

2007

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Recommended Citation

Holly Fernandez Lynch *Give Them What They Want? The Permissibility of Pediatric Placebo-Controlled Trials under the Best Pharmaceuticals for Children Act*, 16 *Annals Health L.* 79 (2007).
Available at: <http://lawcommons.luc.edu/annals/vol16/iss1/5>

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Give Them What They Want?

The Permissibility of Pediatric Placebo-Controlled Trials Under the Best Pharmaceuticals for Children Act

*Holly Fernandez Lynch, J.D., M.Bioethics**

INTRODUCTION

Despite their similar appearance, children¹ are not just miniature adults. They experience different thought processes, are given different legal rights and responsibilities, and are even cared for by their own medical specialty, pediatrics. For years, however, these differences have been largely ignored in the area of pharmaceutical development, leaving children to be treated as though they truly were just smaller versions of their adult counterparts. Crushing half of a tablet of an adult's drug into applesauce for a five-year-old has become the norm for many parents. However, this tactic, often recommended by pediatricians who lack a better alternative, can lead to disastrous results or no result at all when the dose or drug is ineffective for children.

The reasons for this lack of information are many and varied, but the main problem has been the lack of an internal incentive within the pharmaceutical industry to develop and test drugs specifically for pediatric indications. Recognizing this problem, the Food and Drug Administration (FDA) and Congress recently took two important steps in the right direction after several unfruitful attempts at improvement since the 1960s. The "carrot-and-stick" combination of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) will increase

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1. This article will use the term "child" to refer to non-adults from birth to the age at which their bodies metabolize and react to drugs in the same way as fully-developed adults and at which they are able to legally (and developmentally) provide consent for medical care and research enrollment.

much needed research into the use of new and currently marketed drugs in children. However, with this increase will come a plethora of ethical difficulties associated with conducting pediatric studies. The FDA's specific requests for legally and morally questionable placebo-controlled pediatric trials of drugs used to treat obsessive-compulsive disorder (OCD) and depression will only further complicate these issues.

Placebo-controlled trials compare an experimental drug with an inactive substance designed to look and taste like the experimental drug, often called a dummy pill. When conducted with adult populations, these trials are generally accepted so long as subjects give their informed consent for enrollment and are not denied an effective life-saving therapy. In contrast, pediatric subjects are developmentally and legally incapable of providing informed consent and thus require more protection from abuse and exploitation in research. Still, using placebo controls with children is not ethically prohibited, and those who recognize the dire need for pediatric research generally concur that placebo arms can be used in some narrowly constrained circumstances—the question is whether the FDA's requests meet these criteria.

Physicians already routinely prescribe the drugs at issue for pediatric treatment of OCD and depression. While some drugs have been approved for these indications in children through the written request system established by the BPCA, their recent association with increased suicidality² when used in the pediatric population has essentially returned the treatment of these disorders in children back to square one. New and existing pediatric OCD and antidepressant drugs will need to undergo rigorous safety tests that focus on this particular concern. However, because even the currently approved treatments have not been proven safe with regard to suicidality, clinical equipoise between these drugs and placebo will exist and active-comparator or add-on studies will be impossible. Therefore, the placebo controls requested by the FDA will likely be legally approvable, ethically permissible, and practically necessary to re-determine the safety of these drugs for children.

Once safety is re-established for even a single drug effective for OCD or depression in children, the use of placebo controls becomes objectionable for studies of other drug treatments for these indications as a safe and effective alternative will be available. In that situation, the question should not be whether a new drug is better than nothing, but rather, whether a new

2. Suicidality is a broad term that "appears to include [suicidal] ideation, self-harm, and actual suicide attempts." David Brent & Boris Birmaher, Letter to the Editor, *British Warnings on SSRIs Questioned*, 43(4) J. AM. ACAD. CHILD & ADOLESCENT PSYCHIATRY 379, 379 (2004).

drug is better than the treatment currently available to pediatric patients. Importantly, placebo controls cannot answer this question. Some commentators argue that existing safe and effective treatments can be withheld for research on drugs intended to treat relatively mild conditions because denial of that treatment for the duration of the study would not harm the subject in any serious or permanent way. The FDA appears to accept this reasoning, requesting placebo-controlled studies of OCD drugs and antidepressants, but not for drugs used to treat more severe diseases like cancer or HIV.

While the distinction between mild and serious conditions may be justifiable in adults who are able to personally consent to enrollment in a placebo-controlled study and effectively refuse proven treatment, children are incapable of making such reasoned decisions and must rely on the substituted consent of their parents. Based on the best interest standard of proxy decision-making, parents should not be able to enroll their children in placebo-controlled trials for even mild conditions when a safe and effective alternative exists; it is in no child's best interest to continue needlessly suffering, from a headache or something far more serious. Further, even assuming that this mild/severe distinction holds for pediatric subjects, it is not clear that childhood OCD and depression should be categorized as mild conditions. As this article will demonstrate, however, this ethical discussion may be moot because placebo-controlled studies denying pediatric subjects safe and effective treatment will not likely be legally approvable under an appropriate application of the risk categories established by federal regulations to protect children in research.

Part I of this article will explain the need to test drugs in pediatric populations. Part II will outline the major reasons that this sort of testing has not occurred in the past. Part III will briefly describe two important initiatives launched by Congress and the FDA in hopes of reversing this trend, including a program through which the FDA has made specific requests for pediatric trials. Finally, Parts IV and V will apply legal and ethical analyses, respectively, to the FDA's requests for placebo-controlled studies of drugs to treat OCD and depression in children. While these requests may be currently acceptable, once current suicidality concerns are overcome and safe and effective alternatives become available, the placebo arms of these trials will be both legally and ethically objectionable and must be replaced with active controls.

PART I—WHY DO WE NEED TO TEST DRUGS ON CHILDREN?

A. Lack of Information About Pediatric Prescribing

The American government has made a

general policy determination, under Federal law governing drugs and medical devices, that proof of safety and effectiveness generally requires substantial human subjects research. Federal law generally finds even the longstanding use of drugs or medical devices by physicians, and the general view of physicians that such are safe and effective, as insufficient to meet federal regulatory standards.³

Unfortunately, this “longstanding use” and “general view,” combined with evidence of adult safety and efficacy, often constitute the only information available to pediatricians. Doctors currently lack adequate dosing, safety, and efficacy data regarding pediatric use of at least sixty-five percent of drugs prescribed to children.⁴ Further, a pediatric patient’s age directly correlates with the availability of information regarding pediatric prescribing, with the least data available for the youngest children.⁵

This paucity of information leaves doctors with no choice other than off-label use of medications that have only been approved for adult populations. While such prescribing practices are legally and professionally permitted, widespread off-label use of drugs can be

3. David M. Smolin, *Nontherapeutic Research with Children: The Virtues and Vices of Legal Uncertainty*, 33 CUMB. L. REV. 621, 627 (2002/2003).

4. Allecia Vermillion, *Information Lacking on Antidepressants’ Effects*, BUCKS COUNTY COURIER TIMES, Apr. 26, 2004, at 3A, available at 2004 WLNR 17314063. See also Am. Acad. of Pediatrics, Committee on Drugs, *Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286, 286 (1995) (noting that in 1991, 81% of the drugs in the Physician’s Desk Reference contained a disclaimer warning that use in children had not been determined safe or effective or restricting use to certain age groups); Rosemary Roberts, *What’s So Special About Children?*, http://www.fda.gov/cder/pediatric/presentation/tox_peds_nov2001/tsld001.htm (last visited Sep. 2, 2006) (estimating that physicians lack information regarding the pediatric use of about 75% of prescription medications).

5. Rosemary Roberts et al., *Pediatric Drug Labeling: Improving the Safety and Efficacy of Pediatric Therapies*, 290(7) J. Am. Med. Ass’n. 905, 905 (2003). Notably, this problem is not unique to the United States: data demonstrates that the majority of drugs approved for adults have not been approved for children in the United Kingdom, Australia, or New Zealand, and presumably many other developed countries around the world. Joanne Grieve et al., *Effect of the Pediatric Exclusivity Provision on Children’s Access to Medicines*, 59(6) BRIT. J. CLINICAL. PHARMACOLOGY. 730, 730 (2004).

dangerous, or at least inefficacious.⁶ Physicians are forced to estimate the appropriate pediatric dosage based on weight alone, guess about possible adverse effects,⁷ and hope that the drug formulation available for adults is amenable for use in children.⁸ Without appropriate prescribing information, doctors may withhold potentially helpful medicines for fear of their unintended and damaging consequences. Alternatively, doctors may prescribe medicines that have no effect on the condition in children at all. Both practices result in under-treatment of pediatric illness.⁹ Of course, a worse result is that the prescribed drugs have toxic or other detrimental effects on pediatric patients that are not witnessed in adult populations.¹⁰

Rather than withhold drugs with no approved pediatric indication altogether, physicians often recommend a milder dose than that prescribed for an adult patient, resulting in a trial-and-error mini-experiment every time these treatments are given to children.¹¹ While some commentators believe that conducting drug tests on pediatric subjects is unethical,¹² it essentially occurs in pediatricians' offices every day. Moreover, providing drugs that have not undergone appropriate testing on children may pose more significant ethical problems.¹³ Not only is this experimental in itself, but it is research without informed consent, not approved by federal regulations, and lacks a design capable of providing useful data that will improve future pediatric prescribing practices.¹⁴ Off-label use as practiced

6. Smolin, *supra* note 3, at 629. Although these concerns may confront off-label use in adult patients as well, the situations are distinguishable. With adults, the drugs have at least been tested and approved by the FDA for some indication, whereas for children, there has been no such testing and approval for the purposes of this article. *Id.* at 628.

7. Lauren Hammer Breslow, Note, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 146 (2003).

8. Christopher-Paul Milne, *Exploring the Frontiers of Law and Science: FDAMA's Pediatric Studies Incentive*, 57 FOOD & DRUG L.J. 491, 493 (2002) [hereinafter *Exploring the Frontiers*].

9. Roberts, *supra* note 4; Roberts et al., *supra* note 5, at 905.

10. Roberts, *supra* note 4.

11. *Id.*; Roberts et al., *supra* note 5.

12. See, e.g., PAUL RAMSEY, *THE PATIENT AS PERSON: EXPLORATION IN MEDICAL ETHICS* 11-12 (1970) (arguing that children should never be involved in research unless all other remedies have failed to relieve their grave illness and the experimental intervention has a chance to further the child's own recovery).

13. Jane E. Henney, Comm'r of Food and Drugs, U.S. Food and Drug Administration, *Pediatrics in the New Millennium: Compelling Issues in Public Policy – Increasing Pediatric Access to Medical Therapies*, Remarks at the Pediatric Academic Societies and American Academy of Pediatrics Joint Meeting (May 15, 2000), <http://www.fda.gov/oc/speeches/2000/pediatricacademic.html> (last visited Sept. 2, 2006).

14. Am. Acad. of Pediatrics, *supra* note 4, at 286-87; see Roberts et al., *supra* note 5, at 905 (noting the experimental nature of off-label drug prescribing in children and its inability to accrue data in a scientifically rigorous manner in order to build knowledge for the future);

today imposes risks on individual children without any potential to benefit the entire population.

B. Inability to Extrapolate from Adult Data

At this point, one question is obvious: if adequate safety and efficacy data exist for adults, as it must for a drug to be on the market at all, why is this data insufficient to support use in the pediatric population? The answer is that in certain circumstances, extrapolation from adult data may be perfectly appropriate. For the most part, however, children are so physiologically different from adults that physicians cannot freely assume that they will react similarly to pharmaceutical agents. When dealing with diseases and conditions that afflict both children and adults, pharmacokinetic¹⁵ and pharmacodynamic¹⁶ studies may show significant resemblance in the way a drug is metabolized by both groups of patients. Such studies may also indicate that the disease processes themselves are alike in adults and children.¹⁷ In these relatively uncommon situations, extrapolation from adult studies may be permissible, but even when the pediatric disease and drug responses are virtually identical to those occurring in adult patients, research in children may still be necessary to develop “age-appropriate formulations [such as dissolvable tablets or liquid varieties] that allow the accurate, safe, and palatable administration of medicines to children of a wide range of weights and with a wide range of developmental characteristics.”¹⁸

and Roberts, *supra* note 4.

15. Pharmacokinetics refers to “the action of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.” RICHARD SLOANE, SLOANE-DORLAND ANNOTATED MEDICAL-LEGAL DICTIONARY 406 (Supp. 1992).

16. Pharmacodynamics refers to “the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure; also, such effects on the actions of a particular drug or drugs.” *Id.*

17. “Pharmacokinetics studies are performed to learn how a living organism (e.g., experimental animal) handles a foreign substance like cancer, i.e., the rate of uptake, distribution and excretion of the substance, and the metabolites formed in the organism following exposure.” *Id.*

18. INST. OF MED., ETHICAL CONDUCT OF CLINICAL RESEARCH INVOLVING CHILDREN 66 (Marilyn J. Field & Richard E. Behrman, eds., 2004). See also Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER MAGAZINE, June 1981 at 18, 18-21, available at <http://www.fda.gov/oc/history/elixir.html> (last visited Sept. 2, 2006) (discussing the Elixir Sulfanilamide disaster in which the manufacturer failed to conduct safety tests of a new formulation of an effective drug, and thus did not discover that the chemical used to create the new formulation, normally found in antifreeze, is a deadly poison).

Usually, pediatric patients present with child-specific diseases not found in adults at all, or they respond differently than adults to the very same interventions.¹⁹ For this reason, extrapolation from adult data will often not suffice to protect pediatric patients.²⁰ Children are not simply lighter adults, so weight-based dosage of adult medications is frequently inappropriate. In fact, “children may metabolize or absorb drugs at a different rate from adults, and therefore a suitable dose is difficult to estimate from the size of the children.”²¹ Pediatric patients have different physiology, body size and composition, growth and development, cognitive and motor function, and special organ system maturation, each of which can impact drug disposition and action in the body and create different outcomes from those seen in adults.²² “Antihistamines and alcohol, for example, two common ingredients in cold medications, can have adverse effects on young patients, causing excitability or excessive drowsiness. Some drugs, like aspirin, can cause serious illness or even death in children with chickenpox or flu symptoms.”²³

Several recent examples demonstrate the need for independent pediatric research rather than reliance on adult data alone. For example, in tests of *Strattera*, a drug used to treat attention-deficit hyper-activity disorder, five out of 1,357 pediatric subjects in the experimental arm of the study reported having suicidal thoughts.²⁴ That number becomes increasingly alarming considering how many thousands more children might take the drug outside of the research context. Notably, none of the 851 subjects receiving placebo reported a similar effect.²⁵ This finding was particularly important because no evidence of increased suicidality occurred among adults taking the drug.²⁶ Researchers suspect a similar phenomenon in pediatric patients

19. Carrie Fisher & Thomas G. Keens, *Participation of Children in Research*, 26 WHITTIER L. REV. 823, 831 (2005); INST. OF MED., *supra* note 18, at 58.

20. Joseph T. Flynn, *Ethics of Placebo Use in Pediatric Clinical Trials: The Case of Antihypertensive Drug Studies*, 42(5) HYPERTENSION 865, 866 (2003); Michelle Meadows, *Drug Research and Children*, 37(1) FDA CONSUMER MAGAZINE, Jan.-Feb. 2003 at 12, 13.

21. Interview by Lawrence Bachorik with Paula Botstein, Deputy Director, FDA's Office of Drug Evaluation I, *Why FDA is Encouraging Drug Testing in Children*, FDA CONSUMER SPECIAL REPORT (Jan. 1995), <http://www.fda.gov/fdac/special/newdrug/kidmed.html>.

22. Roberts, *supra* note 4; Am. Acad. of Pediatrics, *supra* note 4, at 286.

23. Rebecca D. Williams, *How to Give Medicine to Children*, 30(1) FDA CONSUMER 6, 8-9 (Jan.-Feb. 1996) (also noting “[s]ome barbiturates, for example, which make adults feel sluggish, will make a child hyperactive. Amphetamines, which stimulate adults, can calm children”).

24. John Lumpkin, *FDA Warns of Suicidal Thoughts Linked to ADHD Drug*, PHILA. INQUIRER, Sept. 30, 2005, at A6.

25. *Id.*

26. *Id.*

suffering from major depressive disorder, OCD, and other psychiatric problems who have been treated with selective serotonin reuptake inhibitors (SSRIs) approved for use in adults.²⁷ The major physiological and developmental differences between adults and children, combined with these examples, demonstrate that children, as a class of patients, will benefit significantly from research done in the pediatric population.²⁸

PART II—WHAT ARE THE GENERAL PROBLEMS ASSOCIATED WITH CONDUCTING RESEARCH IN CHILDREN?

Given the obvious need for pediatric research discussed above, the glaring lack of information in this field may be perplexing. After all, it seems as though the pharmaceutical industry would jump to meet this demand. If manufacturers conducted the studies, they could gain FDA approval for pediatric indications, market those uses, and reap revenue greater than that generated by off-label prescribing alone. However, for a variety of reasons, drug companies have largely decided that pediatric trials are far more trouble than they are worth.

A. Ethical Concerns

In recent decades, children have been routinely excluded from research following some serious historical abuses.²⁹ Unfortunately, that protective attitude went too far and helped foster the current situation in which information on pediatric prescribing is virtually non-existent.³⁰ As

27. FDA, *FDA Public Health Advisory: Suicidality in Children and Adolescents Being Treated With Antidepressant Medications*, Oct. 15, 2004, <http://www.fda.gov/cder/drug/antidepressants/default.htm> (last visited Sept. 2, 2006) (explaining that the increase in suicidality was discovered through placebo-controlled studies of SSRIs in pediatric subjects and resulted in a “black box” labeling change for many antidepressants); this problem will be addressed in more detail below, in Part IV.

