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LESSONS TO BE LEARNED FROM THE 407 PROCESS

Lainie Friedman Ross†

I. INTRODUCTION

Subpart D of 45 C.F.R. § 46 provides additional protection for children in research. To determine whether pediatric research is permissible, the regulations require a risk-benefit assessment of research involving children. All children can participate in minimal risk research. If there is the potential for direct benefit, then the potential benefits must justify the risks. If there is no potential for direct benefit, children with a "disorder or condition" can participate if it entails no more than a minor increase over minimal risk. Research that seeks to enroll either (1) healthy children, but offers no prospect of direct benefit and entails more than minimal risk; or (2) children with a disorder or condition, but offers no prospect of direct benefit and entails more than a minor increase over minimal risk, can be permitted if, and only if, it is approved by a panel convened by the Secretary of the Department of Health and Human Services (DHHS) pursuant to 45 C.F.R. § 46.407.

In the more than two decades since passage of Subpart D, only fourteen 407 panels have been convened. The first two were in the

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3 § 46.405.

4 § 46.406.

5 § 46.407 (providing an exception to C.F.R. §§ 46.404-.406).

early 1990s. However, in 2002, Dr. Greg Koski, then director of the Office for Human Research Protections (OHRP), stated that OHRP had received over two dozen requests for 407 review in the previous year, and from February 2001 through June 2003, eleven protocols were reviewed. The impetus for 407 review may be due in part to concerns of institutional reprisal if federal oversight were not sought.

In 1999 and 2000, a number of major universities were sanctioned by the Office for the Protection of Research Risks (OPRR, now OHRP) for failure of researchers and institutions to protect human subjects adequately.

In this manuscript I provide a brief history of the first ten 407 panels, and then consider in more depth three of the last four review panels. I conclude with several observations that can be gleaned

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note 10.


Nelson, supra note 6. Dr. Nelson chaired all but one of the 407 panels.


The most recent protocol, “Effects of Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder (ADHD): A Functional Magnetic Resonance Study,” was reviewed in September 2004. The protocol was different because it involved the administration of a drug to healthy children and therefore both the Food and Drug Administration (FDA) and OHRP participated in the 407 review. See Pediatric Ethics Subcommittee of the Pediatric Advisory Committee; Notice of Meeting, 69 Fed. Reg. 47157 (Aug. 4, 2004).

The Panel that convened to discuss the research consisted of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee of the FDA. This committee is a federal advisory committee (FAC) and therefore the meeting was open to the public in contrast with all the other 407 panels which were not established as a FAC. The pediatric ethics subcommittee recommended approval of the protocol with modifications. For the consensus position of the committee (and not individual comments from each panelist), see Summary of Minutes of the Pediatrics Ethics Subcommittee of the Pediatrics Advisory Committee, at http://www.fda.gov/ohrms/dockets/ac/04/minutes/2004-4066m1_summary%20Minutes.pdf (Sept. 10, 2004). Neither the committee’s report nor its recommendations are publicly available on OHRP’s website (May 6, 2005). On March 2, 2005, however, OHRP received an e-mail request to terminate the 407 review determination for this protocol, and OHRP complied. See Memorandum to File from Kevin A. Prohaska, D.O., OHRP: Children’s Research
from a historical and ethical analysis of the 407 process: observations that may be instructive for future 407 panels and for pediatric research regulations more generally.

II. THE 1990s: THE FIRST TWO 407 PANELS

There is scant public information about the first two protocols, except their reporting in the Federal Register. The first, "Myoblast Transfer in Duchenne Muscular Dystrophy (DMD)" was denied approval in June 1991. There are no public records that explain why the research was disapproved by the 407 panel. Despite this, at least five human trials involving myoblast transfer were conducted in the early 1990s. Four of the five studies found no improvement. The fifth claimed benefit, but it has been widely discredited. All these studies involved boys (mid-childhood to adolescence) with DMD.

In order for a local institutional review board (IRB) to approve this research, it would have to decide that the research either (1) had the potential to provide direct benefit and the benefits justified the risks; or (2) had no potential to provide direct benefit, but the risks

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Whether the 407 committee was different because it involved both OHRP and the FDA; or whether it has set a new precedent is not known at this time. In light of the lack of available documents and the other procedural unknowns, this protocol and its review will not be considered further.

