the research shall certify within 30 days after receipt of a request for such a certification from the department or agency, that the application or proposal has been approved by the IRB. If the certification is not submitted within these time limits, the application or proposal may be returned to the institution.

§ 46.107 IRB membership.

(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 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.

§ 46.108 IRB functions and operations.

In order to fulfill the requirements of this policy each IRB shall:

(a) Follow written procedures in the same detail as described in § 46.103(b)(4) and, to the extent required by, § 46.103(b)(5).

(b) Except when an expedited review procedure is used (see § 46.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

§ 46.109 IRB Review of Research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, 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.

(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with § 46.117.

(d) 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.

(e) An IRB shall conduct continuing review of research covered by this policy 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.

§ 46.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Secretary, HHS, has established, and published as a Notice in the FEDERAL REGISTER, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate after consultation with other departments and agencies, through periodic republication by the Secretary, HHS, in the FEDERAL REGISTER. A copy of the list is available from the Office for Protection from Research Risks, National Institutes of Health, HHS, Bethesda, Maryland 20892.

(b) An IRB may use the expedited review procedure to review either or both of the following:

(1) Some or all of the research appearing on the list and found by the reviewer(s) to involve no more than minimal risk,

(2) Minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB

chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 46.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The department or agency head may restrict, suspend, terminate, or choose not to authorize an institution's or IRB's use of the expedited review procedure.

§ 46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by

§ 46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

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

§ 46.114 Cooperative research.

Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

§ 46.115 IRB records.

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in § 46.103(b)(3).

(6) Written procedures for the IRB in the same detail as described in § 46.103(b)(4) and § 46.103(b)(5).

(7) Statements of significant new findings provided to subjects, as required by § 46.116(b)(5).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of the research. All records shall be accessible for inspection and copying by authorized representatives of the department or agency at reasonable times and in a reasonable manner.

DO PREGNANT WOMEN HAVE (LIVING) WILL?*

DANIEL SPERLING**

Living wills are documents that instruct health care providers about particular kinds of medical care that an individual would or would not want to have if rendered incompetent.¹ Under the American legal system, pregnant women are not typically allowed to express their will merely due to the fact they are pregnant. In other cases, their will is much weaker than those of other women, not to mention those of other men. In Canada, however, the law is silent on this matter: in contrast to the American legal system, no special provision relates to the state of pregnancy. From this silence one can infer two possible conclusions. According to the first, Canada has a gap in its living will legislation concerning pregnant women. This gap could be attributed to legislators who were not fully aware of the possibility that incompetency may also occur during pregnancy. According to the second potential conclusion, Canada considered the American model and decided to reject it due to legal and cultural differences between the two nations. Of course, choosing one interpretation over the other has far-reaching practical implications. But, what do we have to choose?

It is believed that advance directives in general, and living wills in particular, have three important purposes.² First, by issuing an advance directive, an individual is exercising her control over health care decisions concerning her body and state of health. Validating an advance directive is giving respect to the patient's prior wishes and to her right to self-determination, which does not extinguish should the signor of the advance directive become incompetent.³ However, advance directives also have an important procedural role: they prevent the need to go to court whenever a problem occurs as to what the patient would have decided in the relevant case had she had the opportunity to do so. Just as

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1. The degree of incompetency under which an advance directive should operate is debatable. Originally, advance directives apply when the patient is alive but incapacitated, and unable to make reasonable, or indeed, any decision concerning his or her health matters. However, it seems plausible to argue that advance directives can also apply when the patient becomes dead. Under these circumstances, an advance directive functions like a donor card or a will, providing for treatment of the body after death. Ed Newman, *Ethical Issues in Terminal Health Care, Part Four: Patients Have Rights, but Doctors Have Rights, Too* (1992), <http://www.cp.duluth.mn.us/~ennyman/DAS-4.html> (last visited May 18, 2005).

2. ALAN MEISEL, *THE RIGHT TO DIE* 6 (2d ed. 1995).

3. *Id.*

important, they provide physicians with immunity from civil and criminal liability by offering solutions that reside with the patient, even when incompetent.⁴

Legislation usually regulates advance directives. Advance directive statutes allow individuals to make decisions about the kind of care they want, if they are unable to make decisions on their own, and to appoint another person to make those decisions for them. They provide a mechanism that advances the ethical principles of individual autonomy, self-determination, and bodily integrity. The legislation provides the form of the document, the procedure to create it, and the scope of its effect. Living will legislation actually reflects the recognition by the state that the incompetent adult has the right, if the expression of intent is made, to have medical treatment discontinued or otherwise prescribed, and, thus, that courts should uphold the individual's living will.