28. Fisher & Keens, *supra* note 19, at 832.

29. Breslow, *supra* note 7, at 136-38. Institutionalized children were often exploited by investigators because there were no parents to deal with and the institutions provided nicely controlled scientific environments in which to perform experiments. *Id.* See also Tom L. Beauchamp & Ruth R. Faden, *History of Informed Consent*, 3 *ENCYC. OF BIOETHICS* 1271, 1274-75 (Stephen Garrard Post, ed., 3rd ed. 2004) (discussing the 1956 Willowbrook study in which newly admitted patients in an institution for mentally disabled children were purposefully infected with hepatitis in order to conduct research in hopes of finding an effective prophylactic agent).

30. Fisher & Keens, *supra* note 19, at 827-31; Jennifer Rosato, *The Ethics of Clinical Trials: A Child's View*, 28 *J.L. MED. & ETHICS* 362, 362 (2000). “Until a few years ago, the prevailing view was that children should not be participants in clinical research trials because children were incapable of consenting to such nontherapeutic interventions and are particularly vulnerable to abuse.” *Id.* The concern about using institutionalized children is still present, as demonstrated by the recent public outcry over the enrollment of New York City foster children in Phase I and II HIV drug trials. Alliance for Human Research

commentators have begun to recognize the need for a more moderate approach, the question has moved from *whether* children should participate to *when and how* they should be enrolled in clinical trials.³¹ With this shift, pediatric research has raised two important ethical concerns: lack of capacity to consent and conflict of interest.³²

First, children are unable to consent to their own participation in research.³³ Children lack the facility to fully understand the potential risks and benefits of research, or what that research entails.³⁴ These are the most basic elements of informed consent. Further, emotional and cognitive development, level of autonomy, and dependence on the influence of their families all impede a child's self-determination.³⁵ In fact, most commentators recognize that, unlike adults, children usually lack the legal right and the intellectual and emotional maturity to consent to research participation on their own behalf. Their vulnerability demands special consideration from researchers and policymakers and additional protections beyond those provided to mentally competent adult participants in research.³⁶

A child's inability to make decisions creates a need to obtain both parental permission for and child assent to the conduct of pediatric research.³⁷ The capacity problem also raises concerns about the level of risk to which pediatric subjects may be exposed, an issue generally solved by the informed consent process for adults.³⁸ These additional complexities are enough to scare some sponsors away.³⁹

Additionally, given the potential conflicts of interest among parents, researchers, and institutional review boards (IRBs), reliance on these individuals and bodies for decision-making may be insufficient to protect

Protection, *NGO Probe to Look at Foster Kids in AIDS Trials—NYC*, Apr. 23, 2005, <http://www.ahrp.org/infomail/05/04/23a.php>.

31. Rosato, *supra* note 30, at 362.

32. See, e.g., FDA, GUIDANCE FOR INDUSTRY: E11 CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION 12-14 (Dec. 2000), available at <http://www.fda.gov/cder/guidance/4099fnl.pdf> (discussing generally the ethical issues in pediatric studies, such as the role of the Institutional Review Board, subject recruitment, consent and assent, and minimizing risk and distress).

33. This issue will be discussed in more detail with regard to the ethics of placebo-controlled pediatric studies, *infra* Part V.A.3.c.

34. Meadows, *supra* note 20.

35. Benjamin S. Wilfond et al., *Ethical Issues in Conducting Behavioral Genetics Research: The Case of Smoking Prevention Trials Among Adolescents*, 6 J. HEALTH CARE L. & POL'Y 73, 76 (2002).

36. INST. OF MED., *supra* note 18, at 28.

37. See the discussion of assent and permission, *infra* Part V.A.3.c.

38. This issue will also be elaborated upon below in Part V, *infra*.

39. Meadows, *supra* note 20.

children from abuse in the research setting.⁴⁰ The psychological effects of a child's disease on his or her whole family can play a detrimental, if inadvertent, role in preventing parents from choosing what is truly in the best interest of their sick child.⁴¹ Specifically, monetary inducements could sway parents to expose their children to greater risks than are appropriate.⁴² In addition, researchers may have financial or professional interests at odds with the individual child's welfare,⁴³ and IRBs can face conflicts between reviewing the work performed by their colleagues and encouraging "cutting edge" research at their institutions. Of course, these latter concerns apply in adult research studies as well.⁴⁴

While these ethical issues certainly render pediatric research more complicated and burdensome for clinical trial sponsors, other practical barriers and disincentives in this area more fully explain the lack of adequate research on drugs for children.

B. Practical Concerns

Perhaps the most important reason the pharmaceutical industry has failed to conduct adequate pediatric research is that for years it simply lacked any economic incentive to do so.⁴⁵ The pharmaceutical industry operates as a for-profit model for commercial purposes and can be expected to make decisions driven by financial interest.⁴⁶ In this context, the pediatric population offers small sales potential compared to the adult market,⁴⁷ and until recently, manufacturers did not need pediatric trials for FDA approval.⁴⁸ Sponsors seek to place products on the market quickly to recoup their research investment and turn a profit, so they simply chose to conduct the less complex and less regulated adult studies necessary for FDA approval. Sponsors had little remaining incentive to conduct studies

40. Leonard H. Glantz, *Research with Children*, 24 AM. J.L. & MED. 213, 218-19 (1998); See, e.g., Rosato, *supra* note 30, at 363.

41. Glantz, *supra* note 40, at 218-19.

42. *Id.*

43. *Id.*

44. See Rosato, *supra* note 30, at 363.

45. *Exploring the Frontiers*, *supra* note 8, at 491-93.

46. *Drug & Device: A Prescription for Better Drug Trials*, 41(3) TRIAL, Mar. 2005, at 54, 56.

47. *Exploring the Frontiers*, *supra* note 8, at 493; Michael S. Labson, *Pediatric Priorities: Legislative and Regulatory Initiatives to Expand Research on the Use of Medicines in Pediatric Patients*, 6 J. HEALTH CARE L. & POL'Y 34, 35 (2002).

48. The 1998 FDA Pediatric Rule and the 2003 Pediatric Research Equity Act attempted to address this loophole, hoping to induce market incentives that had been previously absent. These government interventions are discussed *infra* Part III.C.

in children, other than the ability to openly market pediatric uses to physicians.⁴⁹

Along with this economic non-incentive for pediatric research comes an economic disincentive: the industry's product liability⁵⁰ and public relations concerns.⁵¹ If manufacturers do not label and market drugs for use in children, they might have a better chance of avoiding liability for adverse reactions in pediatric patients, even though the drug may still be prescribed to children through off-label use.⁵² While this strategy begs questions of ethics and efficacy, given the fact that manufacturers might still be held liable if they were aware of the off-label use resulting in problems or illegally promoted that use,⁵³ for manufacturers it might be less expensive to risk liability from off-label use than to risk liability *and* conduct the studies needed for pediatric indications. In addition, the possibility for off-label use in children may lead manufacturers to avoid pediatric research and marketing entirely to escape disastrous financial and public relations consequences if the studies were conducted unethically or harmed the child subjects. Children make very sympathetic victims, even if researchers and sponsors did nothing wrong.⁵⁴

Pediatric research poses other practical problems that would remain even if off-label prescribing practices were prohibited. First, there is a shortage of clinical investigators trained in the nuances of pediatric research⁵⁵ and it is very difficult to enroll child subjects.⁵⁶ As noted above, the market for

49. *Exploring the Frontiers*, *supra* note 8, at 493.

50. For examples of the sort of claims brought against manufacturers for pediatric uses, see the discussion of the SSRI litigation at <http://www.sskrplaw.com/adhd/> (last visited Sept. 10, 2006).

51. *See Exploring the Frontiers*, *supra* note 8, at 491.

52. Breslow, *supra* note 7, at 142 (“[T]he pharmaceutical industry generally sought to avoid pediatric liability by neither labeling nor marketing drugs for children.”).

53. *See, e.g., Proctor v. Davis*, 682 N.E.2d 1203, 1216 (Ill. App. 1997) (finding that there was sufficient evidence of willful and wanton misconduct to justify punitive damages against a drug manufacturer that failed to warn physicians of the adverse effects associated with a particular off-label use that it was aware of and actually promoted through financial and technical assistance to doctors, as well as by helping to create a body of literature touting the particular off-label use).

54. *See* Ferdinand D. Yates, Jr., *Consent Process May Not Be Adequate in Medical Studies Involving Children*, BUFFALO NEWS, May 29, 2005, at F2; *Clinical Trials: House Panel Considers Protections for Foster Children*, AM. HEALTH LINE, May 19, 2005; Deepti Hajela, *AIDS Trials Elicit Outrage*, ALBANY TIMES UNION, May 6, 2005, at B3, available at 2005 WLNR 7226438; Glenn Thrush, *Probe Demanded in Kid Drug Trials*, NEWSDAY, Apr. 25, 2005, at A14, available at 2005 WLNR 6427329 (all discussing the controversial pediatric HIV research that recently came to light in New York City, introduced *supra* note 30).

55. *Exploring the Frontiers*, *supra* note 8, at 493.

56. *Id.* at 491.

pediatric medications remains comparatively small, which is in part because children as a group are relatively healthy. This size does not mean that children do not need pharmaceuticals; instead, the small numbers of pediatric patients with any particular disease make finding subjects to recruit difficult.⁵⁷ In fact, for every fifty pediatric subjects screened for participation in a given study, usually only one will actually be enrolled.⁵⁸ The fact that many parents are unwilling to enroll their children in research, due to its risks and unpredictability, further compounds the shortage.⁵⁹

Even if appropriately qualified investigators are found and a sufficient number of subjects are enrolled, several other difficulties arise with regard to the study itself. Pediatric research involves a more pronounced risk of compliance failure than research with adult subjects because the formulation of the drug being tested might be hard for children to swallow or generally unpalatable.⁶⁰ To ease administration and help parents follow the study protocol, the sponsor may need to develop pediatric formulations from scratch, adding a potentially significant expense.⁶¹ Those conducting the trial may also face “difficulty in determining and measuring endpoints in children.”⁶² Many studies, particularly those involving drugs for pain or psychiatric disorders, have no clear physical indicators of efficacy observable by the investigators, who must instead rely on self-evaluation by subjects.⁶³ Objectivity concerns related to self-evaluation are further exacerbated in pediatric studies, because children must clearly explain how they feel in a way that can be operationalized for data comparison.

Finally, these practical considerations are multiplied because performing only one additional study in children as a follow up to adult trials will not suffice. The pediatric population is diverse and ranges from neonates to toddlers, to children, to adolescents. Each of these subgroups might react differently to a given drug.⁶⁴ Thus, sponsors potentially need to conduct several distinct studies to obtain all the information that doctors need to treat these groups.⁶⁵ These factors impact both enrollment and study

57. Labson, *supra* note 47, at 35.

58. Christopher-Paul Milne, *Pediatric Research: Coming of Age in the New Millennium*, 6 AM. J. OF THERAPEUTICS 263, 269 (1999) [hereinafter *Coming of Age*].

59. See Breslow, *supra* note 7, at 144.

60. *Id.* at 272.

61. See Labson, *supra* note 47, at 35-36 (stating that the disincentives for conducting pediatric research can be significant, such as the difficulty associated with developing a drug formulation specifically for pediatric use, particularly when pharmaceutical companies are allocating their limited research dollars).

62. Henney, *supra* note 13.

63. Labson, *supra* note 47, at 36.

64. INST. OF MED., *supra* note 18, at 61.

65. *Id.*

design, which can make pediatric studies “frustratingly and necessarily slow because safety must be assured, controls must be in place, and scientific conduct must be professional.”⁶⁶ In light of these ethical and economic considerations, for years the pharmaceutical industry made the logical choice to focus almost entirely on research and development for adult drugs.

PART III—WHAT HAS THE GOVERNMENT DONE TO ADDRESS THE DOUBLE-EDGED SWORD OF PEDIATRIC RESEARCH?

It makes economic, legal, and ethical sense to begin clinical trials in adult populations,⁶⁷ but until the past decade, drug companies have lacked any internal incentive to extend research into pediatric subgroups after gleaning important information from adult studies. However, “[t]here is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents.”⁶⁸ In accord, government intervention has necessarily recalibrated industry incentives. Several attempts were made to accomplish this feat and balance protective exclusion of children against protective inclusion in pharmaceutical research.⁶⁹ However, only the most recent attempts directly addressed the root of the problem and come closer to realizing the ultimate goal of improving the amount of information available to pediatric prescribers.

A. Historical Interventions

The 1962 Kefauver-Harris Drug Amendments to the Food, Drug, and Cosmetic Act added the current regulatory requirement of efficacy of new drugs to existing safety standards.⁷⁰ However, this legislation neither required nor induced pediatric research in any way: sponsors of applications

66. Yates, *supra* note 54.

67. The official view of the American Academy of Pediatrics is that investigators “must strive to obtain as much information as possible about the safety and efficacy of the drug under study before enrolling children as subjects.” “In most cases, studies in children should be preceded by initial clinical trials in adults to provide preliminary pharmacokinetic, safety, and efficacy data. In some instances drugs intended to treat specific diseases that primarily or exclusively occur in children may be studied initially in children.” Am. Acad. of Pediatrics, *supra* note 4, at 287.

68. *Id.* (emphasis omitted).

69. Fisher & Keens, *supra* note 19, at 832; See also Loretta M. Kopelman, *Group Benefit and Protection of Pediatric Research Subjects: Grimes v. Kennedy Krieger and the Lead Abatement Study*, 9 ACCOUNTABILITY RESEARCH 177, 177 (2002) [hereinafter *Group Benefit*] (explaining “[t]he problem is that with too few protections for children, some can be exploited; but with too many obstacles, advances for them as a group will be slow.”).

70. Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (codified in scattered sections of 21 U.S.C.).

for approval could simply submit adult studies demonstrating that their drug was safe and effective for the claimed indication, and then rely on off-label prescribing for all uses in other populations.⁷¹ In 1979, the FDA required that pediatric labeling claims be supported by adequate pediatric tests,⁷² but this rule did nothing to change the system, which permitted approval of drugs not tested in children so long as the labeling indicated the lack of such testing. Such labels became known as “orphaning” clauses.⁷³

While the FDA intended for this regulation to spur pediatric research, it actually backfired. Sponsors decided it was more efficient to forgo the pediatric tests and simply accept disclaimers on their labels.⁷⁴ Therefore, while the 1979 rule could guard children against false or unsubstantiated claims, it resulted in another dangerous situation for pediatric patients—a complete lack of *any* informative labeling.⁷⁵ Unfortunately, this ineffective and hazardous strategy remained the government’s approach to protect children until the 1990s.⁷⁶ In that decade, the emergence of HIV/AIDS as a pediatric disease created a new sense of urgency with regard to pediatric drugs and sparked both the FDA and Congress to make serious changes.⁷⁷

In 1990, the FDA began to incorporate into its review process the “Pediatric Page,” which is a form used for reviews of all new molecular entities submitted for approval that details the adequacy of the label with regard to pediatric information and any need, plans, or agreements between the FDA and the sponsor for further studies in children.⁷⁸ The FDA took another step toward improvement in 1994 by allowing pharmaceutical companies to use “adequate and well-controlled” adult studies, in addition to pharmacokinetic, safety, and pharmacodynamic data, to support pediatric

71. *Exploring the Frontiers*, *supra* note 8, at 491, 493.

72. Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434 (June 26, 1979) (codified as amended in 21 C.F.R. pt. 201 and 202).

73. Breslow, *supra* note 7, at 151.

74. *Id.*

75. *Id.* at 148. This virtual abandonment of children is particularly ironic given that several changes in the regulation of pharmaceuticals by the FDA have been sparked by adverse events impacting children. For example, the 1906 Act resulted from the death of several children from a diphtheria antitoxin infected with tetanus. The 1937 Amendments came on the tails of the elixir of sulfanilamide disaster described *supra* note 18, and the 1962 Amendments stemmed from the Thalidomide-induced birth defects seen in Europe. Labson, *supra* note 47, at 34-35.

76. Breslow, *supra* note 7, at 148.

77. *Exploring the Frontiers*, *supra* note 8, at 493.

78. *Coming of Age*, *supra* note 58, at 264. However, these forms are rarely completed in any level of detail and often seem to be more of an afterthought in the approval process than a substantive requirement because they simply summarize the state of pediatric studies at the time an FDA action is taken on an application.

labeling.⁷⁹ This rule did not actually require any new testing, but it did require “all sponsors of drug and biologics products [to] examine available data on pediatric use and submit a supplemental application for a pediatric indication if supported by the existing data.”⁸⁰ Nevertheless, manufacturers could still opt for the disclaimer approach if the necessary information was absent.⁸¹

Despite good intentions, these FDA initiatives failed to achieve their goals. As the FDA began to face increasing popular pressure on a number of fronts in the late 1990s stemming from delayed access to new products, increased competition from overseas, and disincentives for research due to increased generic competition, it became clear that Congress needed to intervene.⁸² This pressure finally led to a broad piece of responsive legislation: the Food and Drug Administration Modernization Act of 1997 (FDAMA),⁸³ and the carrot-and-stick incentive/mandate system currently in place.

B. FDAMA/Best Pharmaceuticals for Children Act

The FDAMA established a pediatric studies incentive program in section 505A of the Federal Food, Drug, and Cosmetic Act.⁸⁴ As a reward for conducting pediatric trials specifically requested by the FDA, drug sponsors holding approved applications and existing patents or other exclusivity were offered a six-month extension of market exclusivity for all of their drug products with the same active ingredient as the one studied.⁸⁵ During this six-month period, the FDA could not approve an abbreviated new drug application for generics relying on the safety and efficacy data from the original sponsor’s new drug application (NDA).⁸⁶ This legislation provided a lucrative economic incentive for sponsors to perform the requested research because they could delay generic competition.

79. Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 Fed. Reg. 64,240 (Dec. 13, 1994) (codified as amended in 21 C.F.R. pt. 201).

80. Labson, *supra* note 47, at 40.

81. Breslow, *supra* note 7, at 152.

82. *Coming of Age*, *supra* note 58, at 264-65.

83. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

84. See Federal Food, Drug, and Cosmetic Act § 505A, 21 U.S.C.A. § 355a(b-c) (West Supp. 2006).

85. *Exploring the Frontiers*, *supra* note 8, at 491 (explaining the incentive created by this statute).

86. *Coming of Age*, *supra* note 58, at 265. However, generics could still be approved during this six month period if they submitted their own research and did not rely on materials from the pioneer’s submission. *Id.*

The process worked as follows: first, the FDA would issue a written request that the sponsor outline the specific studies to be undertaken, the study designs and goals, and the age groups to be tested.⁸⁷ Studies had to be completed and submitted as part of an NDA or supplemental NDA for the new pediatric indication, but the application need not be approved to qualify for exclusivity.⁸⁸ In other words, no labeling change had to occur so long as the sponsor provided the FDA with information and data responsive to the written request.⁸⁹ Finally, the FDA would negotiate with the sponsor for the new indication or appropriate labeling revisions based on the research.⁹⁰ Because the program was completely voluntary, sponsors who received written requests could choose to conduct the studies based on their own determination of whether the six-month exclusivity incentive justified the costs of conducting the requested trials. This rewards structure made the program the “carrot” in the current regulatory scheme for pediatric research.

The pediatric exclusivity provision of the FDAMA included a sunset provision and expired in 2002. However, due to its moderate success in spurring pediatric testing and labeling changes, its basic premise and incentives were reenacted, with some improvements, as the Best Pharmaceuticals for Children Act (BPCA) that same year.⁹¹ Under the BPCA, the FDA is authorized to make written requests for pediatric studies based on the availability of information concerning the safe and effective use of the drug in the pediatric population, whether new pediatric studies concerning the drug will produce health benefits for children, and whether reformulation of the drug for children is necessary.⁹²

The BPCA still involves a voluntary system, but it establishes a two-tiered approach to help ensure that important pediatric research is performed even if sponsors do not take advantage of the statute’s incentive.⁹³ If a sponsor responds to an FDA request, things then proceed very similarly to how they would have under the FDAMA. However, a sponsor’s failure to respond triggers a new system. The BPCA establishes a private foundation to support third party research on drugs still entitled to

87. *Id.*

88. *Id.*

89. Breslow, *supra* note 7, at 155.

90. *Exploring the Frontiers*, *supra* note 8, at 497.

91. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended in scattered sections of U.S.C.). This statute has its own sunset clause for 2007. Best Pharmaceuticals for Children Act, 21 U.S.C.A. §355a(n) (West Supp. 2006).

92. Best Pharmaceuticals for Children Act, 42 U.S.C.A. §284m (West Supp. 2006).

93. Breslow, *supra* note 7, at 134.

patent protection or exclusivity.⁹⁴ This foundation issues contracts for the requested studies, though in the case of insufficient foundation funding, the drug can be included on a list for public contract research on off-patent/off-exclusivity drugs.⁹⁵ If a sponsor rejects a written request because the drug is ineligible for the incentive or if the drug was included on the list created by the private foundation, the FDA will publish a request for a contractor to conduct the research using public funds.⁹⁶ Between this two-tiered system and a new provision that requires public dissemination of all studies conducted under the FDA's written requests,⁹⁷ the BPCA seems well poised to improve the amount of information available to pediatric prescribers. This goal is buttressed by the "stick" to the BPCA's "carrot"—the Pediatric Research Equity Act (PREA).

C. Pediatric Research Equity Act

Passed in December of 2003, the PREA⁹⁸ codified the 1998 Pediatric Rule promulgated by the FDA, which a federal district court struck down for exceeding the FDA's authority.⁹⁹ This rule "empowered the FDA to require pediatric testing of already marketed drugs and instituted a presumption favoring pediatric testing and labeling for new drugs,"¹⁰⁰ thus creating a non-voluntary correlate to the FDAMA/BPCA pediatric incentive. The PREA requires adequate data¹⁰¹ to assess safety and efficacy

94. Public Health Services Act, 42 U.S.C. §290b (West Supp. 2002).

95. I. Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661, 670 (2003).

96. See *id.* (describing this two-tiered system and the workings of the BPCA more generally).

97. Best Pharmaceuticals for Children Act, 21 U.S.C.A. §355a(j) (West Supp. 2006). All reports completed pursuant to the Act are part of the public domain and will be published in the Federal Register. Breslow, *supra* note 7, at 175. Other improvements to the BPCA include elimination of the user fee waiver for pediatric supplemental applications, the creation of the Office of Pediatric Therapeutics to coordinate all FDA policy regarding research in pediatric populations, and a requirement that the Institute of Medicine review federal regulations governing pediatric research and submit a report including recommendations on best practices relating to research involving children. Cohen, *supra* note 95, at 670-71.

98. Pediatric Research Equality Act, Pub. L. No. 108-155 117 Stat. 1936 (2003) (codified as amended in scattered sections of 21 U.S.C.).

99. Ass'n Am. Physicians & Surgeons, Inc. v. U.S Food and Drug Admin., 226 F.Supp.2d 204, 212 (D.D.C. 2002).

100. Breslow, *supra* note 7, at 160. The rule also allowed the FDA to punish manufacturers for noncompliance by deeming an existing drug misbranded or a new drug unlicensed. *Id.*

101. This data need not come exclusively from pediatric studies, but can also be extrapolated from well-controlled adult studies when possible. Federal Food, Drug, and

of a drug or biologic for the claimed indications of an NDA in all relevant pediatric subpopulations, even if the sponsor has not specifically claimed any pediatric uses.¹⁰² The statute also requires data to support dosing and administration for any pediatric subpopulations in which the drug is found to be safe and effective.¹⁰³

The PREA is not all-inclusive and does recognize several waivers that exempt NDAs from pediatric testing when sponsors make certain showings. The requirements can be deferred if pediatric studies should be delayed until additional safety or efficacy data have been collected in adult subjects.¹⁰⁴ Additionally, where evidence strongly suggests the drug would be ineffective or unsafe in all pediatric age groups, the requirements can be waived entirely.¹⁰⁵ The requirements can also be waived if the drug does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of such patients.¹⁰⁶

The FDA can also require pediatric data for drugs already approved and thus not covered by the requirements surrounding NDAs. This occurs if the drug is used for a substantial number of pediatric patients for its labeled indications, or if there is reason to believe the drug would represent meaningful therapeutic benefit¹⁰⁷ over existing therapies for pediatric patients.¹⁰⁸ Both of these situations must be accompanied by a finding that

Cosmetic Act, § 505B, 21 U.S.C.A. § 355c(a)(2)(B)(i) (West Supp. 2006).

102. Federal Food, Drug, and Cosmetic Act § 505B 21 U.S.C.A. § 355c(a)(2)(A)(i) (West Supp. 2006). This information must accompany applications for a new indication, dosage form, route of administration, dosing regimen, or active ingredient. Federal Food, Drug, and Cosmetic Act § 505B, 21 U.S.C.A. § 355c(a)(1)(A-B) (West Supp. 2006).

103. Federal Food, Drug, and Cosmetic Act § 505B, 21 U.S.C.A. § 355c(a)(2)(A)(ii) (West Supp. 2006).

104. Federal Food, Drug, and Cosmetic Act § 505B, 21 U.S.C.A. § 355c(a)(3)(A)(i) (West Supp. 2006).

105. Federal Food, Drug, and Cosmetic Act § 505B, 21 U.S.C.A. § 355c(a)(4)(A) (West Supp. 2006).

106. *Id.* These deferral and waiver provisions provide an indirect comment on when children's participation research is ethically justified in the eyes of the FDA. Rosato, *supra* note 30, at 365.

107. Meaningful therapeutic benefit is defined in the Federal Food, Drug, and Cosmetic Act as: "(1) if approved, the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or (2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options." Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C.A. § 355c(c) (West Supp. 2006).

108. Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C.A. § 355c(b)(1) (West Supp. 2006). These requirements may also be waived in certain conditions. Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C.A. § 355c(b)(2) (West Supp. 2006).

the absence of adequate labeling could pose significant risks to pediatric patients.¹⁰⁹

D. Impact of These Initiatives

With this carrot-and-stick approach, the regulation of pediatric research may finally be on track to fill the informational void left by years without industry incentive to conduct these studies. The tandem system has helped to build the infrastructure for trials using child subjects, which occur far more frequently now than ten years ago.¹¹⁰ Between the passage of the FDAMA in 1997 and the passage of PREA in 2003, the number of child subjects nearly tripled¹¹¹ as pharmaceutical companies began to “think pediatric.”¹¹² However, the question now is whether child subjects will be adequately protected in this new environment,¹¹³ a question that will be asked specifically with regard to studies requested by the FDA under the BPCA and will serve as the focal point for the remainder of this article.

PART IV—ARE THE REQUESTED PLACEBO-CONTROLLED PEDIATRIC STUDIES APPROVABLE UNDER THE FEDERAL REGULATIONS?

Under its authority from the BPCA, the FDA has created templates to serve as written request models for pediatric studies of drugs used to treat depression, OCD, HIV, and cancer. The OCD¹¹⁴ and depression¹¹⁵ templates both specifically request placebo-controlled trials, while the

109. Federal Food, Drug, and Cosmetic Act § 505, 21 U.S.C.A. §355c(b)(1) (West Supp. 2006).

110. Meadows, *supra* note 20, at 13-14.

111. VERA HASSNER SHARAV, ET AL., THE ALLIANCE FOR HUMAN RESEARCH PROTECTION, COMMENTS TO THE NATIONAL ACADEMY OF SCIENCES COMMITTEE OF THE INSTITUTE OF MEDICINE ON CLINICAL RESEARCH INVOLVING CHILDREN (Aug. 18, 2003), <http://www.ahrp.org/testimonypresentations/BestPharmaAct0803.php> (last visited Sept. 22, 2006)

112. *Exploring the Frontiers*, *supra* note 8, at 496.

113. *E.g.*, Flynn, *supra* note 20, at 868 (“[I]t is incumbent on researchers to develop research procedures that will not only answer the scientific questions of interest but also protect this vulnerable patient population from harm.”); SHARAV, *supra* note 111 (“Unfortunately, the law failed to balance financial incentives with new (or improved) safeguards to protect an increased number of young children who are being exposed to the hazards of research. As a result, children who are legally precluded from exercising the right to refuse are being aggressively recruited to bear the burden of testing drugs that may (or may not) be safe or in their best interest.”).

114. FDA, OCD Template, http://www.fda.gov/cder/pediatric/OCD_wr_template.htm (last visited Sept. 29, 2006).

115. FDA, Antidepressant Template, http://www.fda.gov/cder/pediatric/antidepressant_wr_template.htm (last visited Sept. 29, 2006).

HIV¹¹⁶ and oncology¹¹⁷ drug study requests are far more open-ended regarding trial design and do not require placebo controls. Before asking whether the use of placebos to test these drugs in children is ethically acceptable, this article will first explore whether that issue is moot through a legal analysis of whether these studies are even approvable under an appropriate application of the federal regulations governing the conduct of pediatric research.

A. History of Regulations Governing Pediatric Research

The development of research ethics did not begin in earnest until the middle of the twentieth century. Following World War II and the Holocaust, the Nuremberg Code¹¹⁸ forbade research using non-consenting subjects, which effectively, although not explicitly, prohibited all research on children because of their incapacity to consent.¹¹⁹ Given the demonstrated need for pediatric research and due to its wide recognition as overly restrictive,¹²⁰ the Nuremberg Code was displaced on the international stage in 1964 by the World Medical Association's Declaration of Helsinki.¹²¹ This declaration directly responded to the Nuremberg Code's shortcomings by permitting surrogate consent for nontherapeutic research on those legally unable to provide consent themselves, such as children and the mentally disabled.¹²² Though certainly important, these international codes simply served as guidelines lacking the force of law and the ability to bind researchers, highlighting the need for government intervention in this area. By the late 1960s and early 1970s, several exposés of unethical

116. FDA, HIV Template, http://www.fda.gov/cder/pediatric/HIV2_template.htm (last visited Sept. 29, 2006).

117. FDA, Oncology Template, <http://www.fda.gov/cder/pediatric/oncologytemplate.htm> (last visited Sept. 29, 2006). This template is far less detailed than the others, probably because there are so many different types of cancer that a more general template would not have been feasible. *Id.*

118. 2 TRIALS OF WAR CRIMINALS BEFORE THE NUERNBERG MILITARY TRIBUNALS UNDER CONTROL COUNCIL LAW NO. 10 181-82 (U.S. Gov't Printing Office, Oct. 1946 – Apr. 1949), available at <http://ohsr.od.nih.gov/guidelines/nuremberg.html>.

119. Loretta M. Kopelman, *What Conditions Justify Risky Nontherapeutic or "No Benefit" Pediatric Studies: A Sliding Scale Analysis*, 32 J.L. MED. & ETHICS. 749, 749 (2004) [hereinafter *Sliding Scale*].

120. Rupali Gandhi, *Research Involving Children: Regulations, Review Boards and Reform*, 8 J. HEALTH CARE L. & POL'Y 264, 268 (2005) (noting that Nuremberg's strict prohibition would be harmful because it would prevent medicine from advancing in the treatment of childhood diseases).

121. WORLD MED. ASS'N, DECLARATION OF HELSINKI (1964), <http://www.wma.net/e/policy/pdf/17c.pdf>.

122. INST. OF MED., *supra* note 18, at 49-50.

research on vulnerable populations forced American policy-makers to confront the lack of ethical guidelines in research.¹²³

Finally, in 1973, the Department of Health, Education, and Welfare (now the Department of Health and Human Services (HHS)) issued a working document on experimentation with children that proposed several specific protections.¹²⁴ Though HHS failed to publish final rules governing the conduct of clinical research until almost a decade later, these rules, codified at 45 C.F.R. § 46, were based on the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and include special protections for certain groups, such as children, pregnant women, and prisoners. These regulations initially covered only studies funded by HHS and did not apply to privately conducted research submitted to the FDA to support the approval of various drug applications.¹²⁵ Fortunately, after nearly twenty years of this differential treatment, Congress enacted the Children's Health Act of 2000, which required that all research involving children conducted, supported, or *regulated* by HHS be in compliance with the existing pediatric rules, widely known as Subpart D,¹²⁶ thus extending these rules to all studies submitted to the FDA.¹²⁷

B. The Federal Risk Categories

The FDA, like its umbrella agency HHS, uses a system of risk categories to guide IRBs faced with the decision of whether to approve proposed

123. *Id.* at 50. Several research scandals were highlighted in Henry K. Beecher's influential article describing twenty-two problematic studies in which consent was never obtained from subjects. *Ethics and Clinical Research*, 274 NEW ENG. J. MED. 1354, 1355-59 (1966). In addition, the Tuskegee study was exposed in 1972, probably the most important research scandal to ever occur in the United States and one of the major driving forces finally sparking federal intervention into the medical research arena. This study was intended to observe the natural course of syphilis in untreated African-American patients. When it began, there was no effective treatment, but even after penicillin became widely available as the standard of care, patients were denied treatment, and even deceived into avoiding appropriate medication. Beauchamp & Faden, *supra* note 29, at 1275.

124. INST. OF MED., *supra* note 18, at 51.

125. Breslow, *supra* note 7, at 138-39.

126. Children's Health Act of 2000, Pub. L. No. 106-310, 114 Stat. 1167.

127. FDA did not adopt the existing HHS regulations wholesale, but made minor changes based on its particular responsibilities and functions, consciously trying to keep things as uniform as possible so as to reduce regulatory burden on institutions and IRBs. Additional Safeguards for Children in Clinical Investigations of FDA—Regulated Products, 66 FED. REG. 20,589, 20,591 (Apr. 24, 2001) (codified at 21 C.F.R. pt. 50, 56) [hereinafter Additional Safeguards]. In its Interim Rule following the Children's Health Act, the FDA stated that it was requiring additional safeguards to protect children because of expected increases in the enrollment of children in clinical investigations as a result of recent pediatric initiatives, at that time, the FDAMA and the 1998 Pediatric Rule. *Id.* at 20,589.

pediatric research.¹²⁸ This system requires the board to balance the risks and benefits to the child posed by the research, the potential benefit to children as a group, and the individual child's ability to assent.¹²⁹ Based on these considerations, the research must fall into one of four categories of approvable research or it cannot proceed.¹³⁰ The risk categories essentially create a sliding scale, so that "[t]he more the research project resembles standard medical care, the less it is regulated. The closer it comes to pure research, in which the creation of new knowledge is the sole or primary goal, the more it is regulated."¹³¹

Importantly, the risk categories established in Subpart D apply to each individual intervention included in a study protocol and not to the study as a whole, such that the placebo and experimental arms of a study could potentially be categorized differently.¹³² If the entire study was viewed together, the benefit from one component could justify the risks of the other components. However, under the regulations, IRBs must separately analyze risks for each procedure involved in the protocol.¹³³ These federal regulations nonetheless fail to deal specifically with the use of placebo controls in pediatric research,¹³⁴ leaving researchers without clear guidance on how the FDA's requests for pediatric OCD and depression studies should be classified and whether they are approvable at all.