12 Peter K. Law et al., Dystrophin Production Induced by Myoblast Transfer Therapy in Duchenne Muscular Dystrophy, 336 LANCET 114 (1990) (describing the first myoblast transfer study in humans); Emanuela Gussoni et al., Normal Dystrophin Transcripts Detected in Duchenne Muscular Dystrophy Patients After Myoblast Transplantation, 346 NATURE 435 (1992); J. Huard et al., Human Myoblast Transplantation Between Immunohistocompatible Donors and Recipients Produces Immune Reactions, 18 TRANSPLANTATION PROC. 3049 (1992); George Karpati et al., Myoblast Transfer in Duchenne Muscular Dystrophy, 34 ANNALS NEUROLOGY 8 (1993); Jerry R. Mendell et al., Myoblast Transfer in the Treatment of Duchenne's Muscular Dystrophy, 333 NEW ENG. J. MED. 832 (1995).
13 See Gussoni et al., supra note 12, at 438; Huard et al., supra note 12, at 3051; Karpati et al., supra note 12, at 15; and Mendell et al., supra note 12, at 836.
14 See Law et al., supra note 12, at 114-15.
were either minimal\textsuperscript{17} or a minor increase over minimal risk.\textsuperscript{18} The five studies were probably approved by their local IRBs under C.F.R. § 46.405 as the animal data may have suggested some potential for at least transient benefit.\textsuperscript{19} But to approve the study under C.F.R. § 46.405, the local IRB also needed to believe that the putative benefits justified the risks. Given the lack of knowledge about stem cell/precursor cell transfers, and the potential for immune rejection, a benefit to risk ratio would have been difficult to quantify. It is also not clear why, or how, a local IRB could have approved the first myoblast transfer trials using children as subjects. In 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) recommended that children not be used in research if the scientific question could be answered using adults,\textsuperscript{20} and the National Commission’s reports are the basis for most of our federal regulations on research protections. The scientific goal of these studies was to understand the toxicity of myoblast transfer. While adults with DMD may have been too weak and less responsive to transplant, there are adults with Becker muscular dystrophy (a milder non-lethal form of muscular dystrophy) who could have been the subjects of the initial studies.\textsuperscript{21}

The second 407 panel was convened to review research on “Cognitive Function and Hypoglycemia in Children with IDDM [Insulin Dependent Diabetes Mellitus, now known as Type I Diabetes].”\textsuperscript{22} The study design involved both children with Type I Diabetes (a condition) and healthy controls. The children would be asked to undergo neurocognitive testing both at baseline and with low blood sugar (the low blood sugar, or hypoglycemia, would be induced by an insulin clamp technique). This technique involves infusing glucose and insulin at varying infusion rates to attain a specific blood glucose level. It involves the placement of two intravenous lines (one for the infusion of glucose and insulin and one for blood glucose measurements). The

\textsuperscript{17} § 46.404.
\textsuperscript{18} § 46.406.
\textsuperscript{22} Cognitive Function and Hypoglycemia in Children with IDDM, 58 Fed. Reg. 40819 (July 30, 1993).
danger is miscalculation or an error in calibration, with the result of severe hypoglycemia which can lead to seizures, coma, and even death, although to date this procedure has been done on thousands of volunteers without any serious adverse events.

Although there are no public records, it is clear that the IRB that sought 407 review clearly believed that the research risks were more than minimal or it could have approved the research locally under C.F.R. § 46.404. If the research risks entailed a minor increase over minimal risk, then the research could be approved for children with diabetes (a condition), but given the level of risk, the healthy children could only serve as controls if the research were reviewed nationally. If the research risks were found to entail more than a minor increase over minimal risk, then the research would require national review for both the children with diabetes and the healthy controls [C.F.R. § 46.407]. In speaking with the principal investigator, the panel was convened only for the healthy controls. It was approved by OPRR (now OHRP) in July 1993.

A literature search reveals that the insulin clamp technique, first described in 1979, had been used in research studies in the 1980s that enrolled not only children with diabetes but also healthy children without 407 review. In 2000, however, a research project using the clamp technique was halted by OHRP because of concerns that the study involved more than minimal risk, offered no prospect of direct benefit, and enrolled healthy children without 407 review. The researchers argued that their "healthy" children were obese, or were children of obese parents, and therefore were at increased risk for developing diabetes, and therefore the research could qualify under

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24 § 46.407.
25 Id.
26 Interview with Dorothy Becker, M.D., Chief of Endocrinology and Diabetes; Director, Diabetes Program at Children's Hospital of Pittsburgh; Professor of Pediatrics, University of Pittsburgh School of Medicine, in Pittsburgh, PA (Oct. 2003).
28 See Stephanie A. Amiel et al., Impaired Insulin Action in Puberty: A Contributing Factor to Poor Glycemic Control in Adolescents with Diabetes, 315 NEW ENG. J. MED. 215 (1986); and Silva Arslanian et al., Impact of Physical Fitness and Glycemic Control on In Vivo Insulin Action in Adolescents With IDDM, 13 DIABETES CARE 9, 10 (1990).
OHRP accepted this explanation and the research resumed. And yet, other healthy controls who are not at an increased risk were enrolled, and continue to be enrolled, in clamp studies in Minnesota.