A. CANADA

In Canada, advance directive legislation exists over almost all the country.⁵ Such legislation covers the provinces of Alberta,⁶ British Columbia,⁷ Manitoba,⁸ New Brunswick,⁹ Newfoundland,¹⁰ Nova Scotia,¹¹ Ontario,¹² Quebec,¹³ Saskatchewan,¹⁴ Prince Edward Island,¹⁵ and Yukon Territory.¹⁶ Although legislation varies among these provinces and territories, *none* of these extensive

4. *Id.* at 7.

5. For a discussion of the legal status of living wills in Canada see UNIV. OF TORONTO JOINT CENTRE FOR BIOETHICS, LIVING WILLS, http://www.utoronto.ca/jcb/outreach/living_wills_download.htm (last visited May 18, 2005). See generally *Quality of End-of-Life Care: The Right of Every Canadian: Subcomm. To update "Of Life and Death" of the Standing Senate Comm. on Social Affairs, Science and Technology*, (2000), <http://www.parl.gc.ca/36/2/parlbus/commbus/senate/Comme/upda-e/rep-e/repfinjun00-e.htm> (last visited May 18, 2005) (providing a detailed explanation of the legislation).

6. Personal Directives Act, S.A., ch. P-4.03 (1996) (Can.), *repealed by* R.S.A., ch. S-19, § 7 (2000) (Can.).

7. Representation Agreement Act, R.S.B.C., ch. 405 (1996) (Can.), http://www.qp.gov.bc.ca/statreg/stat/R/96405_01.htm (last visited May 18, 2005).

8. The Health Care Directives and Consequential Amendments Act, S.M., ch. 33 (1992) (Can.).

9. Infirm Persons Act, R.S.N.B. 1973, ch. I-8. (1973), amended by ch. 45, 2000 S.N.B. 1 (Can.).

10. Advance Health Care Directives Act, S.NFLD., ch. A-4.1 (1995) (Can.), <http://www.gov.nf.ca/hoa/sr> (last visited May 18, 2005).

11. Medical Consent Act, R.S.N.S., ch. 279, § 1 (1989) (Can.), <http://www.canlii.org/ns/laws/sta/r1989c.279/20041103/whole.html> (last visited May 18, 2005).

12. Substitute Decisions Act, S.O., ch. 30 (1992) (Can.).

13. Civil Code of Quebec, S.Q., ch. 64, § I (1991) (Can.).

14. Health Care Directive and Substitute Health Care Decision Makers Act, S.S., ch. H-0.001 (1997) (Can.).

15. Consent to Treatment and Health Care Directives Act, R.S.P.E.I., ch. 10 (1996), amended by ch. 5, 2000 R.S.P.E.I. (Can.).

16. Enduring Power of Attorney Act, R.S.Y.T., ch. 73 (2002) (Can.), <http://www.canlii.org/yk/sta/pdf/ch73.pdf> (last visited May 18, 2005).

legislative frameworks has a specific provision from which one can infer that the legal effect of an advance directive is influenced by whether the patient, who issued the living will, is pregnant or not. Thus, it seems that without any specific regulations for pregnant women deemed incompetent, Canadian law treats the incompetent pregnant woman who issued an advance directive while competent the same way as it treats other incompetent patients, that is, it respects the patient's right to control his or her care.

B. UNITED STATES

1. Regulation of Pregnancy Clauses

The legal structure of living will legislation regarding incompetent pregnant women is different in the United States than in Canada. Generally, in the United States, living will legislation of states differs from the Canadian legislation in that they allow the use of a living will only when a patient is terminally ill, or after a prognosis showing that the patient would not recover. While all the states have enacted some form of advance directive legislation, only 35 contemplate the validity of the advance directive when a woman is pregnant.¹⁷ Each of these statutes has specific guidelines as to the applicability of an advance directive when a woman who makes the advance directive is pregnant. While these guidelines reflect a practical balance between the constitutional rights of an incompetent