128. "In addition to other responsibilities assigned to IRBs under this part and part 56 of this chapter, each IRB must review clinical investigations involving children as subjects covered by this subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51 [minimal risk], 50.52 [greater than minimal risk and direct benefit], or 50.53 [greater than minimal risk and no direct benefit] and the conditions of all other applicable sections of this subpart D." 21 C.F.R. § 50.50 (2006). This part of the regulation lists only three risk categories because the fourth is a catchall that cannot be approved by an IRB, but needs approval by the Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines, following opportunity for public review and comment. 21 C.F.R. § 50.54 (2006).

129. William J. Wenner, *Does the Legal System Provide Adequate Protection for Children in Scientific Experiments? The Unanswered Question of Grimes v. Kennedy Krieger Institute*, 8 U.C. DAVIS J. JUV. L. & POL'Y 243, 258 (2004).

130. 21 C.F.R. § 50.50. These risk categories and their related requirements are endorsed, adopted, and agreed with by the American Academy of Pediatrics. Am. Acad. of Pediatrics, *supra* note 4, at 288.

131. Glantz, *supra* note 40, at 232.

132. Gandhi, *supra* note 120, at 280. See also Franklin G. Miller et al., *When Do the Federal Regulations Allow Placebo-Controlled Trials in Children?*, 142(2) J. PEDIATRICS 102, 103-04 (2003) (pointing out that reviewers cannot justify a risky procedure just because something else in the protocol would have a benefit because that sort of analysis exemplifies the "fallacy of the package deal").

133. Gandhi, *supra* note 120, at 280.

134. Rosato, *supra* note 30, at 366.

1. Minimal Risk (21 C.F.R. § 50.51)

The first category under which pediatric research is approvable is not very controversial because it involves an insignificant chance of harm to child subjects. The regulation provides that

[a]ny clinical investigation . . . in which no greater than minimal risk to children is presented may involve children as subjects . . . if the IRB finds and documents that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians¹³⁵

Such research need not present direct benefit to the subjects because the risk to the child is minimal. That is, “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”¹³⁶ However, this definition leaves open the important question of whose daily life should serve as the comparator.

A technical or literal reading of the language in this modestly regulated risk category could permit research posing substantial risk to children because the risks of daily life vary based on age, health status, social strata, and geographic location.¹³⁷ If minimal risk is truly tied to such subjective variables, researchers could conduct riskier research on children already disadvantaged by the risky situations they face in their own lives, raising concern about the unjust distribution of research burdens.¹³⁸ For this reason, a more objective definition of minimal risk is almost universally used in place of the unacceptable relativistic theory of minimal risk. Ethicists and responsible IRBs generally understand minimal risk to refer to the daily life of the average healthy child, as opposed to those risks facing the particular subject in his or her particular life.¹³⁹

135. 21 C.F.R. § 50.51 (2006). The permission of one parent may suffice for this type of research. 21 C.F.R. § 50.55(e)(1) (2006). Examples of procedures that the FDA considers to fall into this category include “clean-catch urinalysis, obtaining stool samples, administering electroencephalograms, requiring minimal changes in diet or routine, the use of standard physiological tests,” and taste tests or temperature readings orally or in the ear. Additional Safeguards, *supra* note 127, at 20,593. None of these examples describe protocol options, such as the use of placebo controls or other study designs, and they fail to provide potentially more helpful examples of what sorts of procedures would *not* be minimal risk.

136. 21 C.F.R. § 50.3(k) (2006).

137. Cohen, *supra* note 95, at 689-90. See also Glantz, *supra* note 40, at 233 (exploring this problem).

138. Cohen, *supra* note 95, at 690.

139. This objective interpretation has been supported by the National Human Research Protections Advisory Committee, Gandhi, *supra* note 120, at 282, the Institute of Medicine, INST. OF MED., *supra* note 18, at 122, the Office of Protection from Research Risks, and

Nevertheless, some commentators rely on the current dearth of information on pediatric prescriptions to conclude, controversially, that many pediatric trials could be categorized as minimal risk even under this objective definition. They reason that “[w]hen there is no known effective treatment for the condition under study, the use of placebo poses minimal risks to children.”¹⁴⁰ This is because

[t]he category of “no known effective treatment” includes both no treatment and a treatment whose safety and efficacy have not been established. In these cases, children who receive placebo in research are receiving essentially the same thing they would receive outside of the research context, namely, no effective treatment for their condition.¹⁴¹

Moreover, minimal risk has been described as the “socially permissible level of risk that parents would normally permit their children to be exposed to in non-research settings.”¹⁴² As discussed in Part I.A., as many as eighty percent of drugs currently on the market pose some risk of adverse events or ineffectiveness when prescribed to children due to inadequate labeling for pediatric use and deficiency of information about safety and efficacy.¹⁴³ Therefore, placebo control arms seem to meet the requirements of this risk category because the risk of receiving ineffective treatment is the same as that encountered by the average child during the course of ordinary clinical practice.

While this reasoning could theoretically extend to the placebo-controlled studies requested by the FDA for pediatric OCD and depression, the severity of these conditions gives reason for pause. Unlike otherwise healthy children who only need medication for routine ear infections or twenty-four hour “bugs,” children suffering from OCD and depression are neither average nor healthy. These children face more than minimal risk because the probability and magnitude of harm or discomfort anticipated from placebo, no treatment, or ineffective treatment are greater than those ordinarily encountered in the daily lives of average healthy children. Thus, it is not the use of placebos that place these FDA requests outside of the

President Clinton’s National Bioethics Advisory Commission, *Group Benefit*, *supra* note 69, at 184. There is additional support for the objective approach based on 21 C.F.R. § 50.53, permitting research that poses only a minor increase over minimal risk, keyed to the specific lives of the subjects themselves. 21 C.F.R. § 50.53 (2006). The relativistic interpretation would render § 50.53 virtually meaningless because then minimal risk and minor increase over minimal risk would refer to the same thing: this objective approach best preserves the independent value of each section.

140. Miller et al., *supra* note 132, at 104.

141. *Id.* at 104-05.

142. Gandhi, *supra* note 120, at 281.

143. Am. Acad. of Pediatrics, *supra* note 4, at 286.

minimal risk category, but rather the *conditions* themselves for which research is needed that prevent both the experimental and control arms of the FDA's requests from being approvable under 21 C.F.R. § 50.51.

2. Therapeutic Research (21 C.F.R. § 50.52)

The placebo-controlled trials requested by the FDA for OCD and depression fare better under the therapeutic research risk category, but not for long. Unlike minimal risk, this category is defined by the level of potential benefit the intervention offers to participants, which can offset more risk than is normally experienced in the daily lives of average healthy children.¹⁴⁴ The regulation provides that:

Any clinical investigation . . . in which 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 . . . may involve children as subjects only if the IRB finds and documents 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 guardians¹⁴⁵

Importantly, the presence of a direct benefit does not end the inquiry. The IRB must consider whether that benefit is of sufficient magnitude to outweigh the likelihood of any risks associated with the research. Additionally, the requirement that the anticipated risk-benefit ratio of the intervention mirror that of available alternatives seems to mandate a determination of clinical equipoise.¹⁴⁶ If neither arm of the study is known to be better or worse, and the same is true for all available alternatives to those arms, then equipoise exists and the study meets the “at least as favorable” requirement of the regulation.¹⁴⁷ Although research approved under this category can be quite risky, section 50.52 causes little controversy because child subjects stand to gain direct benefit from their

144. 21 C.F.R. § 50.52 (2006).

145. *Id.* Each of the federal risk categories demands that adequate provisions are made for soliciting the assent of the child subjects and the permission of their parents as an approval criterion. Under §§ 50.51 and 50.52, the permission of only one parent is sufficient, if consistent with state law, but both parents must give permission for research approved under §§ 50.53 and 50.54, unless only one parent has full legal responsibility for the child. 21 C.F.R. § 50.55(e). The more important difference in each category lies in the level of risk permitted.

146. Fisher & Keens, *supra* note 19, at 843.

147. *Id.* For a more detailed discussion of clinical equipoise, see *infra* Part V.A.1.

participation.¹⁴⁸ However, things can become more complex depending on the definition of “direct benefit.”

“Hold[ing] out the prospect of direct benefit for the individual subject”¹⁴⁹ is both broad and vague, and, despite its centrality to the therapeutic research risk category, federal regulations fail to define this phrase. “Benefit” could be defined to include the entire range of research “perks,” such as payment, physical examinations, increased medical attention over what a subject would normally receive (or could afford) in clinical care, or even the psychological benefit of doing something good for others. While an IRB might interpret direct benefit this expansively, a narrow definition is necessary to avoid characterizing all research as therapeutic.

In 1999, the FDA’s Pediatric Advisory Subcommittee issued a consensus statement classifying altruism or other psychological benefits as insufficient to qualify research for approval under this risk category.¹⁵⁰ Nonetheless, the statement is still overly broad because it includes benefit to the general population of children as conferring direct benefit to the subjects themselves.¹⁵¹ The consensus statement explains that if the affliction under study is one likely to affect a large proportion of the pediatric population, such as a routine ear infection, research could fall under this risk category.¹⁵² It will do so even if the individual subjects are not presently afflicted because they are likely to suffer from the problem at some point and direct benefit would accrue to them at that time.¹⁵³

This definition focuses on the “holding out” language of the regulation, allowing future benefit to satisfy the direct benefit requirement. While this understanding does technically fit the regulation, it is more appropriate to assume that this risk category requires the direct benefit to occur during the subject’s enrollment period. This interpretation best protects child subjects as a group and helps ensure the meaningfulness of the direct benefit requirement. Because the very point of clinical research is to benefit future

148. 21 C.F.R. § 50.52. Some commentators, however, consider it inappropriate to label any research as therapeutic because it risks propagation of the misconception that research will focus on the individual well-being of the subject when the real goal of research is generalizable knowledge that will help not necessarily the research patient, but future patients. Fisher & Keens, *supra* note 19., at 825. This category seems to mask the fact that the very point of research is based on the fact that investigators are unsure whether the intervention will offer any benefit at all, let alone its adverse effects. *Id.* at 824.

149. 21 C.F.R. § 50.52.

150. FDA, FDA Ethics Working Group Consensus Statement on the Pediatric Advisory Subcommittee’s November 15, 1999 Meeting, <http://www.fda.gov/cder/pediatric/ethics-statement.htm> [hereinafter Consensus Statement].

151. *Id.*; Rosato, *supra* note 30, at 366-67.

152. Consensus Statement, *supra* note 150.

153. Rosato, *supra* note 30, at 366.

patients, this requirement could be too easily satisfied if all researchers must demonstrate is some chance of future benefit to the individual subjects. Furthermore, the heavy focus of the consensus statement on benefit to the general population comes at the expense of the individual subject who may never suffer from the affliction.¹⁵⁴ The fact that the regulation discusses only the *prospect* of direct benefit demonstrates that this category does not require an actual *guarantee* of direct benefit to subjects. However, consideration of the general population edges towards the nontherapeutic risk category, discussed below, suggesting that the definition of direct benefit must be further narrowed in order for each section of the regulations to have independent meaning.

So far, this article has established that the direct benefit to child subjects required by section 50.52 cannot simply be the psychological benefit associated with helping others and that the benefit should accrue to individual child subjects during the course of their participation in the study. But can benefits from the placebo effect or increased medical attention from investigators suffice? The FDA has explicitly recognized the ambiguity that the direct benefit requirement poses. In the 2001 Interim Rule, in which it adopted Subpart D following the Children's Health Act, the FDA stated that "clinical investigations involving placebos in children may be conducted in accord with Sec. 50.52. There is evidence of direct benefit to subjects from participating in placebo-controlled trials, including increased monitoring and care of subjects even though a subject may not actually receive the test product."¹⁵⁵

This explanation appropriately recognizes that risks associated with a placebo control arm cannot be justified based on the benefits of the experimental arm and that the placebo group must have its own direct benefits. Importantly, under this formulation both the experimental and control arms of the requested studies for pediatric OCD and depression drugs would likely satisfy the direct benefit requirement, and thus fall under the relatively nonrestrictive therapeutic category of Subpart D. However, the FDA's statement is not normatively appropriate because the "benefits" listed are still too broad.

Assessment of a research procedure's potential benefits should not include consideration of unrelated collateral, indirect, or side benefits not related to the research objectives.¹⁵⁶ In other words, direct benefits should include only those benefits actually *intended* by the research hypotheses.¹⁵⁷

154. See *Group Benefit*, *supra* note 69, at 186.

155. *Additional Safeguards*, *supra* note 127, at 20, 593.

156. INST. OF MED., *supra* note 18, at 132.

157. See Cohen, *supra* note 95, at 679 (explaining direct benefit as that expected if the

For example, the hypothesis of one of the FDA's requested studies would be that an antidepressant that works well in adults, but is unproven in children, would also work well in children. Subjects who receive this antidepressant stand to gain a direct benefit because if that hypothesis is correct, their depression will improve. The hypothesis intends no benefit to the placebo group and if there is any benefit, either through the placebo effect¹⁵⁸ or increased medical attention, it is purely incidental. Therefore, the best definition of "direct benefit" would require that the benefit at least be intended as the very reason that the research was undertaken. This definition allows for the experimental arms of pediatric research to be categorized as therapeutic, but prevents placebo controls from ever meeting the direct benefit standard, despite the FDA's own statement to the contrary.¹⁵⁹ Adopting this definition does not mean that placebo controls could never be approved for use in child subjects, but rather that their use is more appropriately categorized as nontherapeutic research subject to more stringent requirements and stricter subject protections.

Clearly, the FDA has the authority to reasonably interpret its own regulations, and IRBs could permissibly evaluate both the experimental and control arms of the OCD and depression studies requested under the BPCA according to the requirements of the therapeutic risk category. However, under the most normatively appropriate definition of "direct benefit," which requires an intentional benefit that accrues to individual child subjects during their participation, a placebo-control arm cannot meet this standard. Therefore, the next subsection of this article will analyze the approvability of the FDA's requests under the nontherapeutic risk category. The section will also explain why this use of placebos will soon be non-approvable under any risk category, even assuming that the FDA's definition of direct benefit is appropriate.

hypothesis of the research is correct).

158. The placebo effect may actually provide significant benefit to a subject. In fact, some commentators note that between 35% and 75% of research subjects derive some benefit from taking inactive agents alone. Sharona Hoffman, *The Use of Placebos in Clinical Trials: Responsible Research or Unethical Practice?*, 33 CONN. L. REV. 449, 455-56 (2001).

159. See, e.g., Jack Schwartz, *Research and Children's Health: The Court of Appeals as Bioethics Commission*, 36 MD. B.J. 8, 10 (Jan./Feb. 2003) (stating that the placebo arm is something that would be considered nontherapeutic); and Benjamin Wilfond, *Ethical Issues in Pediatric Research: Placebo Controlled Trials for Gastroesophageal Reflux*, June 25, 2002, http://www.fda.gov/ohrms/dockets/ac/02/slides/3870S1_04_Wilfond/ (noting that the placebo arm does not offer the prospect of direct benefit).

3. Nontherapeutic Research (21 C.F.R. § 50.53)

As compared to sections 50.51 and 50.52, the nontherapeutic research category found in 21 C.F.R. § 50.53 is far more controversial among ethicists because of its inherently utilitarian nature.¹⁶⁰ In a structure similar to the previous two, the regulation provides that:

Any clinical investigation . . . in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit to the individual subject . . . may involve children as subjects only if the IRB finds and documents 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 that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and (d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians¹⁶¹

The utilitarian “problem” arises due to the fact that child subjects are exposed to more risk than would be experienced by an average, healthy child, but that risk is compensated only by benefit to children generally and not to the individual subject.

In other words, child participants in this category of research are asked to undertake risks solely for the benefit of others. While adults are routinely permitted and asked to do this, it may be problematic for children who are not yet legally or developmentally able to consent to such self-sacrifice. Some ethicists are opposed to nontherapeutic research in children for this important reason.¹⁶² Though it may be less than ideal, and unacceptable to

160. See JOHN STUART MILL, UTILITARIANISM 22-23 (Oskar Piest ed., Bobbs-Merrill Co, Inc, 1957) (1861). Utilitarianism is a moral philosophy that considers ethical actions to be those that produce the greatest good for the greatest number of people, permitting the sacrifice of some for the benefit of others. *Id.* The comparisons to the context of human subjects research are obvious, but some research is more clearly utilitarian than others, especially those trials that intend no direct benefit to research participants but are hoping for scientific breakthroughs for the benefit of society more generally.

161. 21 C.F.R. § 50.53.

162. Ramsey, *supra* note 12, at 11. (stating that “children who cannot give a mature and informed consent . . . should not be made the subjects of medical experimentation unless, other remedies having failed to relieve their grave illness . . .”). For an important discussion of the consent issue in more detail, see Part V.C *infra*. Importantly, however, Ramsey’s approach would prevent much needed research to obtain information about pediatric prescribing. The American Academy of Pediatrics recognizes the need to avoid abandonment of pediatric research necessary for the benefit of children as a class and thus

a strict deontologist,¹⁶³ the utilitarian category is extraordinarily important because it remains unclear whether necessary information about the use of pharmaceuticals in pediatric patients could be gleaned through therapeutic research alone.¹⁶⁴ In fact, “[t]he openness of the federal regulations to nontherapeutic pediatric research suggests the viewpoint that nontherapeutic research, despite its ethical difficulties, may sometimes be critical to the advancement of important knowledge.”¹⁶⁵ Further, the sort of research approvable under this nontherapeutic category exposes subjects only to the levels of risk that are standard for their conditions, helping to justify the lack of benefit they can personally expect as a result of their participation.