III. RE-EMERGENCE OF 407 PANELS

Between August 2001 and June 2003, eleven 407 panels were assembled. The panels included scientific, ethical, and regulatory experts and community representatives. The first seven panels were convened in August 2001, and the panelists were promised anonymity and submitted “unstructured” written reports shortly after the meeting. The reports were unstructured in the sense that the panelists were not given guidelines about what issues to consider. No votes were taken. Of these seven protocols, three were retracted after the panels met because they were found to be approvable under 45 C.F.R. §§ 46.404-406, and two were withdrawn because they had closed enrollment. OHRP produced a written summary of panel deliberations from notes and individual reports of the other two. One of these studies included using the insulin clamp technique with Japanese American youth, who are considered at higher risk for developing Type I diabetes, and their Caucasian cousins who would serve as controls. It was approved and has been examined in detail elsewhere.

31 See Carome, supra note 30.
32 See Antoinette Moran et al., Insulin Resistance During Puberty: Results from Clamp Studies in 357 Children, 48 DIABETES 2039 (1999) (discussing the results of clamp studies on children with hypertension (who can be classified at increased risk) and children with normal blood pressure (who are healthy controls)). Of note, Moran et al. are working out of the University of Minnesota, which continues to recruit healthy children for clamp studies. See UNIV. OF MINN., GENERAL CLINICAL RESEARCH CENTER: PROTOCOL 488, at http://www.gcrc.umn.edu/gcrc/PROTO.php?p488 (last visited Feb. 9, 2005).
33 See Nelson supra note 6.
34 Id.
The other study, "Alcohol, Sleep and Circadian Rhythms in Young Humans, Study 2 -- Effects of Evening Ingestion of Alcohol on Sleep, Circadian Phase, and Performance as a Function of Parental History of Alcohol Abuse/Dependence," also involved adolescents and adults. The part of the grant requiring 407 review was a study that sought to examine the effect of a moderate evening dose of alcohol on sleep and waking performance in adolescents (aged fifteen and sixteen) and young adults (aged twenty-one and twenty-two). In December 2003, OHRP sent a letter to Rhode Island Hospital stating that the study was disapproved and that the researchers should postpone the enrollment of adolescents until the research has been performed in the adult sub-population and the data analyzed. After the adult data is analyzed, "re-review of the proposed research would be warranted." This recommendation was consistent with the National Commission's position to begin with adult subjects and only to enroll children-subjects if the information is still needed as discussed above.

In October 2002, a panel was convened to evaluate the ethics of a research study on Dryvax (smallpox vaccine) in children. Although the panel never physically met, they submitted individual signed reports. The protocol was eventually withdrawn because bioterrorism preparedness plans had evolved, such that diluted Dryvax in children would not be used, and therefore there was no justification for the particular clinical investigation to proceed.

In May-June 2003, three additional panels met to review the following three protocols (1) "Characterization of mucus and mucins in bronchoalveolar lavage fluids from infants with cystic fibrosis"; (2) "Sleep Mechanisms in Children: Role of Metabolism"; and (3) "HIV Replication and Thymopoiesis in Adolescents." The panelists were asked to consider specific questions regarding risks and benefits, consent, and other aspects of research ethics review. These structured, signed (i.e., non-anonymized) reports were submitted to OHRP.

38 See NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RESEARCH, supra note 20; see also supra text accompanying note 20.
Given the development and refinement of the process over the past 2.5 years, it is these three proposals and the expert panel reports that I examine in depth. Relevant aspects of the protocols, IRB minutes, communication with OHRP, and the individual panelist reports are available on the OHRP web-site.40

IV. BRONCHOALVEOLAR LAVAGE FLUID FROM INFANTS WITH CYSTIC FIBROSIS:

A. Study Description

Cystic Fibrosis (CF) is a genetic condition that presents with pulmonary (lung) disease and gastrointestinal problems including meconium ileus (colonic obstruction) in the newborn, pancreatic insufficiency, and failure to thrive. The purpose of this study is to investigate the initial pathogenesis of airway disease in CF. The researchers seek to examine the relationship between hypothesized abnormalities in airway surface liquid and chronic infection and inflammation. To do this, the researchers propose performing three non-therapeutic bronchoscopies (examination of the lower airways of the lung with a special lens at the end of a long tube) and bronchoalveolar lavage (BAL). Bronchoalveolar lavage involves inserting a thin tube through the nose into the lungs (airways). A small amount of sterile salt water (2 teaspoonfuls) is placed into the airways through the tube, and then suctioned out. The researchers propose to perform BAL three times over a twelve month period on infants diagnosed prior to, or just after, birth with CF (either because they have meconium ileus or a family history that leads to early diagnosis), and to compare their data with control data from children without CF who are undergoing BAL for clinical indications.

Two parent consent is sought for the children with CF who will undergo the BAL for research purposes. No assent is sought because the children are too young. The children will be paid $100 for each bronchoscopy and a $50 bonus if they undergo all three (total of $350). The parents will be paid $50 for filling out a questionnaire at the time of the child's bronchoscopy and a $50 bonus for the completion of the study (total of $200).