17. These states are: Alabama, ALA. CODE § 22-8A (1997 & Supp. 2004); Alaska, ALASKA STAT. § 13.52.055 (Michie 2004); Arizona, ARIZ. REV. STAT. ANN. § 36-3262 (West 2003 & Supp. 2004); Arkansas, ARK. CODE ANN. § 20-17-206 (Michie 2000 & Supp. 2003); California, CAL. PROB. CODE § 4670-8 (West 1991 & Supp. 2005); Colorado, COLO. REV. STAT. ANN. § 15-18-104 (West 1997 & Supp. 2004); Connecticut, CONN. GEN. STAT. ANN. § 19a-574 (West 2003); Delaware, DEL. CODE. ANN. tit. 16, § 2503(j) (2003); Florida, FLA. STAT. ANN. § 765.113 (West 1997 & Supp. 2005); Georgia, GA. CODE ANN. § 31-32-8(a)(1) (2001); Hawaii, HAW. REV. STAT. ANN. § 327E-3 (West 2004) (repealed 1999); Idaho, IDAHO CODE § 39-4504(4) (Michie 1996); Illinois, 755 ILL. COMP. STAT. ANN. 35/3(c) (West 1992 & Supp. 2004); Indiana, IND. CODE ANN. § 16-36-4-8(d) (Michie 1993); Kansas, KAN. STAT. ANN. § 65-28, 103 (2002); Kentucky, KY. REV. STAT. ANN. § 311.631 (Banks-Baldwin 2004); Minnesota, MINN. STAT. ANN. § 145B.13 (West 1996 & Supp. 2005); Missouri, MO. ANN. STAT. § 459.025 (West 1992); Montana, MONT. CODE ANN. § 50-9-106 (2003); Nebraska, NEB. REV. STAT. ANN. § 20-408 (Michie 1997); Nevada, NEV. REV. STAT. ANN. § 449.624 (Michie 2000); New Hampshire, N.H. REV. STAT. ANN. § 137-H:14 (1996); North Dakota, N.D. CENT. CODE § 23-06.4-03 (2002); Ohio, OHIO REV. CODE ANN. §§ 1337.13, 1337.15, 1337.17, 2133.06, 2133.08 (Anderson 2002 & Supp. 2003); Oklahoma, OKLA. STAT. ANN. tit. 63, §§ 3101.4, 3101.8 (West 2004 & Supp. 2005); Pennsylvania, 20 PA. CONS. STAT. ANN. § 5414 (West Supp. 2004); Rhode Island, R.I. GEN. LAWS § 23-4.11-6 (1996); South Carolina, S.C. CODE ANN. § 62-5-504 (Law. Co-op. 1986 & Supp. 2004); South Dakota, S.D. CODIFIED LAWS § 34-12D-10 (Michie 1994); Texas, TEX. HEALTH & SAFETY CODE ANN. § 166.049 (Vernon 2001 & Supp. 2004); Utah, UTAH CODE ANN. § 75-2-1109 (1993); Washington, WASH. REV. CODE ANN. § 70.122.030(1)(d) (West 2002 & Supp. 2005); Wisconsin, WIS. STAT. ANN. § 154.03 (West 1997 & Supp. 2004); Wyoming, WYO. STAT. ANN. § 35-22-102(b) (Michie 2003). See generally, Amy Lynn Jerdee, Note, *Breaking Through the Silence: Minnesota's Pregnancy Presumption and the Right to Refuse Medical Treatment*, 84 MINN. L. REV. 971 (2000) (discussing refusal of medical treatment by pregnant women).

pregnant woman and the interests of the state in protecting potential life (or, even further, the interests of a fetus), the requirements represented in each of the statutes differ from one state to another. Nevertheless, they can be roughly divided into the following six categories:

1. Total Disregard of An Advance Directive During the Entire Pregnancy.

This category is the most frequent, appearing in 17 states.¹⁸ Statutes under this category declare that an advance directive of a person who becomes pregnant has no effect during pregnancy.

2. Possibility, Probability, or Medical Certainty that the Fetus Will Develop to Live Birth.

Some states have legislation that does not give effect to an advance directive if it is probable,¹⁹ possible,²⁰ or supported by medical certainty²¹ that the fetus will develop to live birth.