Section 50.53 permits research that poses only a minor increase over minimal risk; however, it fails to clearly define that phrase, leaving it generally to the discretion of IRBs.¹⁶⁶ Recall that minimal risk is keyed to the amount of risk experienced in the daily lives of average healthy children.¹⁶⁷ In contrast, this nontherapeutic category does not use the average healthy child as a reference point, but rather focuses on the *subjective* risks faced in the daily lives of the research subjects themselves. Thus, if a pediatric cancer patient experiences spinal taps on a weekly basis, then spinal taps and other experiences with similar pain and risk levels would be permitted in a research study under this category, even though the

permits studies that either have a potential benefit to the individual child (i.e. § 50.52) or provide generalizable knowledge (i.e. § 50.53) when potential benefits outweigh potential risks. Am. Acad. of Pediatrics, *supra* note 4, at 288.

163. Deontologists are characterized by a belief that individuals should never be used merely as means, but always treated as ends in themselves. Because the research enterprise is focused almost exclusively on obtaining generalizable knowledge and not on individual treatment and benefit for the subject, it has a utilitarian slant, but when individual benefit is a requirement, as under § 50.52, the subject is not treated as a mere means, and thus, the research is justifiable even under deontological theory. For a foundation of deontological philosophy, see IMMANUEL KANT, *GROUNDWORK OF THE METAPHYSIC OF MORALS* (H.J. Patton trans., Harper & Rowe 1964); IMMANUEL KANT, *CRITIQUE OF PRACTICAL REASON* (Lewis White Beck trans., Liberal Arts Press 1956); and IMMANUEL KANT *METAPHYSICS OF MORALS* (Mary Gregor trans., ed., Cambridge University Press 1996).

164. See *Sliding Scale*, *supra* note 119, at 754 (discussing the utilitarian nature of the risk categories utilized by Subpart D). See also Lainie Friedman Ross, *Children As Research Subjects: A Proposal to Revise the Current Federal Regulations Using a Moral Framework*, 8 STAN. L. & POL’Y REV. 159, 166 (1997) (addressing the particularly problematic nature of 21 C.F.R. § 50.54 that permits great risks for child subjects for the benefit of society).

165. Smolin, *supra* note 3, at 631. However, the FDA will not accept information submitted for pediatric exclusivity if that data is derived from children who do not suffer from the condition under study and for whom there is no foreseeable benefit. SHARAV, ET AL., *supra* note 111.

166. See 21 C.F.R. § 50.53.

167. See *supra* Part IV.B.1.

risks go beyond what an average healthy child routinely experiences. “[M]inor increase over minimal risk” can therefore be thought of as the equivalent of minimal risk specifically keyed to that group of children with the disorder or condition under study.¹⁶⁸

The definition of “condition” within the regulation has also sparked significant debate because a broad definition of the term could cover even the simple “condition” of being a child, allowing all pediatric research to satisfy that criterion. Nonetheless, OCD and depression clearly fit the more narrow definition of condition as “a specific (or set of specific) physical, psychological, neurodevelopmental, or social characteristic(s) that an established body of scientific evidence or clinical knowledge has shown to negatively affect children’s health or well-being or to increase their risk of developing a health problem in the future.”¹⁶⁹ Therefore, the placebo control arms of the studies requested by the FDA of drugs to treat OCD and depression in children easily satisfy the section 50.53 requirement that the intervention be likely to yield generalizable knowledge about OCD and depression because they will be used to gauge whether the response to the experimental intervention is statistically significant. The knowledge gained is also vital to the understanding and amelioration of these prevalent pediatric conditions, given the dearth of existing information on how to treat pediatric OCD and depression that prompted the FDA to request these studies in the first place.¹⁷⁰ Assuming that researchers can adequately obtain assent and permission, taking a placebo and being closely monitored by researchers will present experiences that are reasonably commensurate with what the child subjects would experience in their normal clinical encounters. Therefore, when questioning whether placebo controls are

168. *Group Benefit*, *supra* note 69, at 189. Some commentators have argued that this definition suffers from the same ethical problem that was cause for rejection of the subjective definition under the minimal risk category because it permits researchers to impose more risk on sicker children even without the prospect of direct benefit—if one spinal tap is risky, then two are riskier, and that risk should be compensated by direct benefit. See Glantz, *supra* note 40, at 233.

169. INST. OF MED., *supra* note 18, at 6. If “condition” is understood as only a fully expressed disease or disability, it would be much more difficult to do pediatric research that is of more than minimal risk because the scope of possible subjects would be significantly narrowed. See *Sliding Scale*, *supra* note 119, at 751. In reality, the boundaries between being healthy, at risk, and having a disease are blurry, so if the definition of condition is broader, more children can be subjected to greater than minimal risk research of their “conditions.” See *id.* However, if the term is interpreted too broadly so as to include anything associated with illness, such as race, ethnicity, age, environment, social and economic circumstances, and the like, then almost anything, including the mere fact of being a child, could be approved under this risk category and the condition requirement would no longer pose a real barrier, *id.* at 751-52, allowing the research on healthy children that this category was intended to exclude. Cohen, *supra* note 95, at 702.

170. Miller et al., *supra* note 132, at 106.

approvable under the nontherapeutic risk category, the only real issue is whether they pose no more than a minor increase over minimal risk.

Minor increase over minimal risk occurs when subjects are simply exposed to the same level of risk that they would face in their own lives, even if that is more risk than what the average, healthy child would face. When a pediatric subject is denied treatment of questionable safety or efficacy when no proven alternative exists, the use of placebo controls will likely satisfy the minor increase over minimal risk criterion because subjects receiving placebo would not receive anything better for their condition in ordinary clinical care. Because no treatments have been proven safe since the recent pediatric suicidality concerns associated with drugs used or approved to treat OCD and depression in children, this precisely describes the present situation.

Prozac is the only drug currently approved and labeled for pediatric depression, and no other antidepressants have proven more effective than placebo in pediatric subjects.¹⁷¹ Despite this singular approval, all antidepressants, including *Prozac*, have recently been required to include a “black box” warning describing “the increased risk of suicidality in children and adolescents given antidepressant medications These labeling changes are applicable to the entire category of antidepressant medications because the currently available data are not adequate to exclude any single medication from the increased risk of suicidality.”¹⁷²

Concerns regarding antidepressant drugs in children are not limited to their use for pediatric depression, but also extend to their use for treating pediatric OCD,¹⁷³ including the handful of antidepressant medications

171. FDA, Questions and Answers on Paxil (paroxetine hydrochloride), June 19, 2003, <http://www.fda.gov/cder/drug/infopage/paxil/paxilQ&A.htm> (stating that “Prozac (fluoxetine) is the only drug approved for the treatment of major depressive disorder in children . . . 8 to 18 years of age.”). *Prozac* was approved for this indication in children ages 8-18 following studies requested under the BPCA. FDA, Pediatric Program Study Statistics 1, http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006B1_04_Ped%20Exclusivity-OCD_wr_template.doc (last visited Sept. 25, 2006). Efficacy was established in this population “based on two placebo controlled clinical trials in depressed outpatients whose diagnoses corresponded to standard rating criteria (under the American Psychiatric Association’s Diagnostic and Statistical Manual). . . . The studies of Prozac for depression produced a statistically significant effect for the drug compared to placebo on the ‘Childhood Depression Rating Scale R (revised).’” FDA, FDA Talk Paper: FDA Approves Prozac for Pediatric Use to Treat Depression and OCD, Jan. 3, 2003, <http://www.fda.gov/bbs/topics/ANSWERS/2003/ANS01187.html>.

172. Press Release, FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated With Antidepressant Medications (Oct. 15, 2004), http://www.fda.gov/bbs/topics/news/2004/NEW_01124.html.

173. FDA, Class Suicidality Labeling Language for Antidepressants, Jan. 26, 2005, http://www.fda.gov/CDER/DRUG/antidepressants/PI_template.pdf (“The risk of suicidality was most consistently observed in the MDD [Major Depressive Disorder] trials, but there

approved with specific indications for that condition: *Prozac*, *Zoloft*, *Luvox*, and *Anafranil*.¹⁷⁴ While effective drugs exist to treat both OCD and depression in pediatric patients, the fact that all available treatments are of questionable safety permits placebo controls to be categorized as only a minor increase over minimal risk. The risk facing those subjects randomized to receive placebo mirrors the risk that those particular subjects would face in their everyday lives, namely the lack of appropriate treatment for their condition, which satisfies the final criterion for approval under section 50.53.¹⁷⁵

However, this situation will change as soon as even a single drug for OCD and/or depression overcomes the existing suicidality concerns. Once there is a safe and effective alternative treatment for either of these conditions, denial of that treatment in favor of placebo would pose more than a minor increase over minimal risk because the placebo group would be exposed to the risk of non-treatment.¹⁷⁶ However, now that risk would be greater than what the subjects would face in their daily lives because they would receive safe and effective treatment as the standard of care if they were not part of the study. If a minor increase over minimal risk is defined as the subjective version (average risks faced by the particular study subjects) of the objective minimal risk standard (average risks faced by normal healthy children) from section 50.51, this would clearly not meet the risk level necessary for approval under the nontherapeutic risk category.

This likely situation, in which safe and effective treatment once again exists for pediatric users, would also prevent approval of the placebo arms of requested studies under the therapeutic research category described in the previous section. Assuming the direct benefit criterion was satisfied by providing only placebo, the risk-benefit ratio between placebo and *currently* available alternatives would be approximately the same because the currently available alternatives include no treatment, safe but ineffective

were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well.”).

174. FDA, FDA Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications, Oct. 15, 2004, <http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm>.

175. There are claims that the link between increased suicidality and the use of these treatments in pediatric patients are overstated and not nearly the cause for concern that they have been made out to be. *See, e.g.*, Brent & Birmaher, *supra* note 2, at 379 (“the [British Medicines and Healthcare Products Regulatory Agency] has overstated the risks and underestimated the possible benefits of antidepressants for the treatment of pediatric depression.”). This may in fact be true, but this article will give the FDA’s requests their strongest case for legal approvability and ethical permissibility and thus assume that the suicidality concerns are sufficient to create a situation in which there is currently no safe and effective treatment for pediatric OCD and depression. *But see, infra* Part V.B.

176. *See, e.g.*, Gandhi, *supra* note 120, at 296.

treatment, or effective but unsafe treatment. With the potential development of a both safe *and* effective alternative for the treatment of OCD and depression in children, the relation of the anticipated benefit of placebo to the risk of non-treatment would no longer be “at least as favorable to the subjects as that provided by available alternative approaches.”¹⁷⁷ Finally, with a safe and effective treatment available, the placebo arm would not be approvable under the catchall established by section 50.54¹⁷⁸ because it could not be conducted according to sound ethical principles, as will be demonstrated in Part V below.

Therefore, when the federal risk categories are appropriately applied, the placebo arms of the FDA’s requested pediatric OCD and depression trials will only be approvable until existing treatments or entirely new treatments are proven safe and effective in light of recent suicidality concerns. These placebo arms are certainly not minimal risk because these psychiatric conditions in children require more stringent research protections than are required under that category. The FDA categorizes placebo controls under the therapeutic risk category based on a broad definition of “direct benefit,”¹⁷⁹ although they are probably more appropriately classified as nontherapeutic. At this time, the use of placebos for these studies is probably approvable under either category because, absent a safe and effective treatment, the placebo intervention presents a risk-benefit ratio

177. 21 C.F.R. § 50.52.

178. 21 C.F.R. § 50.54 establishes criteria for the approval of research that poses more than a minor increase over minimal risk, but offers no prospect of direct benefit and is thus not approvable under §§ 50.51, 50.52, or 50.53. If an intervention or procedure is not approvable under one of the other three categories, it may still proceed, but only if:

(a) The IRB finds and documents that the clinical investigation 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 Commissioner of Food and Drugs, 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, determines either: (1) That the clinical investigation in fact satisfies the conditions of § 50.51, § 50.52, or § 50.53, as applicable, or (2) That the following conditions are met: (i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) The clinical investigation will be conducted in accordance with sound ethical principles; and (iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in § 50.55.

21 C.F.R. § 50.54.

179. The experimental arms of these studies would be appropriately approved under this therapeutic category due to their potential for direct benefit regardless of whether there was a safe and effective alternative, so long as the risk-benefit associated with the experimental intervention was at least as favorable as the available alternative, essentially requiring clinical equipoise. See *infra* Part V.A.1.

that is at least as favorable as that provided by available alternatives (section 50.52), and it presents only a minor increase over minimal risk (section 50.53). However, as soon as safe and effective therapy exists, the placebo control arm will not satisfy either of these requirements and its use would no longer be legally approvable.¹⁸⁰ Nevertheless, pediatric research for drugs to treat OCD and depression should not come to a standstill. Instead, the FDA should replace its requests for placebo controls with requests for active controls using the safe and effective treatment in all future studies.¹⁸¹ Active controls would restore the conditions necessary for IRB approval under Subpart D.

Assuming the FDA's requests for placebo controls to test drugs for the treatment of pediatric OCD and depression are legally approvable now and in the future, the question becomes whether the studies are ethically acceptable. As Part V will demonstrate, the answer closely mirrors the result obtained through this legal analysis, which demonstrates the moral excellence of the federal regulations when stringently applied.

PART V—ARE THE REQUESTED PLACEBO-CONTROLLED PEDIATRIC STUDIES ETHICALLY ACCEPTABLE?

The current lag in pharmaceutical development for pediatric patients leaves children as therapeutic orphans and justifies the protective inclusion of children in at least some research. However, the need for this research must be weighed against ethical considerations. Its conduct must be carefully planned and monitored to avoid ethical lapses that unduly risk sacrificing the well being of some children for the good of others. With this background in mind, an ethical analysis of the FDA's requested placebo controls would permit placebo use during the initial safety trials following the suicidality scare, but would require the use of active controls once there is a safe and effective alternative.

180. This analysis demonstrates a relatively sharp break from the FDA's position, considering that it requested placebo controlled studies for OCD drugs and antidepressants even before the suicidality concerns were raised with regard to the drugs already approved for these indications in children.

181. Some question exists as to whether the FDA could require active-controlled studies instead of placebos or other designs in pediatric research, but this is really a non-issue in the context of studies that are merely requested by the FDA under the BPCA in return for market exclusivity because sponsors are not required to conduct the research and the statute gives the agency authority to dictate the types of trials that will be responsive. The issue may be more relevant in light of PREA, which actually requires pediatric research in some circumstances, but even there, the FDA will likely have the authority to prescribe what types of trials cannot be conducted given its current regulation of the sort of research that can be approved by IRBs.

A. When Are Placebo Controls Generally Acceptable?

1. The Need for Adequately Controlled Trials

The presence of a sound research design that does not impose unnecessary risks on subjects is a fundamental consideration of research ethics.¹⁸² Because research participants cannot be subjected to any level of risk that will not personally benefit them, unless the results of the research will be scientifically legitimate,¹⁸³ ethical research must address a scientifically valuable “question by means of valid methods likely to produce meaningful results.”¹⁸⁴ Including control arms in the study design contributes to the necessary validity by providing “a mechanism by which to compare results from subjects taking an experimental intervention to results from a group that is not receiving the treatment.”¹⁸⁵ This helps establish that any change witnessed in the experimental arm is truly due to the intervention and not to other confounding variables. Without a control group, it would be virtually impossible to determine whether the experimental treatment yields a favorable effect, a dangerous effect, or no effect at all—in fact, controlled clinical trials are almost universally recognized as “the best way science has come up with to determine what a new drug really does.”¹⁸⁶

However, no concurrent control arm can be ethically included in clinical research without the presence of clinical equipoise, which

demands that there be genuine uncertainty or disagreement *in the expert medical community* about the relative merits of two or more therapies for a given condition. An RCT [randomized controlled trial] is conducted to resolve this professional uncertainty. This is the ethical equivalent of the statistical dictum that an RCT must begin with an honest null hypothesis.

182. Wilfond, *supra* note 159. Avoidance of unnecessary risks involves ensuring that the risks are proportionate to the likely benefits to subjects themselves and to the potential for generalizable knowledge that will help future patients, maximization of subject safety, equitable subject selection so that the burdens and benefits of research are fairly distributed, protection of confidentiality and privacy, and informed consent (or assent and permission) is obtained from all subjects or their legally authorized representatives. *Id.*

183. See CANCER MEDICINE 1005 (Robert Bast et al., eds. 5th ed. 2000) (“The scientific methods used to conduct the study must be reliable and valid so that there is a reasonable chance that the question asked will ultimately be answered. Trivial questions or invalid methods cannot result in ethical research because no amount of risk or inconvenience to subjects can be justified. Thus, bad science is inherently unethical science.”) (footnotes omitted).

184. Miller et al., *supra* note 132, at 105.

185. Hoffman, *supra* note 158, at 452.

186. Ken Flieger, *Testing Drugs in People*, FDA CONSUMER SPECIAL REPORT, July-Aug. 2004, at 16, 16-17.

While an individual physician may have a feeling that one arm of the trial is preferable to the other, the absence of consensus in the community legitimizes enrolling patients in RCTs.¹⁸⁷

If clinical equipoise does not exist between the proposed experimental and control interventions, the study cannot proceed. Lack of clinical equipoise occurs either because the experimental treatment is generally accepted as superior to the control, and so all subjects should receive that intervention, or vice versa.

2. Types of Controls Available for Clinical Research

Assuming that equipoise is present, several types of controls are available for well-designed, valid research. First, historical controls compare subjects given the investigational drug with similar patients treated with a control drug at a different time and place,¹⁸⁸ or with data gathered regarding the natural progression of the disease under study without any treatment.¹⁸⁹ This study design provides all current subjects with the experimental intervention and therefore removes the issue of withholding potentially beneficial therapy. However, historical controls are not particularly effective because the design often cannot account for many variables. The control arm may differ demographically from the current experimental group because the two groups were not selected at the same time or randomized from similarly situated individuals; also, the mere separation in time can impact results.¹⁹⁰ For these reasons, historical controls are not considered highly scientifically valid, although they may be useful in studying diseases with high and predictable mortality rates.¹⁹¹ Under those circumstances, any reduction could then be appropriately attributed to the experimental drug.