Although the researchers tried to suggest that there was some possible benefit to the individual children, the University of North Caro-

lina (UNC) IRB argued that the research exposed children with a condition to more than a minor increase over minimal risk without the prospect of direct therapeutic benefit and suggested that the research could only be done with a 407 review.

B. Ethical Issues

All of the 407 panel members agreed that the research could potentially yield important generalizable information, and that the research did not offer the prospect of direct benefit. They also agreed that the research needed to be done on children, as no adequate animal model exists and most individuals with CF are symptomatic by one year of age. This may or may not be scientifically accurate. A review article in 2001 describes eleven different mouse models of CF,\textsuperscript{41} including one that is studying "the role of CFTR [the gene] in determining either the volume or the ionic concentration of the ASL [airway surface lining] in the lung epithelia."\textsuperscript{42} The review also notes that "[a]ll these potential influences, and others (e.g., the role and distribution of submucosal glands) can be controlled for, and altered, in future studies."\textsuperscript{43} These are some of the factors that this study seeks to examine in infants. Thus, although expert number five was convinced that the question: "Why children now?" could be justified,\textsuperscript{44} it could be argued that the research team needs to explain whether advances in animal models should be pursued further before using this most vulnerable population (infants with a life-threatening condition) in invasive research.

The panel members raised two methodological questions regarding the protocol. The first was the need for greater clarification about sedation. The second was whether at least one of the bronchoscopies could be piggy-backed onto clinical care. The panel members agreed that the research risks to the control children was negligible given that the children would be undergoing BAL for clinical indications and could be approved under 45 C.F.R. § 46.404. To minimize the risks to the children-subjects with CF, the panelists asked the researchers to propose time-frame windows, rather than specific dates, during which

\textsuperscript{41} Donald J. Davidson & Mark Rolfe, \textit{Mouse Models of Cystic Fibrosis}, 17 \textit{TRENDS GENETICS} S29 (Supp. 2001).
\textsuperscript{42} \textit{Id.} at S35.
\textsuperscript{43} \textit{Id.}
each bronchoscopy needed to be done to possibly allow one or more of the BAL samples to be collected simultaneous with clinical care (e.g., if the infants were to undergo a bronchoscopy or intubation during that time period).

As currently designed, the panel members disagreed as to the level of risk that three non-therapeutic bronchoscopies would pose to infants with CF. Two panelists thought that given the experience of the researchers at UNC, the risks could be classified as a minor increase over minimal risk and that the research could be approved under C.F.R. § 46.406. Four of six panelists, however, thought that three bronchoscopies performed under sedation when there was no clinical indication to do so otherwise, constituted more than a minor increase over minimal risk which would require 407 review. Nevertheless, a literature review reveals that performing BAL without clinical indications has been a part of pediatric research throughout the world for years, without 407 review for those done in the U.S. Like the myoblast transfer research and the insulin clamp studies a decade earlier, this is further evidence that there is wide variation in interpreting what a minor increase over minimal risk entails.

Some concern was raised by panel members regarding the consent process. Two panelists expressed the need for a separation between the clinician caring for the child and the investigator who presents the research opportunity to avoid both parental perception of undue pressure to enroll and parental misperception of therapeutic benefit. This is particularly important given the vulnerability of families with young children with a life-threatening condition.

Concerns were also raised about costs and payments. Several panelists were concerned that in the event of research-related injury, the consent form stated that the investigators would assist in obtaining appropriate medical treatment, but the cost would be borne by the family. As one panelist (number five) noted: "Although compensation for research injury is not required by regulation, virtually all federal human research advisory committees have recognized it as a

45 David S. Armstrong et al., Lower Respiratory Infection and Inflammation in Infants with Newly Diagnosed Cystic Fibrosis, 310 BRIT. MED. J. 1571 (1995); Carolyn J. Dakin et al., Inflammation, Infection, and Pulmonary Function in Infants and Young Children with Cystic Fibrosis, 165 AM. J. RESPIRATORY & CRITICAL CARE MED. 904 (2002); G.M. Nixon et al., Early Airway Infection, Inflammation, and Lung Function in Cystic Fibrosis, 87 ARCHIVES DISEASE CHILDHOOD 306 (2002); Jane L. Burns et al., Longitudinal Assessment of Pseudomonas Aeruginosa in Young Children with Cystic Fibrosis, 183 J. INFECTIOUS DISEASES 444 (2001); and K. Balough et al., The Relationship Between Infection and Inflammation in the Early Stages of Lung Disease from Cystic Fibrosis, 20 PEDIATRIC PULMONOLOGY 63 (1995).