18. Alabama, ALA. CODE § 22-8A (1997 & Supp. 2004); California, CAL. PROB. CODE § 4670-8 (West 1991 & Supp. 2005); Connecticut, CONN. GEN. STAT. ANN. § 19a-574 (West 2003); Hawaii, HAW. REV. STAT. ANN. § 327E-3 (West 2004) (repealed 1999); Idaho, IDAHO CODE § 39-4504(4) (Michie 1996); Indiana, IND. CODE ANN. § 16-36-4-8(d) (Michie 1993); Kansas, KAN. STAT. ANN. § 65-28,103(a) (2002); Missouri, MO. ANN. STAT. § 459.025 (West 1992); New Hampshire, N.H. REV. STAT. ANN. § 137-H:14 (1996); Ohio, OHIO REV. CODE ANN. § 2133.06(B) (Anderson 2002); Oklahoma, OKLA. STAT. ANN. tit. 63, §3101.4, 3101.8 (West 2004 & Supp. 2005); South Carolina, S.C. CODE ANN. § 44-77-70 (Law Co-op. 1986 & Supp. 2004); Texas, TEX. HEALTH & SAFETY CODE ANN. § 166.049 (Vernon 2001 & Supp. 2004-05); Utah, UTAH CODE ANN. § 75-2-1109 (1993); Washington, WASH. REV. CODE ANN. §70.122.030(1)(d) (West 2002 & Supp. 2005); Wisconsin, WIS. STAT. ANN. § 154.03 (West 1997 & Supp. 2004); Wyoming, WYO. STAT. ANN. § 35-22-102(b) (Michie 2003). It is interesting to note here that Oregon law lists abortion as one of the limitations for which the durable power of attorney is not authorized to consent. OR. REV. STAT. § 127.540 (2003).

19. ALASKA STAT. § 18.12.040 (Michie 2004); DEL. CODE ANN. tit.16, § 2503(j) (2003); MONT. CODE ANN. § 50-9-106(6) (2003); NEB. REV. STAT. § 20-408(3) (1997); NEV. REV. STAT. ANN. § 449.624(4) (Michie 2000); R.I. GEN. LAWS § 23-4.11-6(c) (1996). This language can also be found in the Uniform Rights of the Terminally Ill Act, which reads: "Life sustaining treatment must not be withheld or withdrawn pursuant to a declaration from an individual known to the attending physician to be pregnant so long as it is probable that the fetus will develop to the point of live birth with continued application of life-sustaining treatment." NAT'L CONFERENCE OF COMM'RS ON UNIF. STATE LAWS, Uniform Rights of the Terminally Ill Act § 6(c), (1989), available at <http://www.law.upenn.edu/bl/ulc/fnact99/1980s/urtia89.pdf> (last visited May 18, 2005).

20. ARIZ. REV. STAT. ANN. § 36-3262(3) (West 2003 & Supp. 2004); ARK. CODE ANN. § 20-17-206(c) (Michie 2000 & Supp. 2003); 755 ILL. COMP. STAT. ANN. 35/3(c) (West 1992 & Supp. 2004); MINN. STAT. ANN. § 145B.13(3) (West 1998 & Supp. 2005).

21. KY. REV. STAT. ANN. § 311-629(4) (Banks-Baldwin 2004); N.D. CENT. CODE § 23-06.4-07(3) (2002).

3. *Viability of the Fetus.*

Two states mention the viability criterion as a limit on the effect of the advance directive. Colorado requires fetal viability before voiding an advance care directive.²² Georgia requires that the fetus be non-viable for the discontinuation of medical treatment.²³

4. *Physical Harm or Pain to the Pregnant Woman.*

In addition to the requirement of reasonable medical certainty that the fetus will develop to live birth, Pennsylvania and South Dakota require the assurance that physical harm or pain to the woman can be alleviated.²⁴

5. *Rebuttable Presumption of Continuation of Treatment.*

The Minnesota advance directive law offers a unique approach. In 1998, the Minnesota legislature fundamentally revised their existing advance directive law.²⁵ Prior to 1998, Minnesota's pregnancy provision provided that:

In the case of a living will of a patient that the attending physician knows is pregnant, the living will must not be given effect as long as it is possible that the fetus could develop to the point of live birth with continued application of life-sustaining treatment.²⁶