Active controls, or “head-to-head” studies, are more useful than historical controls, but they have their own limitations. This type of trial design involves the concurrent randomization of potential subjects, with one group receiving the experimental drug and the other receiving an active drug known to be safe and effective.¹⁹² Clearly, this requires the existence of an alternative to the experimental intervention, which will not be the case

187. CANCER MEDICINE, *supra* note 183 at 1005.

188. Flieger, *supra* note 186, at 17.

189. Hoffman, *supra* note 158, at 453.

190. See Susan K. McCune, *Creative Clinical Trials for Pediatric Drug Development*, <http://www.fda.gov/cder/present/DIA2005/McCune.pdf> (last visited Sept. 29, 2006) (discussing the advantages and disadvantages of clinical trials with external controls).

191. *Id.*

192. Hoffman, *supra* note 158, at 453.

for the evaluation of first-line therapies. However, when an active comparator is available, head-to-head trials offer several advantages. First, because all subjects receive treatment, these trials avoid any ethical problems associated with denying all therapy to a group of human subjects. This advantage is especially important for children who cannot personally consent to the refusal of such therapy outside of the research setting, a fact that will become integral in the discussion of the FDA's requests below.¹⁹³ Also, active controls will generally provide more useful information to doctors, patients, and third-party payors than placebo because active controls can indicate whether an experimental drug is superior to existing therapies, as opposed to whether it is merely better than no treatment at all.¹⁹⁴

Despite these benefits, active comparators have some practical drawbacks. Most importantly, they could have significant placebo effects of their own.¹⁹⁵ Therefore, even if the study seems to demonstrate an equal level of benefit between the two groups, investigators cannot be certain that either drug is actually effective.¹⁹⁶ This problem can be overcome if the comparator used has already been determined effective in its own placebo-controlled trial, thus preserving the scientific validity of the current study design. However, the high economic cost of active-controlled studies might also present a problem for the pharmaceutical industry.¹⁹⁷ The increased cost results at least in part from the necessary provision of active drugs to both study arms, the requirement of larger sample sizes to counter any variables stemming from the introduction of a second active drug, and the longer amount of time needed to complete the study.¹⁹⁸ Ultimately, the FDA might hesitate in accepting these studies to prove safety and efficacy.¹⁹⁹ Even more worrisome to drug sponsors than the costs is the possibility that a head-to-head trial will expose a new drug as no better than

193. See *infra*, Part V.C.

194. Comm. for Advanced Sci. Educ., Food & Drug Admin. Ctr. for Drug Evaluation & Res., *The Use of Placebos in Clinical Trials and the Ethics of the Use of Placebos*, (Apr. 21, 1999), <http://www.fda.gov/cder/foi/special/99/case-trans-42199.txt> [hereinafter Comm. for Advanced Sci. Educ.].

195. See Tamar Nordenberg, *The Healing Power of Placebos*, FDA CONSUMER MAGAZINE, Jan.-Feb. 2000, at 14, 15 (describing the placebo effect in more detail: “[s]ham medication can sometimes improve a patient’s condition simply because the person has the expectation that it will be helpful.”).

196. Hoffman, *supra* note 158, at 456.

197. John March et al., *AACAP 2002 Research Forum: Placebo and Alternatives to Placebo in Randomized Controlled Trials in Pediatric Psychopharmacology*, 43(8) J. AM. ACAD. CHILD & ADOLESC. PSYCHIATRY 1046, 1050 (2004).

198. *Id.*

199. *Id.*

an existing drug, even if both are effective—precisely the reason that these trials are so valuable to prescribers and payors.²⁰⁰

Finally, placebo controls are largely accepted as the most efficient and informative way to determine safety and efficacy of a drug, given the natural variability among people.²⁰¹ This study design is widely considered the scientific gold standard for clinical research.²⁰² Using the placebo control design minimizes both researcher and subject bias, thereby avoiding the placebo effect that might otherwise confound data.²⁰³ Any statistically significant difference between the placebo and experimental arm can be clearly attributed to the active ingredient found within the experimental drug because it is the only variable between the two groups. The FDA does not require a drug study to include a placebo control; it does recognize, however, that placebos can often

provide the clearest insight into what a treatment can accomplish, . . . especially with some psychiatric and other drugs in which the placebo effect is known to play a particularly weighty role. In fact, . . . in some cases the placebo effect “makes it almost hopeless, statistically” to use studies that test a new treatment side-by-side against an existing one and determine whether the new treatment works.²⁰⁴

In addition to these validity benefits, placebo controls generally require fewer subjects than a head-to-head study and are easier and less expensive to conduct.²⁰⁵ These benefits, combined with the eliminated risk of the experimental drug proving to be less effective than existing therapy, make this study design particularly attractive to the pharmaceutical industry.²⁰⁶

However, placebo controls are not perfect. They have serious ethical drawbacks when an effective active therapy exists that could be used as a comparator. In these situations, subjects refuse a beneficial therapy and potentially accept no clinically active therapy at all—the dummy pill.²⁰⁷ This

200. *Id.*

201. Comm. for Advanced Sci. Educ., *supra* note 194.

202. Flynn, *supra* note 20, at 866.

203. McCune, *supra* note 190.

204. Nordenberg, *supra* note 195 (quoting Robert DeLap, M.D., head of one of the FDA’s Offices of Drug Evaluation).

205. March, *supra* note 197, at 1047.

206. See Lainie Friedman Ross & M. Justin Coffey, *(Women and) Children First: Applicable to Lifeboats? Applicable to Human Experimentation?*, 6 J. HEALTH CARE L. & POL’Y 14, 31 (2002) (stating that a trial that compares experimental medication against a placebo shows a greater difference than a trial that compares an experimental medication against a competitor. Consequently, the research can function as a medical advertisement to increase market share and as groundbreaking research.).

207. Flynn, *supra* note 20, at 866; Comm. for Advanced Sci. Educ., *supra* note 194.

ethical dilemma can often be overcome with variations on the standard placebo-controlled design. For example, add-on studies combine placebo and active controls so that one arm receives the standard or proven therapy plus the test drug and the other receives the standard treatment plus a placebo, thus avoiding the denial of treatment subjects would otherwise receive outside of the research setting.²⁰⁸ Clearly, the add-on design is impossible when there is no proven alternative or when administering several drugs could be dangerous for dosing or interaction reasons. If these problems are not present, however, this type of study is useful when it would not be ethically appropriate to deny subjects the standard therapy.²⁰⁹

Another approach involves enrolling only non-responders to available therapy in placebo-controlled trials.²¹⁰ This approach, however, introduces its own confounder because these non-responders may be inherently different from most patients who will eventually use the drug.²¹¹ Finally, researchers could attempt to limit exposure to ineffective treatment by using early escape plans for those in the placebo group.²¹² Early escape plans would permit subjects receiving placebo to begin the experimental therapy prior to the scheduled end of the trial if it is showing signs of efficacy in the experimental group.²¹³

Clearly, control groups are very important to appropriately conducted pharmaceutical trials, but none of the existing alternatives flawlessly combine scientific validity with ethical acceptability. Presumably due to the status of placebo-controlled studies as the gold standard, however, the FDA has requested these studies for OCD drugs and antidepressants in children. The question that must now be addressed is whether these are ethically appropriate or whether the FDA should instead shift its approach and request one of the alternative controls described above.

208. Robert Temple, *Overview of Placebo Control Trial Design: Benefits and Difficulties*, Meeting of the FDA's Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, Sept. 11, 2000, 40-41, <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3641t1.pdf>.

209. McCune, *supra* note 190.

210. Temple, *supra* note 208 at 42.

211. *Id.* This situation would be the same as when placebos are used in research for first line therapies because subjects would not be denied treatments that are safe and effective for them and would thus be no worse off if randomized to receive placebo.

212. *Id.*

213. *Id.* at 43.

3. Ethical Analysis of the Use of Placebo Controls

a. No Safe and Effective Alternative

As implied above, placebo controls are not *always* ethically problematic.²¹⁴ In fact, when there is no proven treatment available, and researchers are genuinely uncertain as to whether the study drug will be more effective (or more dangerous) than no treatment at all, placebo use is permissible in both adult and child subjects.²¹⁵ This will often be the case in pediatric research, where the lack of proven therapies is precisely what makes the research so vital.²¹⁶ The lack of proven therapies also renders alternative study designs impossible and necessitates placebo use to generate valid scientific results. The best placement for a patient might even be in the placebo arm of a trial because “those who receive placebos in clinical drug studies avoid exposure to the potential hazards of the therapy being tested although they might receive no benefit from the inactive agent.”²¹⁷ Both the American Academy of Pediatrics and the FDA’s Pediatric Advisory Subcommittee agree that placebo controls are permissible in pediatric research so long as their use does not place children at increased risk; in other words, placebo controls are acceptable when there

214. March et al., *supra* note 197, at 1053.

215. Some considerations normally taken into account to determine whether placebos are desirable and acceptable as a control in a randomized clinical trial include: (1) existing evidence of efficacy and safety for the medication to be studied—the weaker the evidence, the more desirable it is to include a placebo; (2) stability of the disease to be treated—the greater the expected natural fluctuation of symptoms, the more desirable the use of placebo becomes because it would otherwise be difficult to determine whether the change is due to the disease itself or the drug; (3) the known range of placebo response in the same condition and type of medication—the wider the range of response is, the more need for placebo controls to truly establish that a placebo effect is not responsible for changes noted in the experimental group; (4) the risk of harm from withholding active treatment—the greater potential for harm, the less acceptable is the use of placebos; (5) the rescue procedures to minimize possible negative consequences from placebo use—the more liberal the provisos for adding active treatment in response to symptom worsening or lack of improvement, the stronger the acceptability of placebo; and finally, (6) the potential for direct benefit from placebo—the greater the potential benefit from placebo compared with direct benefit from trial participation or receiving the active treatment, the more acceptable is use of placebo. *Id.* at 1053-54.

216. Am. Acad. of Pediatrics, *supra* note 4, at 286-87. Recall that the “nonvalidated administration of medications may place more children at risk than if the drugs were administered as part of well-designed, controlled clinical trials.” *Id.* See also Rosato, *supra* note 30, at 363 (stating “[w]hether children are included in trials or prescribed drugs off label, similar risks are taken. The reality of this Hobson’s choice should inform any ethical framework that is created.”).

217. Hoffman, *supra* note 158, at 477.

is no commonly accepted therapy for the condition or when that therapy is of questionable efficacy or is dangerous.²¹⁸

Of course, the argument remains that it is still unethical to include children in placebo-controlled research, even if they are not being denied any safe and effective therapy, because they will not benefit from their participation. Arguably, these children are being used merely as a means to an end.²¹⁹ While this strong deontological point strikes at the foundation of all nontherapeutic research, as Subpart D appropriately recognizes, the situation truly leaves no other choice: the research must be done for medicine to advance. This utilitarian justification will fail to convince all critics,²²⁰ and the deontological approach should prevail when there are alternatives that avoid using children as a mere means to the development of treatment options. Whether people should sacrifice themselves for the greater good becomes significant in situations where placebo controls may be permitted among adult subjects.

b. Safe and Effective Alternatives to Placebo—Adult Subjects

In adult research, placebo controls may be ethically utilized despite the existence of a safe and effective alternative, depending only on the consent of the adult subject and severity of the condition at issue. For this subject population, it is “generally accepted practice in the United States . . . that well and fully informed patients can consent to take part in a controlled-randomized-blinded clinical trial, even when effective therapy exists, so long as they are not denied therapy that could alter survival or prevent irreversible injury.”²²¹ When an effective therapy is available, one of the biggest problems facing placebo controls is the difficulty justifying the unfavorable risk-benefit ratio. The decision to refuse effective therapy

218. Am. Acad. of Pediatrics, *supra* note 4, at 294. Similarly, the FDA Pediatric Advisory Subcommittee stated that “[p]lacebo controlled trials may be acceptable if there are no approved or adequately studied therapies for children with the condition under study.” FDA, FDA Pediatric Ethics Working Group Consensus Statement on the Pediatric Advisory Subcommittee’s September 11, 2000 Meeting, Placebo Controlled Trials, <http://www.fda.gov/cder/pediatric/ethics-statement-2000.htm> [hereinafter Pediatric Ethics Working Group]. The FDA would also permit add-on placebo controlled trials that do not deny subjects any element of the standard of care. *Id.* However, the AAP would permit placebos alone “when the incidence and severity of undesirable side effects produced by adding a new treatment to an established regimen are uncertain.” Ross & Coffey, *supra* note 206 at 26.

219. Hoffman, *supra* note 158, at 476.

220. See generally, *supra* notes 157-61 (discussing nontherapeutic research in pediatric subjects and the related utilitarian-deontological conflict).

221. Flieger, *supra* note 186, at 18. See also Hoffman, *supra* note 158, at 451-52.

carries a substantial risk while receiving only placebo is likely to have no direct benefit, which creates a wide gap between what could be expected in the clinical care and research settings. However, when the condition under study is not particularly severe, the risk-benefit ratio of refusing a proven drug is less problematic because both the benefit of treatment and the risk of non-treatment are relatively insubstantial. In the latter situation, an autonomous and informed decision to participate in placebo-controlled research is all that is necessary for placebo use to pass ethical muster.²²²

While this approach may raise concerns about disregarding the professional duty of physicians to provide the best care for their patients, physicians have different responsibilities in the research setting. They are no longer engaged in a doctor-patient relationship, but rather in a researcher-subject relationship.²²³ Here lies a critical distinction. In standard practice, classic fiduciary duties apply and a physician's primary loyalties must be focused on the health and well-being of the individual patient.²²⁴ In research, the investigator's allegiance is to the protocol and the creation of generalizable knowledge, with the limitation of ensuring subject safety to the greatest extent possible.²²⁵ The investigator has no obligation, or even ability, to tailor the protocol to the interests of individual subjects.²²⁶ Even in the standard clinical setting, patient autonomy holds a position of utmost importance, and the physician's duty to treat yields to the patient's informed, competent refusal of care. Treatment against a patient's wishes is classic battery, even if the physician's intervention is beneficial.²²⁷ Focusing on the consent of the adult subject in determining the ethics of placebo controls does no damage to the professional ethics of physicians because it merely recognizes a current physician duty.

222. Hoffman, *supra* note 158, at 479.

223. See E. Haavi Morreim, *Litigation in Clinical Research: Malpractice Doctrines Versus Research Realities*, 32 J.L. MED. & ETHICS 474, 475-77 (2004) (providing a detailed discussion of the differences between a physician in the clinical care context and a researcher, who also happens to be a physician).

224. *Id.* at 447.

225. *Id.* ("The investigator does not owe his top loyalty to the subject in the same way a physician owes his to the patient.")

226. *Id.* The differences between the ethical responsibilities contribute to the therapeutic misconception, discussed *infra* note 231, and the associated belief that the researcher is truly looking out for the best interests of the subjects, rather than for the advancement of science. Hoffman, *supra* note 158, at 482.

227. E.g., *Schloendorff v. Society of New York Hospitals*, 105 N.E. 92 (N.Y. 1914) (explaining that a doctor removed a tumor after the patient had consented to an abdominal exam under anesthesia, but had specifically requested that there be no operation. The court stated, "[e]very human being of adult years and sound mind has a right to determine what shall be done to his own body," and held that a doctor is liable for battery by touching without consent, despite the fact that the touch might be in the patient's best medical interests.).

The inverse relationship within this consent/severity model requires that permission to the adult subject to consent must be progressively scaled back as the risks associated with the underlying condition become more serious. For example, individuals experiencing male pattern baldness could be ethically enrolled in a placebo-controlled trial of an experimental new therapy despite the existence of *Rogaine* because the result is merely continuing baldness, a purely cosmetic problem that does not impair the subject's capacity to consent.²²⁸ The same is true for adult sufferers of routine headaches. Patients who receive placebo may experience some discomfort, but they do not risk lasting health detriments; this establishes a situation where "an [adult] individual's prerogative [is] to say, 'I know what I'm getting into, and I want to further this scientific research.'"²²⁹

The risks of life-threatening cancer, on the other hand, are so severe that they may not be overcome by the consent of an adult subject to potential randomization in a placebo arm,²³⁰ even if that patient could consent to refusal of treatment outside of the research setting. This is partially because research is an entirely different animal than clinical practice, an issue that will be addressed in more detail below. The ability of any patient suffering from a severe disease to fully comprehend the information necessary to enroll in research that will not provide him with personal benefit is uncertain. The tyranny of the disease causes this question; these patients might be desperate, may selectively internalize information, and might not ultimately comprehend their chances of receiving placebo rather than the active, but experimental, intervention.²³¹

Strong proponents of individual autonomy argue that subjects should be able to consent to any level of risk, without limitation based on the severity of their underlying condition. Generally, though, the research community takes the stance that the potential benefit must justify the level of risk the study presents.²³² The level of risk posed by placebo use for severe

228. Temple, *supra* note 208, at 21.

229. Nordenberg, *supra* note 195, at 17.

230. *Id.* ("In . . . oncology, placebo-controlled studies are often unacceptable because of the great risk to cancer patients of any treatment delays.")

231. Hoffman, *supra* note 158, at 482-83. Many subjects do not comprehend that the research will probably be of no benefit to them personally, nor that the researchers are focused on the welfare of future patients rather than current subjects. For example, many subjects who are clearly told that they are involved in a placebo-controlled study still believe that they will benefit and that researchers always act in the subject's best medical interest. *Id.* at 482. This misconception is clearly more problematic when subjects are suffering from more severe ailments, which is precisely why the use of placebo controls in the face of safe and effective treatment is permissible only for mild conditions where even if the subjects failed to understand the protocol, that misunderstanding would not be terribly detrimental.