46 Burns et al., supra note 45, at 444; Balough et al., supra note 45.
moral duty owed by the sponsors of the research.\footnote{Marshall, \textit{supra} note 44.} A second concern was about the payments. If the infants completed all three bronchoscopies, the children would earn $350, the parents $200 which included a bonus payment. While one could argue that research in children should never offer any financial inducements beyond "token gestures" and reimbursement for the actual expenses incurred by the families (e.g., parking),\footnote{See, \textit{e.g.}, \textit{Inst. of Med. Ethics, Medical Research with Children: Ethics, Law and Practice} 204-05 (Richard H. Nicholson ed., 1986) (discussing the financial implications involved in child-focused research studies); and Am. Acad. of Pediatrics Comm. on Drugs, \textit{Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations}, 95 \textit{Pediatrics} 286, 293 (1995) (providing ethical guidelines for the inclusion of children in drug studies).} the panelists appeared to be comfortable that the amount of money was commensurate with the inconveniences (parental time and child discomfort) that the families were being asked to undergo. There was some uneasiness, however, regarding the bonus.

Despite these concerns, the expert panelists unanimously agreed that the research could offer important generalizable knowledge and approved the research. In June 2004, OHRP sent out a determination letter approving the research under C.F.R. \S 46.407 and requiring a number of revisions as recommended by the 407 panel.\footnote{Letter from Bernard A. Schwetz, Director, Office of Human Research Protections, to Stephen A. Bernard, Chairman, Committee on the Protection of the Rights of Human Subjects, University of North Carolina at Chapel Hill School of Medicine (June 4, 2004), \textit{available at} http://www.hhs.gov/ohrp/children/fund2.pdf.} OHRP has not yet given final approval for this project to proceed.

**V. SLEEP MECHANISMS IN CHILDREN**

A. Study Description

The purpose of this study is to measure metabolic function of adolescent children cycling in wakefulness and sleep using nuclear magnetic resonance (MR) spectroscopy. The researchers also propose to study a subset of children in the same way, except after sleep deprivation. Their ultimate goal is to study all age groups, as it is known that the sleep processes of children and adults are different, but in this research project, they will start with five adults and then focus on adolescents aged thirteen to seventeen years.

The research entails three sessions. The first involves a complete medical history, physical exam, and blood and urine tests. The next two sessions involve admission to the clinical research center of the
hospital for duration of between twenty-four and fifty-six hours. The first night entails polysomnography to exclude undiagnosed sleep disorders. During the hospital admissions, two intravenous lines are placed – one for infusions of $^{13}$C-acetate or $^{13}$C-glucose, and the other for blood sampling for up to twelve hours, and MR studies lasting up to ninety minutes. One group receiving acetate and glucose will be studied after normal activities; the other after fifty-two hours of sleep deprivation. The adolescent will be paid up to $100 and the parent(s) up to $350. One parent consent and the adolescent’s assent are sought. Although the researchers describe the risks as minimal in the consent form, however, the Einstein Committee on Clinical Investigations found it to involve more than minimal risk. Since the research is proposed on healthy adolescents, the IRB requested 407 review.

B. Ethical Issues

In this case, all of the expert panelists agreed that the risks were more than minimal and that the subjects were healthy. The main issue for the 407 panel was the decision to enroll children when the researchers explained in the grant application that “[n]one of the studies proposed have been done in adults or children. Indeed, only a small part of what is proposed here has been done in animals with the use of invasive techniques.”$^{50}$ The researchers chose to begin with children at least in part because the NIH grant proposal was written in response to a grant request for application (RFA) that stipulated the inclusion of adolescent subjects.$^{51}$

The primary reason to do research using a novel invasive technique on adults first is to ensure safety. If the adult data are sufficient to answer the research question then the research need not enroll children. If the adult data show greater safety risks or less therapeutic value than was anticipated, then the benefit to risk calculation changes and the research may now be unapprovable in pediatrics. While the researchers give adequate reasons to show that they will need to enroll children to answer their research questions, they do not give any arguments to justify why children should be the first subjects. One panelist believed five adult subjects were adequate to ensure safety,


whereas another panelist was not sure and asked for review by a data safety monitoring board (DSMB) before enrolling adolescents. A third panelist felt that knowledge about the adult subjects would not make the technique safer and therefore did not see the lack of adult data as problematic. The other two panelists felt that greater studies in adults were needed first. They expressed two concerns: (1) the safety of the MR spectroscopy – not in the amount of radiation, but in its performance while using polysomnography (concern that the wires could become heated during the study that could take as long as ninety minutes); and (2) the tolerance of sleep deprivation. Since some adults are to be recruited, the two panelists argued that they should undergo the procedure first so as to better clarify the known risks and to potentially unveil other unanticipated risks.

There was also concern regarding the payment. As stated in the protocol, the parents would receive more money than the adolescent even though only the adolescent would undergo the procedures. While one panelist was able to justify this on the grounds that money may have greater “undue influence” on adolescents who have fewer opportunities to earn money, the others were concerned that this would lead to parental pressure to participate and to remain in the study, even if the adolescent wanted to withdraw. This is made even more problematic by the consent document which describes payment before stating the risks and benefits of the research.