With the 1998 amendment, the current pregnancy provision states that: When a patient lacks decision-making capacity and is pregnant, and in reasonable medical judgment there is real possibility that if health care to sustain her life and the life of the fetus is provided the fetus could survive to the point of live birth, *the health care provider shall presume that the patient would have wanted such health care to be provided, even if the withholding or withdrawal of such health care would be authorized were she not pregnant. This presumption is negated by health care directive provisions . . . or . . . in the absence of such provisions, by clear and convincing evidence that the patient's wishes, while competent, were to the contrary.*²⁷

22. COLO. REV. STAT. ANN. §15-18-104 (West 1997 & Supp. 2004).

23. GA. CODE ANN. § 31-32-8 (2001).

24. 20 PA. CONS. STAT. § 5414 (West 1975 & Supp. 2004); S.D. CODIFIED LAWS § 34-12D-10 (Michie 1994).

25. MINN. STAT. ANN. § 145C (West 1998 & Supp. 2004).

26. *Id.* § 145B.13(3).

27. *Id.* § 145C.10(g) (emphasis added). For a general discussion on the new law in Minnesota see Barbara J. Blumer, *Minnesota's New Health Care Directive*, 81 MINN. MED. 1 (1998) (emphasis added), <http://www.mnmed.org/publications/MnMed1998/September/blumer.cfm> (last visited May 18, 2005).

Hence, the new approach acknowledges the interest of the state in potential fetal life, while still preserving the pregnant patient's right to withdraw treatment. It also encourages health professionals to discuss the issue with women who are or could become pregnant. This view goes beyond simply making the living will void with pregnancy. It attempts to balance the woman's rights with those of the state interest in protecting the life of the fetus.

6. Probability that the Fetus Would Not Be Born Alive.

In Ohio, life-sustaining treatment can be withheld or withdrawn, if "the declarant's attending physician and one other physician who has examined the declarant determine, to a reasonable degree of medical certainty and in accordance with reasonable medical standards, that the fetus would not be born alive."²⁸

The various legislative forms of restricting the woman's right to control her care on the basis that she is pregnant are troubling. Not only are women deprived of their right to determine their own treatment when incompetent, in some states this deprivation occurs regardless of the stage of the incompetent woman's pregnancy and heedless of whether the fetus is viable. This seems illogical: if the woman were competent, she could abort her child without hesitation, at least during her first trimester. But if she becomes incompetent during the first trimester, she cannot ask to withdraw life-sustaining treatment, and is thus compelled to save her pre-viable fetus's life.

2. Constitutionality of Pregnancy Clauses

More disturbing than the fact that pregnancy clauses exist is the fact that they were not found to be unconstitutional under United States jurisprudence. While the issue of constitutionality of pregnancy clauses has been raised in three judicial opinions, none of these cases involved substantial debate over the constitutional questions pregnancy clauses raise, nor about the serious implications they have on women in general.

In *University Health Services v. Piazzi*, the Supreme Court of Georgia implied that it would follow the pregnancy clause of Georgia, notwithstanding the objections of the patient's family.²⁹ The court granted a hospital petition to continue life-support procedures on a brain-dead pregnant woman, *contrary to the request of the patient's husband and family*. The woman's wishes were *unknown*, and there was no living will. The court held that, according to the law of Georgia,

28. OHIO REV. CODE ANN. § 2133.06(B) (Anderson 2002).

29. Molly C. Dyke, Note, *A Matter of Life and Death: Pregnancy Clauses in Living Will Statutes*, 70 B.U. L. REV. 867, 871 (citing *Univ. Health Servs., Inc. v. Piazzi*, No. CV86-RCCV-464 (Ga. Super. Ct. Aug. 4, 1986)).

the woman was dead and therefore had no protectable privacy interest. In addition, the court ruled that because the pregnancy clause of the Georgia legislation determined that the living will would be ineffective during pregnancy, the woman's wishes regarding the living will were irrelevant. The *Piazza* ruling has led commentators to assume that the court's reliance upon the living will statute indicates that it might reject the claim that the pregnancy clause is unconstitutional.³⁰ The court, nevertheless, did not state that it was unconstitutional.³¹

Donna Piazza did not leave any directive. Still, the court based its ruling on the Georgia pregnancy clause. Perhaps the reason that the court relied on the pregnancy clause is that the woman was dead under Georgia law. It is not clear whether the court would have mentioned the pregnancy clause, let alone indirectly validated its constitutional content, had she been legally alive. But if Donna did not have any interests at all – a proposition for which the court did not provide any authority – what additional weight did mentioning the pregnancy clause have in the overall ruling? It seems to be none.