232. 21 C.F.R. § 56.111 (2006) (requiring IRBs to balance the risks and benefits of research when determining approval).

ailments when a safe and effective alternative exists cannot be balanced by the benefits offered to the individual subjects who might receive those placebos. Several governmental and international sources agree and have adopted the severity/consent model for the ethical review of placebo-controlled research.

For example, the FDA and its representatives have stated that placebos are generally acceptable so long as subjects are not denied existing life-prolonging treatment²³³ and would not risk serious and irreversible harm by taking them.²³⁴ When effective treatment exists, the Canadian government permits placebo controls so long as subjects have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment; further, withholding such treatment must not have the possibility of any magnitude of irreversible harm.²³⁵ The Declaration of Helsinki states a preference for active controls whenever possible,²³⁶ but provides in a footnote that placebo controls might be permissible even when proven therapy exists if there are “compelling and scientifically sound methodological reasons” for their use.²³⁷ Moreover, placebo controls may be used if a “prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.”²³⁸ Finally, the International Council for Harmonization’s Guideline E10 permits enrollment of subjects in placebo-controlled trials even if proven therapy exists, as long as the risk of non-treatment involves only discomfort.²³⁹

In summary, there is widespread agreement that competent adult subjects should be permitted to submit to some low level of research risk by refusing proven therapy in favor of potentially receiving no more than placebo.

233. Cohen, *supra* note 95, at 696.

234. Comm. for Advanced Sci. Educ., *supra* note 194.

235. Cohen, *supra* note 95, at 697. Canadian research ethics and regulation also permit placebo controls in the previously discussed situations, such as when there is no standard treatment, standard therapy has been shown to be no better than placebo, there is evidence creating substantial doubt regarding the net therapeutic advantage of standard therapy, effective treatments are not readily available to patients (subject to considerations of justice), subjects are refractory to standard treatment and no second-line treatment exists, or in add-on trials. *Id.*

236. WORLD MED. ASS’N, *supra* note 121, at paragraph 29 (stating “benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.”).

237. *Id.* at n.1.

238. *Id.*

239. Temple, *supra* note 208, at 23-24.

Conversely, patients with severe conditions may bear added vulnerabilities as a result of the disease and researchers should not present them with the option of research that hazards the denial of treatment and its consequent risks.

c. Safe and Effective Alternatives to Placebo—Child Subjects

Several ethical guidelines and commentators extend the severity criteria that justify placebo controls in adult research to pediatric studies as well. This allows the inclusion of placebo arms even when proven therapies, specifically approved and labeled for use in children, exist. In fact, “many bioethicists and pediatric psychopharmacologists believe that placebo-controlled trials are ethical in the pediatric population even when known effective therapies are available as long as the subjects in the trial will not be harmed by deferral of existing therapy.”²⁴⁰ Some rely on analysis of protocols under the federal regulations, arguing that for mild conditions, withholding effective treatments can be categorized only as a minor increase over minimal risk.²⁴¹

The FDA’s Pediatric Advisory Subcommittee has indirectly expressed support for the use of placebo-controlled pediatric research of drugs to treat mild afflictions, stating that “[i]n placebo controlled studies of minor illnesses and symptomatic conditions, exposure to placebo and patient discomfort can often be minimized by use of a randomized withdrawal design, usually with defined individual patient discontinuation criteria (escape rules) so that the time of exposure to ineffective treatment is minimized.”²⁴² Though this statement does not specifically address situations in which a proven therapy exists as an alternative, it demonstrates the FDA’s willingness to categorize pediatric trials based on the severity of the condition at issue, as do its requests for placebo controls to study drugs used to treat psychiatric disorders, but not for HIV and oncology drugs.²⁴³

Physicians also seem to have fallen prey to the difference between research on mild and severe pediatric conditions. The American Academy of Child and Adolescent Psychiatry (AACAP) has stated that “placebo-controlled trials must not be used if safer and equally effective research

240. March et al., *supra* note 197, at 1047.

241. Rosato, *supra* note 30, at 372. Regardless of whether the condition is mild or severe, however, denial of a safe and effective alternative in favor of placebo exposes child subjects to risks that are more than minimal. *See infra* Part IV.B.3.

242. Pediatric Ethics Working Group, *supra* note 218.

243. *See* Comm. for Advanced Sci. Educ., *supra* note 194 (noting that the FDA will not request a placebo controlled study for serious conditions that will create risk of death or irreversible morbidity, but will request them for less risky conditions and diseases).

technologies are available to answer the scientific question.”²⁴⁴ This position appears to favor head-to-head trials whenever possible because they would unquestionably be safer, although the data from these trials may only be as useful as the data obtained through the use of placebo controls.²⁴⁵ Nevertheless, the AACAP encourages placebo controls when “needed to answer appropriate and necessary scientific questions and when the risk is acceptable. In short, placebo controls are ethically justifiable when they are supported by rigorous science and do not expose research participants to excessive risks of harm.”²⁴⁶

Despite these indications, however, analysis of the ethical permissibility of placebo control arms in children is *not* appropriately based on consideration of the severity of the condition under study because pediatric subjects lack the correlate to that consideration in adults—the capacity to consent. The severity/consent model has its foundation in the autonomy of adult subjects,²⁴⁷ and this principle does not apply to children. As skydivers, the tattooed, and cyclists without helmets demonstrate, competent and mature adults can choose to partake in behavior and activities that subject them to a wide range of risks. The independence of adults to make their own decisions is widely respected, so long as their actions will not cause harm to others.²⁴⁸ When the level of risk that adult subjects can be exposed to in the research setting is limited, for example by permitting placebo controls to replace proven therapy only for minor conditions, it is not because the principle of autonomy no longer applies. Rather, limitations exist because there are certain situations in which a person’s capacity to make a rational decision will be questioned—their autonomy is *weakened*.

In the research setting, IRBs, like the managers of tattoo shops, serve a gate-keeping role in which they determine what level of risk can be offered to potential research subjects, regardless of whether those individuals claim to be personally willing to accept more extensive dangers.²⁴⁹ If legally competent (or by decision of a surrogate), an adult patient may refuse

244. March et al., *supra* note 197, at 1048.

245. See *supra* Part V.A.2.

246. March et al., *supra* note 197, at 1048.

247. Smolin, *supra* note 3, at 622.

248. *Id.*

249. Under federal regulations, before an IRB can approve proposed research, it must determine, among other things, that “(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” and “(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.” 21 C.F.R. § 56.111.

clinical care for his or her condition regardless of the condition's severity.²⁵⁰ That same patient, however, could not enroll in a placebo-controlled study of a drug to treat a severe condition. This limitation of patient autonomy demonstrates an important distinction between medical care and research.

To review, though adults' ability to consent to research risks can solve many of the ethical problems associated with clinical studies (up to a cut-off point established by IRBs), the same is not true for children. Children lack the maturity needed to make many decisions for themselves and their autonomy is not afforded the same respect and deference provided to adults.²⁵¹ Instead, decision-making power often resides with parents, who are generally permitted to make choices about their child's welfare within a wide range of acceptability. Importantly, Subpart D substitutes the notion of informed consent with a combination of parental permission ("the agreement of parent[s] or guardian[s] to the participation of their child or ward in a clinical investigation")²⁵² and assent ("a child's affirmative agreement to participate").²⁵³

Admittedly, this is not perfectly equivalent to the consent used to validate the severity model for the permissible use of placebo controls in adult research. In pediatric studies,

[t]he refusal to use the term "consent" in relation to parents and children underscores the lack of an autonomous, legally competent research subject; the rationales for seeking "parental permission" and the "assent of children" therefore are distinct from the rationale for seeking "consent" from a legally-competent adult research subject.²⁵⁴

This imperfect replacement of informed consent with the assent/permission requirement for children is further demonstrated by the limited circumstances under which adult consent to participate in research can be waived, as in the case of a life-threatening emergency when no legally authorized representative can be found and the research would be otherwise impossible to conduct.²⁵⁵ Conversely, assent is far more easily waived

250. See *Cruzan v. Director, Missouri Dept. of Health*, 497 U.S. 261, 278-89 (1990) (recognizing that the right to privacy and the right to consent to medical treatment also create a right to refuse care).

251. See *Parham v. J.R. et al.*, 442 U.S. 584, 603 (1979) (stating "[m]ost children, even in adolescence, simply are not able to make sound judgments concerning many decisions, including their need for medical care or treatment. Parents can and must make those judgments.").

252. 21 C.F.R. § 50.3(r) (2006).

253. 21 C.F.R. § 50.3(n) (2006).

254. Smolin, *supra* note 3, at 631.

255. See 21 C.F.R. §§ 50.23-50.24 (2006) (explaining the conditions under which adult

because it may be impossible to obtain from very young children, and researchers can avoid the requirement to obtain assent for minimal risk research and certain types of direct benefit studies.²⁵⁶

Notably, researchers cannot easily avoid the parental permission requirement.²⁵⁷ Parental permission is closer to the equivalent of consent because parents are the ones provided with all of the information and forms that would usually be given to the competent adult subject. However, relying solely on parental permission still creates a situation in which someone other than the subject chooses whether to accept the risks and benefits of research participation. Despite the protections of requiring parental permission, the reliance on parents as decision-makers differs greatly from the evaluative process in the consent/severity model applied to adults.

American society and jurisprudence share a long history of protecting the ability of parents to make choices about which activities or experiences are desirable or beneficial for their children without interference from the government, outside of exceptional circumstances.²⁵⁸ Clearly, parents are given broad latitude to determine which risks their children are exposed to on a daily basis and they are generally the best people to make those decisions that children lack the capacity to make on their own. With decisions about pediatric medical care and participation in research, parents are the next best thing to a decision made by a competent patient or subject

consent may be waived).

256. See 21 C.F.R. § 50.55 (describing when the assent of child subjects must be solicited and when it may be waived).

257. See Efi Rubinstein, Comment, *Going Beyond Parents and Institutional Review Boards in Protecting Children Involved in Nontherapeutic Research*, 33 GOLDEN GATE U. L. REV. 251 (2003) (describing when federal regulations permit research without parental permission, including situations of abuse, emancipated and mature minors, and research on conditions that minors could consent to treatment for on their own, such as sexual assault, pregnancy, drug and alcohol abuse, and the like).

258. Glantz, *supra* note 40, at 220. Other commentators have also noted that it makes sense that the permission of at least one parent is a minimum requirement for enrollment of children in clinical research because

[i]t is a long-standing tradition in the Western world that parents have tremendous discretion to make decisions for their children regarding a whole range of very important matters. It is parents, after all, who make or facilitate decisions concerning a child's education, religion, habits, sexual initiation, etc. This is perhaps even more true in the context of medical treatment. The law generally acknowledges that parents are in the best position to determine what sort of treatment is best for the child and the family and, not trivially, that parents must significantly bear the untoward consequences of a failed therapeutic attempt.

Randall Baldwin Clark, *Speed, Safety, and Dignity: Pediatric Pharmaceutical Development in an Age of Optimism*, 9 U. CHI. L. SCH. ROUNDTABLE 1, 25 (2002) (internal citations omitted).

him or herself,²⁵⁹ and choices by parents among reasonable alternatives are widely respected. However, their discretion is certainly not unfettered.²⁶⁰

The government may fill the gaps in pediatric autonomy through general restrictions on the activities of children that even parents cannot overcome. Examples include mandatory safety seat and helmet laws for children under a certain age and laws prohibiting sexual contact with minors.²⁶¹ A somewhat surprising, but strong, analogy exists between statutory rape laws and government intervention in the type of research in which parents may enroll their children. The state may freely determine that children below a certain age cannot consent to participate in sexual activity, even if they might choose to participate when they reach adulthood, because of the possible physical and emotional risk to the child. Importantly, parents cannot preempt laws that prohibit statutory rape by giving their children permission to have sex with adults, even if they help ensure that the sexual conduct is “safe.” Similarly, the government could conclude that research denying child subjects safe and effective treatment for OCD or depression is so risky that children cannot enroll, even if they would choose to enroll in such research as adults and even if their parents would allow the enrollment. The same analogy applies with government action that forces children to attend school, prevents them from being employed, or prohibits them from holding certain jobs like exotic dancing, bartending, coal mining, factory work, and other morally or physically risky occupations.²⁶²

With regard to medical decision-making for children, the government cannot intervene simply because the parents’ choices may be disagreeable to the child or because they involve some risk.²⁶³ At the same time, parents are not free “to make martyrs of their children before they have reached the age of full and legal discretion where they can make that choice for themselves.”²⁶⁴ Courts historically have been amenable to parental

259. Rubinstein, *supra* note 257, at 277-78.

260. Clark, *supra* note 258, at 25 (noting that “parental dominion over children is not unlimited. The state limits corporal punishment, requires a certain form of education for a specified term of years, restricts the type of labor that children may perform, prohibits incest, and, not insignificantly, requires parents to emancipate their children at the age of eighteen.”).

261. E.g., Jenna Merten, *Raising a Red Card: Why Freddy Adu Should not be Allowed to Play Professional Soccer*, 15 MARQ. SPORTS L. REV. 205 (2004).

262. See generally Sy Moskowitz, *American Youth in the Workplace: Legal Aberration, Failed Social Policy*, 67 ALB. L. REV. 1071 (2004).

263. Parham v. J.R. et al., 442 U.S. 584, 603 (1979).

264. Prince v. Massachusetts, 321 U.S. 158, 170 (1944). See also Glantz, *supra* note 40, at 220 (explaining that the scope of parental authority is “more questionable when the parent is agreeing to a risky intervention. . .that cannot possibly benefit the child,” but where there is some possibility of benefit, parents are generally left to balance risks and benefits in daily life).

decisions to withhold treatment for a variety of significant, but non-fatal, medical conditions, such as surgeries to repair a cleft palate or non-fatal spinal degeneration. However, courts would almost “invariably intervene when parents refused to consent to life-saving treatment[s] of proven effectiveness and trivial risk” for their ailing children.²⁶⁵ Extending this argument, parents should be similarly unable to reject safe and effective life-saving therapy for their children in favor of enrollment in placebo-controlled research. This result mirrors the severity distinction in adult subjects, where placebo controls are ethically impermissible when proven treatment for severe conditions exists.

A larger issue is whether parents can refuse treatment on behalf of their children who suffer from milder, non-life-threatening conditions. Though refusal in such situations has historically been permitted in deference to parental decision-making, courts have begun to intervene in some of the more egregious situations in which children suffer from serious, but non-lethal, impairments, such as the “elephant man disease,” or neurofibromatosis.²⁶⁶ Again, parents cannot choose placebos for their children in response to these relatively severe health problems, in line with the adult severity distinction. Furthermore, courts have also ordered that children receive necessary dentistry²⁶⁷ and tonsillectomies²⁶⁸ over the objections of the parents. It is unclear precisely which conditions will be considered sufficiently mild for parents to refuse all treatment for their children without state interference.²⁶⁹ Parents can withhold something as minor as headache medicine or cough syrup from their child with no more intrusion than, perhaps, social condemnation from other parents. Yet a strong argument remains that parents should not be able to enroll those same children in placebo-controlled research in which they still might receive no treatment for these or other mild health problems.

At first glance, this argument may seem counterintuitive. After all, why not allow children who would not be given treatment anyway to receive

265. Clark, *supra* note 258, at 25.

266. *Id.*

267. *In re Gregory S.*, 380 N.Y.S.2d 620 (N.Y. Fam. Ct. 1976).

268. *In re Karwath*, 199 N.W.2d 147 (Iowa 1972). However, a court will not order that a child undergo risky, invasive, or life-threatening treatment for a non-emergency, non-lethal condition. 59 AM. JUR. 2D PARENT AND CHILD § 19 (2006).

269. See LaDonna DiCamillo, *Caught Between the Clauses and the Branches: When Parents Deny Their Child Nonemergency Medical Treatment for Religious Reasons*, 19 J. JUV. L. 123, 123-24 (1998) (“Courts have consistently permitted state intervention in cases where the child’s life is threatened. Likewise, courts typically hold parents criminally responsible for the negligent death of a child whose parents fail to seek adequate medical treatment. There is a split of opinion, however, as to whether intervention is constitutional in nonemergency cases.”) (internal citations omitted).

only a placebo? In fact, this closely resembles the situation described above allowing parents to enroll their children in placebo-controlled research when no safe and effective therapy exists because the children would not be denied anything they would otherwise receive. The same is true here, but only artificially because the parents are denying treatment that *does* exist and to which the children would otherwise have access but for their parents' interference. The two situations should be treated differently because of the major distinctions between clinical care and research. Some of these differences were introduced above, but the bottom-line is that regardless of what choices parents can make for their children based on religious or other beliefs in the ordinary medical context, the research environment has a built-in gatekeeper: the IRB.

These boards are a form of mandated government intervention from the very outset of research²⁷⁰ that is simply not present in other areas of life, including decisions about standard medical care. Moreover, they have the ethical obligation to protect subjects as much as possible while allowing needed research to move forward.²⁷¹ IRBs can determine standards for enrollment that differ from what adult subjects, or parents of child subjects, believe to be appropriate. Just as an IRB may refuse to permit adult cancer patients to enroll in placebo-controlled research, even if that patient has refused all available therapies, the IRB may also establish a more stringent best interest standard applicable to pediatric research. IRBs may do so even if that same standard might violate religious freedom and general parental control if applied to the clinical setting. The difference exists because human research is a take-it-or-leave-it proposition in which subjects or their guardians have the legal rights to refuse to enroll if they disagree with the protocol or enrollment criteria and to withdraw from participation at any time.²⁷² Still, there is no legal right to demand changes to those elements that remain purely under the IRB's control.