Another issue is consent. Although not raised by the panelists, the consent forms only seek one parent’s permission. The federal regulations allow IRBs to decide whether one or two parent consent is needed for research classified under C.F.R. § 46.404 and C.F.R. § 46.405, but research covered under C.F.R. § 46.406 and C.F.R. § 46.407 require permission of both parents. Whether the second parent’s consent adds much in a culture in which almost half of children will spend at least part of their childhood in a single parent home is debatable. In this case, however, a large amount of money is being offered to the parents. If one believes that two parents would place additional pressure on the adolescent to participate, then the second parent’s permission offers no protection. If one believes that by seeking the permission of both parents, one parent might look beyond his or her self-interest and focus on the child’s best interest, then the second parent’s permission may offer protection. There are no data. However, whether the second parent’s consent provides additional protection cannot, and should not, be solved at the individual protocol level, but would require a revision of the regulations.

52 Protection of Human Subjects, 45 C.F.R. § 46.408(b) (2004).
The panelists also expressed concern about how the researchers would exclude adolescents with a history of infection, hepatitis, drug abuse, or pregnancy. It is unclear whether this information will be obtained only by history (as suggested in the protocol) or by blood or urine testing (to be performed at the first visit). If determined through blood or urine testing, the consent should describe this explicitly and discuss how and to whom such information will be disclosed.

Although no vote was taken, at least two, if not three, of the five panelists recommended against approving this research (one panelist was willing to consider approval after a DSMB reviewed the safety of the research done on adults). In March 2004, OHRP concluded that the studies on children should be disapproved until the adult data were collected and analyzed.\textsuperscript{53} To date the adult data have not been presented to OHRP for re-consideration.

**VI. HIV REPLICATION AND THYMOPOIESIS IN ADOLESCENTS:**

**A. Study Description**

The purpose of the study is to examine several aspects of the function of the thymus (an organ that plays a key role in the body’s defense against infection and cancer) in subjects aged thirteen to twenty-four years who acquire HIV at birth, versus subjects who acquire HIV through sexual activity or drug abuse, versus subjects who are HIV-negative. All of the potential subjects are followed at the University of California at Los Angeles (UCLA) hospitals. All would undergo medical histories and physical exams as well as computed tomography (CT) exams of the thymus.

The researchers seek to include a sub-study in their research in which the subjects are given deuterium (heavy water) labeled glucose over twenty-four hours, either intravenously or by mouth during a twenty-four hour stay in the General Clinical Research Center, and to continue to take heavy sugar water by mouth over the next month. If the subjects are over eighteen years, they will consent or refuse to participate themselves. Otherwise, the researchers will seek one-parent consent and the assent of the child. For participation in the sub-study, the subjects will be paid seventy-five dollars for the over-

night stay and thirty-five dollars twice for the two blood collections that seek to examine the amount of labeled glucose that enters their white blood cells. The UCLA IRB thought that the research could answer an important research question, but they thought it posed more than a minor increase over minimal risk in a healthy (HIV-negative) population, and could not be approved without 407 review.

B. Ethical Issues

Although the UCLA IRB was mainly concerned about the risks in the sub-study, the 407 panelists were more concerned about radiation exposure from the non-contrast spiral CT of the thymus which was being proposed to measure the gland’s volume. This involves radiation exposure to a gland that is known to be sensitive to radiation. Although the amount of radiation is low, there is debate as to whether even this amount of radiation may increase the risk of cancer. The main study also includes Tanner staging, which is the determination of the level of sexual development in adolescents from stage I (pre-pubescent) to stage V (mature adult phenotype). While Tanner staging is not physically risky or invasive, some adolescents may find the process more stressful than one might anticipate. This issue was not raised by the UCLA IRB, nor any of the 407 panelists.

The panelists concurred that the study and sub-study did not offer the prospect of direct benefit. Some panelists believed the research involved no more than minimal risk and suggested that the research be approved under C.F.R. § 46.404. The others believed it involved at most a minor increase over minimal risk such that the enrollment of HIV-positive adolescents could be approved under C.F.R. § 46.406, but that the enrollment of healthy controls would require national review. One panelist considered whether the HIV-negative controls could be considered “at risk for having a condition” (expert number...
The researchers stated that they will recruit the HIV-negative adolescents from their HIV clinic. These adolescents and young adults are being followed because of their high risk activities. If these “at risk” adolescents are included in the category of children having a disorder or condition (like the obese children in the diabetes study\textsuperscript{60}), then even those panelists who thought that the research involved a minor increase over minimal risk could approve the research under C.F.R. § 46.406 without the need for 407 review.