Another case in which the constitutionality of pregnancy clauses has been raised is *DiNino v. State ex. rel. Gorton*.³² In *DiNino*, the plaintiff executed a living will, adding a sentence declaring that the directive was the final expression of her “legal right to consent to termination of any pregnancy,” and that contrary to the Washington Natural Death Act, it would “still have full force and effect during the course of [her] pregnancy”.³³ DiNino and her physician, who feared including her directive in her medical file, sought a judgment declaring that her directive was valid, and that no physician would be liable for obeying it. DiNino argued that her constitutional right to privacy was infringed under the Act in two respects. First, the provision directly inhibited her right to choose to have an abortion and second, it directly infringed upon her right to choose to forego medical treatment.³⁴

The Superior Court of King County, Washington, granted DiNino partial summary judgment, declaring the pregnancy provision of the Natural Death Act unconstitutional because, as drafted, the subsection inhibited a woman's right to exercise control over her reproductive decisions; therefore, the provision violated DiNino's fundamental right of privacy. The Superior Court, however, denied the declaration of validity of a woman's directive because this directive attempted to exercise full control over DiNino's reproductive decisions *beyond the point where*

30. *Id.* at 871.

31. *Id.*

32. 684 P.2d 1297, 1299 (Wash. 1984).

33. *Id.*

34. It is interesting to note that the state conceded that an individual could draft an advance directive that contains a properly worded abortion provision, or alternatively, delete the pregnancy provision of the model directive. *Id.* at 1300.

the State has a legitimate interest in such decisions. Hence, both DiNino and the state appealed to the Supreme Court of Washington.

On appeal, Justice Brachtenbach, writing for the majority, held that the controversy was not “justiciable” under the meaning of the Uniform Declaratory Judgments Act, under which DiNino and her physician brought the suit against the state of Washington. Because the plaintiff was neither pregnant nor terminally ill, her arguments concerning the unconstitutionality of the Natural Death Act pregnancy provision were “purely hypothetical and speculative.” The only issue in controversy was whether Ms. DiNino could draft a declaration that differed in its terms from that provided in the Natural Death Act. Since the state was willing to concede that the form could differ or be absent from the pregnancy provision, a fact which undermines the state’s objective in enacting the pregnancy provision in the first place, the court concluded that “in the abstract, the NDA itself does not *directly* infringe any constitutional rights as claimed by the respondents.”³⁵

Although the court admitted that the constitutional rights allegedly infringed upon are important, it did not find the case to be one of “broad overriding public import.” Hence, the court did not think an advisory opinion on the constitutionality of the Washington living will provision would be “beneficial to the public or to other branches of government.” However, despite the fact that the court refused to express any opinion regarding the validity of DiNino’s directive and the constitutionality of the Washington pregnancy provision, it implied that in a real controversy, DiNino’s advance directive would have been effective. The court said:

We express no opinion as to the validity of DiNino’s directive as drafted, for this must await a factual controversy. However, under the facts presented, the respondents, as well as this court, can only speculate as to the possible impact of the NDA on an individual who is pregnant and is in a terminal condition.³⁶

In his dissenting opinion, Justice Dimmik explained why it is logically wrong to hold, as the majority did, that there is no justiciability at the time a woman drafts a directive under the Natural Death Act. In his words:

By the majority’s reasoning, a woman must be pregnant and terminally ill before the issue is ripe for determination. Whatever the impact of the [Natural Death Act] in that circumstance, the woman whose directive will then be ‘justiciable’ will never benefit from a ruling on the matter. In fact, the case would run a very real danger of being declared moot before a judicial decision could be made. And if, in its discretion, the court chooses to address the issues on mooted facts, would that

35. *Id.* at 1300 (emphasis added).

36. *Id.*

determination be based on any less speculation than a determination under the circumstances now before us?³⁷

Justice Dimmik's hypothesis was realized six years later when the Court of Appeals for the District of Columbia, in one of the leading decisions in the United States, acknowledged the right of a pregnant woman to refuse a cesarean section that was needed to save the life of her twenty-three-week-old fetus.³⁸ The woman could not benefit from the court's decision because she (and her fetus) died two days after the forced medical treatment. As a result of this outcome, one has to seriously ask whether moot cases are an appropriate forum in which courts should decide these life-and-death issues.