Although subjects have the "right to choose in light of their values whether or not to participate in an approved research project, researchers and independent reviewers have an obligation to not approve and conduct research when, in light of their values, the benefits of the research are insufficient to justify its risks."²⁷³ Some may argue that potential subjects

270. Aside from minor exceptions, clinical trials submitted to the FDA in support of an application for approval "shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part." 21 C.F.R. § 56.103 (2006).

271. BARUCH BRODY, *THE ETHICS OF BIOMEDICAL RESEARCH: AN INTERNATIONAL PERSPECTIVE* 49 (1998).

272. 21 C.F.R. § 50.25(8) (2006).

273. BRODY, *supra* note 271.

have a moral right to research participation to obtain access to needed experimental therapies, and that IRBs have a responsibility to expand enrollment criteria and avoid arbitrary or discriminatory exclusions. However, such a claim certainly does not extend to access to placebos.²⁷⁴ For these reasons, concerns about religious freedom do not present a barrier to the exclusion of children from placebo-controlled research on drugs to treat relatively mild, non-fatal conditions for which safe and effective treatment exists.²⁷⁵ However, the question remains of why this exclusion is morally necessary for pediatric subjects, but not for adults.

As discussed above, parents make decisions for their children because children lack the developmental and legal capacity to make the decisions for themselves. While parents might have an idea of what choices their children *should* make when they reach a competent age, parents truly lack the background information that serves as the basis for substituted judgment as applied to previously competent individuals; unlike adults who have lost their competence to consent, children *never* had such competence. Therefore, parents cannot extrapolate from a child's prior decisions to determine what the child would decide if currently competent to do so. When there is no such background information, either for the adult who was never competent or the child, the decision of which treatment course to pursue or whether to enroll in research should be based on the best interests of the patient or potential subject, focusing on the outcome that would best promote his or her individual well-being.²⁷⁶ Clearly, there may be reasonable disagreement as to which choices will truly be in the child's best interest. While IRBs could certainly impose a very strict view to protect child subjects as much as possible, even the normal moral standard to which parents are held sufficiently prohibits the enrollment of children in placebo-

274. See M.L. Elks, *The Right to Participate in Research*, 122(2) J. LAB. CLINICAL MED. 130 (1993) for a general discussion of the moral right to participate in research.

275. There is no right under the Constitution's religion clauses that protects secular beliefs, and thus neither adult subjects nor the parents of child subjects could claim that their free exercise rights were violated if they had some strongly held, but non-religious, commitment to participation in all types of clinical research or devotion to the progress of science that was hampered by an IRB refusing to permit them or their child to enroll in a study for any reason. See 16A AM. JUR. 2D CONSTITUTIONAL LAW § 424 (2006) (stating "[o]nly beliefs rooted in religion are protected by the Free Exercise Clause of the First Amendment, which, by its terms, gives special protection to the exercise of religion. Religious beliefs need not be acceptable, logical, consistent, or comprehensible to others in order to merit First Amendment protection. However, the Free Exercise Clause does not protect purely secular views or personal preferences." (footnotes omitted)).

276. See Stephen A. Talmadge, *Who Should Determine What Is Best for Children in State Custody Who Object to Psychotropic Medication?*, 15 ANNALS HEALTH L. 183, 191 (2006) (noting that a "decision that is to be made on an incompetent patient's behalf should advance the individual's best interests.").

controlled research for *any* condition, including relatively mild ones, when there is a safe and effective alternative.

Parents are not obligated to act in the objective best interests of their children, mostly because such an objective standard does not exist.²⁷⁷ However, parents do have a *moral* responsibility to act only in a manner that, at least arguably, furthers their child's welfare.²⁷⁸ Applying this standard to pediatric research, when safe, effective, and proven treatment exists for the condition under study, a child's best interest will *never* be to receive no treatment instead of the effective treatment, regardless of how mild the condition might be.

In a decision highly criticized for its poor understanding of the conduct of scientific research and its disregard for common conceptions of research ethics, Maryland's highest court held in 2001 that "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."²⁷⁹ Application of this sweeping statement would severely limit the progress of pediatric medicine and continue the problem of therapeutic orphaning by ignoring the federal regulations that permit essential nontherapeutic research (described in Part IV above). The court retreated slightly from this holding in its response to a motion for reconsideration, defining "any risk" as "any articulable risk beyond the minimal kind of risk that is inherent in any endeavor" and noting that the "context of [its previous statement] was a nontherapeutic study that promises no medical benefit to the child whatever, so that any balance between risk and benefit is necessarily negative."²⁸⁰ However, regardless of whether the court ultimately reached the appropriate result or did in fact go too far, it did make a valid and applicable point to the discussion here:

Whatever the interests of a parent, and whatever the interests of the general public in fostering research that might, according to a researcher's hypothesis, be for the good of all children, this Court's

277. Am. Acad. of Pediatrics, Committee on Bioethics, *Informed Consent, Parental Permission, and Assent in Pediatric Practice*, 95 PEDIATRICS 314, 315 (1995) ("Usually, parental permission articulates what most agree represents the 'best interests of the child.' However, the Academy acknowledges that this standard of decision-making does not always prove easy to define. In a pluralistic society, one can find many religious, social, cultural, and philosophic positions on what constitutes acceptable child rearing and child welfare.").

278. See *Glantz*, *supra* note 40, at 219 (stating "parents must meet a standard of adequacy, not excellence.").

279. *Grimes v. Kennedy-Krieger Inst., Inc.*, 782 A.2d 807, 858 (Md. 2001).

280. *Id.* at 862. This statement fails to solve the problem because it seems to still prohibit nontherapeutic research approvable under 21 CFR § 50.53.

concern for the particular child and particular case, over-arches all other interests. It is, simply, and we hope, succinctly put, not in the best interest of any healthy child to be intentionally put in a nontherapeutic situation where his or her health may be impaired, in order to test methods that may ultimately benefit all children.²⁸¹

While the facts of this particular case limited the court's discussion to healthy subjects, its statement can easily be extended with a few modifications: it is not in the best interest of *any* child to be intentionally put in a nontherapeutic situation where his or her health is *needlessly* impaired through use of placebo rather than available, proven, and active treatment.

For placebo-controlled pediatric research when there is no safe and effective treatment, the child's situation is the same both in and out of the research program. This situation is not an artificial similarity imposed by the child's parent withholding beneficial therapy. The child will have an untreated condition whether he participates or not because there is no alternative that would improve his circumstance, and there are no differential interests to compare. However, when there is a feasible alternative therapy, for example, for a child's headache, no one argues that it is in that child's best interest to continue to suffer even minor and temporary discomfort. The child should be given the available headache medicine in both clinical care and in research, and thus the use of placebos for child subjects facing even such mild conditions is ethically impermissible.²⁸² This position does not contend that children should be precluded from participation in research; rather, until they can autonomously consent to more serious self-sacrifices, they should not be enrolled in placebo-controlled research when there is a more protective approach, such as using active controls, which allows children to help others while minimizing their own discomfort.²⁸³

Children deserve stringent protection because they are not research volunteers in the same sense that adult participants are. Every possible

281. *Id.* at 853.

282. *But see*, Carol Levine, *Placebos and HIV: Lessons Learned* 28(6) HASTINGS CTR. REP. 43, 45 (1998), which notes that there is a utilitarian argument that would permit the use of placebo controls despite the existence of safe and effective treatment for both adults and children suffering from both serious and minor conditions based on the idea that the "most efficient study is the most ethically sound." *Id.* On this rationale, placebos are always permissible, despite the fact that they may risk the health, safety, and even lives, of some subjects, because they will provide the most conclusive data in the fastest possible manner, thus improving the lives of more individuals than were sacrificed.

283. *See* SHARAV ET AL., *supra* note 111 (indirectly examining children's inability to self-sacrifice by emphasizing their incapacity to consent and society's consequent obligation to protect their best interests).

measure should be taken to ensure that their health and safety are maximized—that research is in their best interest to the greatest extent possible.²⁸⁴ Denial of safe and effective therapy in favor of placebos for any condition will do no such thing. Therefore, child subjects should be assured that the current best medical practice standards of treatment will be compared to any new or experimental therapy, even if their parents might be able to legally, if not morally, deny them that standard treatment outside of the research context.

This section has explained the circumstances under which placebo-controlled clinical research is ethically permissible for both adults and children. For all human subjects, placebos are appropriately used in trials examining the safety and efficacy of drugs to treat a condition for which there is currently no safe and effective treatment. However, once a safe and effective therapy is available, the paths of adult and child subjects diverge. Adults are generally competent individuals with the capacity to consent to a wide variety of risks, so they may choose to enroll in placebo-controlled trials. Denial of effective treatment in favor of placebo is ethically permissible for adult subjects suffering from only mild conditions, although it cannot be permitted for severe conditions due to the impact of those conditions on the subject's autonomy and capacity to fully consent.

While it may be tempting to extend this consent/severity framework to pediatric subjects by simply substituting parental permission for the child's consent, this substitution is imperfect. Parents have no basis on which to implement the choices they believe their children would make if competent, and thus they must rely on a best interest standard that does not exist in adult situations.

Parents cannot refuse safe and effective therapy for their children in life-threatening situations in the context of standard care, regardless of religious or other objections. In addition, children, unlike adults, cannot appropriately receive placebos rather than proven therapies for mild conditions because any level of suffering or discomfort caused by such denial could not further their best interests.²⁸⁵ When there is a safe and

284. Rosato, *supra* note 30, at 367. This focus on a child's best interest is in line with the bioethical principle of beneficence, which requires doing good and not doing harm, and is the most important consideration in pediatric research given that autonomy is diminished if not entirely nonexistent. *Id.*

285. There may be instances in which an individual who is legally still considered a minor has full developmental autonomy to make choices for him or herself, in which case, the best interest standard would no longer apply and the "child" should be treated as an adult in the medical arena. Further, autonomy is not an all-or-nothing quality and children will progressively develop more and more autonomy as they grow older. This article does attempt to respect this developing autonomy by supporting the solicitation of child assent to research participation and by not advocating a position that would completely bar a child's

effective treatment for any condition afflicting a child, that alternative must replace placebos as the control in order for research to be ethically sound. Until such treatment exists, placebos remain ethically acceptable, thus mirroring the legal requirements for pediatric placebo-controlled research determined in Part IV above.

B. Application to FDA's Requests

Recall that while some drugs have been specifically labeled for the treatment of pediatric OCD and depression, recent concerns have arisen about the safety of all drugs used to treat these conditions due to data demonstrating an increased risk of suicidality. Therefore, while certain drugs may be effective for these indications, there is currently no treatment that is both safe *and* effective. This fact renders the placebo controls requested by the FDA ethically permissible at the current time, under the generally uncontroversial analysis governing the use of placebo design when no proven treatments could serve as an alternative. As the child subject will not be denied any known safe treatment that he or she would otherwise receive outside of the study, the child is not asked to accept undue risks. Therefore, the interests of the general pediatric population do not unfairly subsume the individual child's interests.

However, consider the argument that rejects this safety analysis because so few children experience an increase in suicidal feelings while taking these drugs. In fact, these drugs have not been taken off the market and are still prescribed to children with black box warnings that instruct careful monitoring.²⁸⁶ In other words, the balance among safety, efficacy, and severity of the condition may weigh in favor of a conclusion that these drugs are more appropriate than placebo. Additionally, the use of a placebo to study drugs that treat these conditions in children does not truly fall within the "no safe and effective alternative" category because subjects would be denied valuable treatment they might otherwise receive. Using this approach or assuming the validity of the FDA's current requests, once safety studies of *Prozac*, *Zoloft*, *Luvox*, or *Anafranil* rule out suicidality concerns (or once an entirely new drug is approved), a safe and effective alternative to placebo will exist, which triggers the more complex ethical analysis outlined in Part V.A.3.

Clearly, it will not be in the best interest of any child to continue to suffer from OCD or depression when a proven therapy exists; therefore, once that

enrollment in research because they cannot yet consent.

286. FDA, Labeling Change Request Letter for Antidepressant Medications, <http://www.fda.gov/cder/drug/antidepressants/SSRIlabelChange.htm> (last visited Oct. 20, 2006).

proven therapy arrives, the use of placebo controls will no longer be justifiable and the FDA should stop requesting them. Future studies should go forward in hopes of improving upon the existing standard of care, but the FDA should request active-controlled studies in return for pediatric exclusivity and require them under the PREA. Notably, the FDA should request active-controlled studies even if one erroneously applies the severity distinction to research on children. Pediatric OCD and depression are certainly less severe than conditions like HIV and cancer, but it does not follow that only life-threatening conditions should be considered serious enough to prohibit subjects from enrolling in placebo-controlled research.

While some might categorize most non-suicidal psychiatric conditions, including outpatient depression, OCD, panic disorder, and anxiety, as sufficiently non-severe to permit study through placebo controls, the FDA has recognized that depression and other psychiatric disorders in pediatric patients can have serious consequences if not appropriately treated.²⁸⁷ Further, OCD has been described as a “chronic, often debilitating mental disorder, causing intensely recurrent, unwanted thoughts, or obsessions, usually coupled with uncontrollable, repetitive behaviors, or compulsions that interfere with daily life,”²⁸⁸ and depression is

characterized by long duration, and is associated with insomnia, irritability, changes in eating habits, and severe impairment of the child’s scholastic and social adjustment. Depression should be considered whenever any behavior problem persists. Depression does not refer to transitory moments of sadness, but rather to a disorder that affects development and interferes with realization of the child’s innate potential. Some manifestations of depression in a school-aged child include anorexia, lethargy, sad affect, aggression, weeping, hyperactivity, somatization, fear of death, frustration, feelings of sadness or hopelessness, self criticism, frequent day dreaming, low self-esteem, school refusal, learning problems, slow movements, vacillating hostility towards parents and teachers, and loss of interest in previously pleasurable activities.²⁸⁹

Clearly, these conditions are not mild and they are associated with more than mere discomfort in children. Therefore, both the severity and best interest standards will prevent placebo-controlled research on OCD and

287. Press Release, *supra* note 172.

288. Melissa Tennen, *Therapy, Meds Can Help OCD Kids*, HEALTH A TO Z (June 2005), available at <http://www.healthatoz.com/healthatoz/Atoz/dc/cen/ment/obcd/alert01202004.jsp> (last visited Nov. 9, 2005).

289. Nat’l Cancer Inst., *Pediatric Considerations for Depression*, available at http://www.nci.nih.gov/cancertopics/pdq/supportivecare/depression/healthprofessional/allpages#Section_243 (last visited Nov. 9, 2005).

depression in children, even if it might be permissible when no undeniably safe treatment exists.

Although placebo controls might help answer research questions more efficiently, when they deny proven therapies they do so at the expense and suffering of some human subjects. While adults can personally consent to some level of suffering for the purpose of research, even when there is a safe and effective therapy available for their condition, children cannot and alternatives to placebos should be utilized whenever possible. Therefore, the FDA should amend its written request templates for studies of OCD drugs and antidepressants in children so that holders of approved applications will perform only head-to-head trials once a proven treatment exists.²⁹⁰

CONCLUSION

This article has demonstrated the dire need for pediatric research and has chronicled several FDA attempts to encourage, and eventually require, sponsors to test their drugs for safety and efficacy in children. Under the Best Pharmaceuticals for Children Act, the FDA makes specific requests for placebo-controlled studies of drugs to treat OCD and depression in children. The FDA has continued to make these requests even after a handful of drugs were specifically approved for those indications. However, this was before the recent suicidality concerns associated with these drugs came to light, indicating that the conclusions reached in this article are a far cry from current FDA policy.

While these requests are probably legally approvable and ethically permissible at the moment, assuming that the suicidality issue creates a situation where there is no safe and effective alternative to placebo, the analysis will change as these suicidality concerns are overcome. At that point in time, the relation of the anticipated benefit to the risk of placebo will no longer be at least as favorable to the subjects as that presented by available alternative approaches. The risk posed by the use of placebo would not be categorized as only a minor increase over minimal risk because it would no longer be equivalent to the level of risk that children suffering from the condition are exposed to outside of the research setting. The studies could not be approved under the minimal risk or catchall

290. Charles Weijer, *Ethical Concerns in Pediatric Placebo-Controlled Trials*, Meeting of the FDA's Pediatric Subcommittee of the Anti-Infective Drugs Advisory Committee, Sept. 11, 2000, 81 <http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3641t1.pdf>. (stating "[a]fter placebo-controlled trials have demonstrated a treatment to be effective for a particular patient population, for second generation treatment, the comparator must be an active control.").

categories, and thus the FDA's requests would be legally impermissible under Subpart D. Similarly, the inapplicability of the severity distinction used to justify placebo controls for mild conditions in adult subjects and the applicability of the stringent best interest standard renders the use of placebo over proven therapies ethically unacceptable. This conclusion rings true regardless of whether parents have the freedom to refuse these treatments for their children in the context of clinical care.

Pediatric research is necessary to protect children from the unavoidable daily experimentation that occurs when their doctors lack information about whether the drugs available for adults will behave similarly in all age groups. Controlled clinical trials are the only valid way to develop the knowledge base that pediatricians need. Placebos offer many advantages, but their efficiency and the clarity of their results cannot always justify their use in pediatric subjects. Now that protective inclusion of children in research is on the rise because of several laudable interventions from Congress and the FDA, protective exclusion will also become increasingly important. When a safe and effective treatment for the pediatric indication under study exists, the FDA must request and require proven therapy to serve as an active control. Under this proposal, doctors will still receive their desperately needed prescribing information and children will be protected both in the clinical setting and in research.