Another important issue is that of consent. Again, the researchers seek the adolescent’s assent and permission from only one parent, despite the requirement in the federal regulations for two-parent permission for research covered under C.F.R. § 46.407 “unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.”\textsuperscript{61}

Two other consent issues were also raised. First, concern was expressed regarding the possibility that a subject would be found to be pregnant, and her right to confidentiality. Clearly this needs to be addressed in the consent form and in the consent process. Second, some of the adolescents will become eighteen years of age during the course of the study, and they should consent for continued participation for themselves.

In summary, four of the eight expert panelists believed that both the HIV main study and the sub-study entailed at most minimal risk and could be approved as C.F.R. § 46.404. The others believed that the risk was a minor increase over minimal risk, such that the research on the HIV-positive adolescents could be approved under C.F.R. § 46.406, but that 407 review was needed for the HIV-negative patients. If a broader interpretation of “condition” were adopted, one could argue that adolescents at “high risk” for HIV should be considered within the purview of “adolescents with a disorder or condition,” and the research could be approved under C.F.R. § 46.406 for all the subjects. However, in March 2004, OHRP approved this research project with modifications under C.F.R. § 46.407\textsuperscript{62}, which means that the “at

\textsuperscript{59} Letter from Rosemary B. Quigley, Center for Medical Ethics and Health Policy, Baylor College of Medicine to Bernard A. Schwetz, Acting Director, Office for Human Research Protections, Department of Health and Human Services 2 (June 27, 2003), available at http://www.hhs.gov/ohrp/panels/407-04pnl/exp7.htm.

\textsuperscript{60} See supra text accompanying notes 30-31.

\textsuperscript{61} § 46.408(b).

\textsuperscript{62} Letter from Bernard A. Schwetz, Acting Director, Office for Human Research Protections, Department of Health and Human Services, to Robert A. Figlin, Chairman, Medical Institutional Review Board, Office for Protection of Research Subjects, University of California Los Angeles (Mar. 23, 2004), available at
risk HIV-negative" controls were not considered to have a condition relevant to the research. In December 2004, OHRP found all the stipulations were addressed and stated that the research could proceed.63

VII. LESSONS LEARNED

The first observation is the evolution in the 407 process since the first cases in the 1990s. The federal regulations do not provide guidance about the structure or process for 407 panels. The decision to make a number of documents available to the public, including relevant parts of the research protocol; the communication between OHRP and the institution that requested the review; and the comments of the expert panelists are important because they introduce greater transparency into the process. Transparency is valuable because it can help reduce referrals by IRBs of protocols that do not fit the criteria for such review.64 Transparency may also promote greater referral to the 407 process by institutions in which research is being done that requires 407 review. Robert Nelson, the chair of virtually all of the recent 407 panels, recommended that these panels become a Federal Advisory Committee (FAC),65 which are required to be open to the public. The recent Institute of Medicine (IOM) report also recommended a standing committee because a continuing panel would accumulate experience and insight.66 In March 2004, the Secretary’s Advisory Committee on Human Research Protections (SACHRP), established after the National Human Research Protections Advisory


64 COMM. ON CLINICAL RESEARCH INVOLVING CHILDREN, BD. ON HEALTH SCIENCES POLICY, INST. OF MED. OF THE NAT’L ACAD., ETHICAL CONDUCT OF CLINICAL RESEARCH INVOLVING CHILDREN 272-73 (Marilyn J. Field & Richard E. Behrman eds., 2004) (discussing the benefits of the OHRP’s § 407 process and potential improvements).


The panel that met in September 2004 regarding Dextroamphetamine in healthy children was a FAC because it consisted in part of the Pediatric Ethics Subcommittee of the Pediatric Advisory Committee of the FDA which is a FAC (see supra note 10).

66 COMM. ON CLINICAL RESEARCH INVOLVING CHILDREN, BD. ON HEALTH SCIENCES POLICY, INST. OF MED. OF THE NAT’L ACAD., supra note 64 at 272-73.
Committee (NHRPAC) was disbanded, endorsed a non-FAC open panel model. 67

And yet, while the process has evolved, the issues raised have not changed. Two 407 panels, one convened in 1993 68 and one in 2001 69 examined the risks of the insulin clamp technique on healthy children. Although each protocol was approved by its 407 panel, one cannot deduce that the insulin clamp technique is always approvable in healthy children because it entails more than minimal risk (two intravenous lines and the infusions of glucose and insulin which can lead to the potentially small, but possible, risk of severe hypoglycemia). However, one could imagine techniques or innovative procedures for which the level of risk decreased with familiarity such that later studies using them would not require 407 review.