Yet, courts continue to hold off on determining the constitutionality of these pregnancy provisions. In *Gabrynowicz v. Heitkamp*,³⁹ the plaintiffs challenged the Uniform Rights of the Terminally Ill Act of North Dakota that invalidated an advance directive at pregnancy.⁴⁰ The plaintiffs were husband and wife. The woman sought to execute a living will and durable power of attorney (for her husband) with the hope that it would have the same effect whether she was pregnant or not. The plaintiffs argued that North Dakota's pregnancy clauses are unconstitutional because they: 1) impose undue burdens on the right to terminate pregnancy and make medical decisions under the First, Fourth, Ninth, and Fourteenth Amendments; 2) deprive women of liberty (bodily integrity) without due process, violating the Fourteenth Amendment; 3) discriminate on the basis of gender, violating the equal protection guarantee of the Fourteenth Amendment; 4) require an expression of adherence to the state's policy of protecting fetal life, violating the right to make and decline to make an expression of belief under the First and Fourteenth Amendments; and, 5) violate the right to free exercise of religion under the First and Fourteenth Amendments.

However, like the majority opinion in *DiNino*, the U.S. District Court for the District of North Dakota chose not to discuss the constitutional questions and dismissed the plaintiffs' motion for the technical reasons of standing and ripeness. The court held that at the time of the claim, Ms. Gabrynowicz was neither pregnant nor incompetent. Hence, the court did not see any "realistic danger" that the statute in question would directly injure the plaintiffs. The court acknowledged that section 23-06.4-07(3) of the statute authorizes medical treatment of a pregnant

37. *Id.* at 1301.

38. *In re A.C.*, 573 A.2d 1235, 1247 (D.C. 1990).

39. 904 F. Supp. 1061, 1062-63 (D. N.D. 1995).

40. N.D. CENT. CODE § 23-06.4-07(3) (2002). The statute provides: "Notwithstanding a declaration executed under this chapter, medical treatment must be provided to a pregnant patient with a terminal condition unless . . . such medical treatment will not maintain the patient in such a way as to permit the continuing development and live birth of the unborn child or will be physically harmful or unreasonably painful to the patient or will prolong severe pain that cannot be alleviated by medication." *Id.*

patient without distinguishing on the basis of fetal viability, and so admitted that at least some of the rights alleged by Ms. Gabrynowicz could be implicated. Nevertheless, the court still considered these questions to be abstract and non-justiciable.⁴¹

Indeed, at the time of the trial, Ms. Gabrynowicz had not issued an advance directive and in that sense her case was less ripe than DiNino's. However, both women were fertile: they were ready to become pregnant and fully aware of the consequences of their proposed (present or future) directives. It is unclear why the courts avoided substantial discussion of their directives under the premise that the issues were not yet ready for review. Is a state of loss of competency in which the woman's wishes cannot be directly examined, a better model than a state of full competency to use in evaluating her constitutional rights? Alternatively, did DiNino or Gabrynowicz have to actually become pregnant to have their claims heard? What if the validity of their advance directives is an important factor in their decision of whether to conceive? Can the courts avoid these women's basic rights as competent healthy persons to make choices concerning their health, body, and reproduction?

Importantly, in *DiNino*, the court stated that Ms. DiNino or her physician had to make a better effort to look for another physician who would be willing to place the directive in her file. The court thus concluded that the real controversy was between DiNino and her physician. But is the question before the court really about who gets to file the directive? Does DiNino's physician have a duty to look for another physician who will agree to file her directive? Will the latter be immune from any possible liability? These questions show that the courts' rulings on these matters may create, rather than resolve, inconsistencies in the law.

C. UNITED KINGDOM AND IRELAND

Advanced directives are valid under English law provided they are made freely, without undue influence. It is also necessary for the person who issued an advance directive to be competent and informed about the directive's legal consequences. If a pregnant woman temporarily loses capacity, an advance directive would be effective only if it *specifically addressed the possibility of pregnancy*. In case of doubt, some scholars have argued that a directive refusing all of the recommended forms of medical treatment is unlikely to be respected, because the courts may assume that "the woman had not addressed her mind to the circumstances which have arisen."⁴² This also seems to be the case in Ireland. Due to the well-recognized constitutional rights of the unborn, scholars have

41. *Gabrynowicz*, 904 F. Supp. at 1064.