A second observation from the 407 process is the wide variability between panelists about the level of risk these protocols entail, a variability previously documented reported between pediatric chairpersons 70 and between IRB chairpersons. 71 NHRPAC attempted to provide greater detail regarding which procedures should be judged to belong to each of the three categories of risk, 72 but NHRPAC was disbanded before its suggestions were debated and adopted. The IOM committee also examined the categories of risk and concluded that SACHRP “should be encouraged to continue its predecessor’s work to develop consensus assessments about the risk of common research procedures.” 73

By publishing the expert panel reports, IRB members, researchers, and the public at large can comment on the panelists’ recommendation regarding risk classification: This is particularly important in the studies in which there was wide variability on the level of risk that the research entailed. Dialogue may lead to a body of cases described as

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69 See U.S. DEP’T OF HEALTH AND HUMAN SERV., supra note 40.


73 COMM. ON CLINICAL RESEARCH INVOLVING CHILDREN, BD. ON HEALTH SCIENCES POLICY, INST. OF MED. OF THE NAT’L ACAD., supra note 64 at 135.
minimal risk, a minor increase over minimal risk, and more than a
minor increase over minimal risk. The data could serve as guidance
for other IRBs about how such research is being classified by compa-
rable institutions, and will provide a forum when serious disagree-
ments arise. It would be a democratic and transparent approach to
guideline development. In fact, it would be useful if OHRP decided
to make publicly available all protocols that it receives for 407 review,
even those in which the 407 referral is voided, to give further guid-
ance to IRBs about what research can be approved at the local level.

A third observation is that the research projects under review had
already received federal funding. This means that they had been peer-
reviewed and found to have significant scientific merit, but that they
may not have been reviewed for their research ethics standard. While
IRB review earlier in the process would avoid the delay that a 407
panel generates, it significantly increases the workload of IRBs by
requiring review of many projects that are not funded and therefore
not executed. An alternate mechanism to avoid funding ethically un-
approvable research would be for scientific review panels to system-
atically include ethicists who could seriously evaluate the research
ethics component of the grant application, and encourage the review
panel to take the research ethics issues into consideration in their
funding decisions. This is important because research designs are
dependent on the current state of knowledge, such that a delay of two
or three years may make the research questions obsolete, and yet the
funding mechanism might not permit or encourage revision of the
research design. A cumbersome process, then, will discourage re-
searchers and their institutions from applying for 407 review, and may
lead institutions to employ an overly liberal interpretation of minimal
risk, or a minor increase over minimal risk, in order to justify approv-
ing a research project, particularly one that is externally funded.

A fourth observation is that despite IRB and expert panel review,
two of the consent forms sought the consent of only one parent, al-
though the federal regulations require two parent consent for all re-
search reviewed under 407. This may have been an oversight, or it
may have been the belief that the second parent would not add much
protection. This suggests that, at minimum, the current policy should
be re-examined.

A fifth observation is the issue of payment. Payment was offered
in all three studies. The studies varied in how much was paid to the
child versus the parent, as well as the actual amount paid. This topic
is not addressed in the federal regulations. Although discouraged by
the American Academy of Pediatrics, it is not prohibited in the United States and has found some ethical support. The public process may help create guidelines by community consensus regarding its legitimacy, and if legitimate, how much children and their parents should be paid. There was also some discussion regarding compensation for injury, another topic not addressed in the federal regulations. Many ethics advisory panels have supported the proposition to compensate all research subjects injured directly by their research participation. This may be even more justified for research requiring a 407 review.

**VIII. RECOMMENDATIONS**

Some important research questions on children will entail more than a minor increase over minimal risk and not offer the prospect of direct benefit. While an Institute of Medical Ethics working group (UK) concluded that such research should never be performed, the National Commission (US) voted to permit such research (with two commissioners dissenting). The concurring commissioners argued that such research should be permitted but restricted in its use. They also argued for national review to ensure greater scrutiny of both the scientific merit and the ethical concerns. While 407 panels can offer this additional scrutiny, I have tried to show that the current structure needs reform. The panelists cannot vote, nor attempt to achieve consensus, lest they act as a committee without authority to do so.

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74 Am. Acad. of Pediatrics Comm. on Drugs, *supra* note 48, at 289.
77 *Inst. of Med. Ethics, supra* note 48, at 234.
78 Nat'l Comm'n For the Prot. of Human Subjects of Biomedical and Behavioral Research, *supra* note 20, at 139.
79 *Id.* at 139-41.
80 *Id.*
Although public comments are solicited by OHRP as required for research to be approved under C.F.R. § 46.407, the public can only attend and participate if the panel is convened as a FAC. While a standing panel may resolve many of the procedural problems, it will not necessarily resolve all of the substantive problems such as: (1) Whether all research approved under C.F.R. § 46.407 ought to require two parent consent; (2) Whether payment to children or parents beyond reimbursement is morally legitimate; and (3) Whether research approved under C.F.R. § 46.407 should be required to have an injury compensation plan. The questions raised by the 407 process may help elucidate how the regulations should be revised for research that is classified under C.F.R. § 46.407 as well as research involving children more generally.