42. Nicola S. Peart et al., *Maintaining a Pregnancy Following Loss of Capacity*, 8 MED. L. REV. 275, 279 (2000).

recognized that courts in Ireland will tend to ignore any advance directive issued and will protect the life of the unborn child, “unless there existed a grave, real and substantial risk to the life of the [incompetent] mother.”⁴³

However, this claim is not supported in legislation, nor in English case law. Moreover, in its “Report on Mental Incapacity,” the English Law Commission *disagreed* with the United States’ approach of suspending the effectiveness of living wills during pregnancies.⁴⁴ The Commission recommended that women of childbearing capacity should address the possibility of a pregnancy when executing advance directives. In section 5.25 of the report, the Law Commission said:

We do not . . . accept that a woman’s right to determine the sorts of bodily interference which she will tolerate somehow evaporates as soon as she becomes pregnant. There can, on the other hand, be no objection to acknowledging that many women do in fact alter their views as to the interventions they find acceptable as a direct result of the fact that they are carrying a child.⁴⁵

The Law Commission view is in accordance with ethical guidelines on this matter. In a supplement to its previous report, the Royal College of Obstetrics and Gynecologists stated that if an incompetent pregnant woman, who was fully informed, refused treatment during pregnancy in advance, her wishes should be respected *even at the expense of the fetus*.⁴⁶ However, if the woman referred in her advance directive to some forms of treatment but had no opportunity to discuss treatment during pregnancy, and if pregnancy is not mentioned in the directive, “the directive could be declared invalid because the circumstances at the critical time of decision were not clearly envisaged when the directive was made”.⁴⁷

Hence, although academic writing in the United Kingdom and Ireland may support the view that a woman’s advance directive should be invalidated during pregnancy, such an approach is contradictory to ethical guidelines concerning a pregnant woman’s right to determine the fate of her care, and to the Law Commission’s 1995 report on mental incapacity that explicitly discussed this issue.

43. Asim A. Sheikh & Denis A. Cusack, *Maternal Brain Death, Pregnancy and the Foetus: The Medico-Legal Implications*, 7 MEDICO-LEGAL J. IR. 75, 83 (2001).

44. LAW COMMISSION, MENTAL INCAPACITY, 1995, Cm. 231, § 5.25.

45. *Id.*

46. ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS, COURT-AUTHORISED OBSTETRIC INTERVENTION: A CONSIDERATION OF THE LAW AND ETHICS, §§ 3.4.2, 4.2, (1996) <http://www.rcog.org.uk/print.asp?PageID=109&Type=guidelines&GuidelineID=33> (last visited May 18, 2005).

47. *Id.* § 3.4.2.

CONCLUSION

A woman's decision to issue an advance directive and to have it effectuated implicates her fundamental right to make decisions regarding procreation, family relationships and bodily integrity. These are the most intimate and personal choices a person makes in a lifetime. They are central to personal dignity and autonomy and to the "life and liberty" interests that are protected under the Canadian Constitution.

Pregnancy clauses that exist under American law should not be a model for Canadian law. Not only do they infringe on a woman's right to refuse medical treatment just because she is pregnant, and hence distinguish them from non-pregnant women on the basis of their pregnancy, but they also discriminate toward them on a gender basis and on the basis of their incompetency. In addition, Pregnancy clauses trivialize the significance of the mother's self-defining and conscientious choice by automatically overriding it. They ignore the pregnant woman's family, pretending to protect potential life without even drawing the line at the viability of the fetus. Finally, they control the woman's body, devalue it, and bring it near a state of involuntary servitude.⁴⁸ The woman's wishes are automatically ignored simply because she is pregnant.

However, it is not enough to conclude that Canada should not follow the American model of pregnancy clauses. A more active step should be taken, similar to that in the United Kingdom, so that the American model should be publicly discussed and rejected. No doubt should be left in such a significant area. It is hoped that this Article initiates the debate on this central issue and helps future pregnant women and their loving families and friends better handle these difficult circumstances of incompetency.

48. Timothy J. Burch, *Incubator or Individual?: The Legal and Policy Deficiencies of Pregnancy Clauses in Living Will and Advance Health Care Directive Statutes*, 54 MD. L. REV. 528, 555 (1995).