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Children as Research Subjects: The Overbroad Regulations in 45 C.F.R. § 46, Subpart D, in Conjunction with Legislative Economic Incentives Allow for Exploitation of this Vulnerable Subject Population

Jacqueline Berg
After describing and examining the disparity in research conducted on adults with that on children and why it exists, this paper will discuss the recent legislative response, will highlight a number of the ambiguities and the questionable ethics of the unsatisfying regulations governing children as research subjects, and will recommend improvements in striking the delicate balance needed to protect children from research abuse and improve their health through useful, careful research.

Why There is a Need for Children to Act as Research Subjects

Roughly seventy-five percent of drugs approved for use in the United States have never been subjected to comprehensive pediatric studies.\(^1\) A General Accounting Office (GAO) study published in 1991 reports that eighty to ninety percent of pediatric patients are prescribed off-label drugs.\(^2\) The Food and Drug Administration (FDA) reports that in 1994 the 10 drugs lacking pediatric labeling which were prescribed most often to children, were prescribed over 5 million times.\(^3\) Albuterol, not labeled for use in children and used for asthma and other respiratory problems, was prescribed 1.6 million times in 1994 to children under 12 years old. Such rampant prescription of off-label drugs presents vast risk to children’s health. Children are not merely mini-adults; because of specific physiological differences from adults, children need carefully tailored drugs and dosages. As the organs that break down drugs or excrete chemicals take many years to mature, children absorb and metabolize medicine more quickly than adults. Also, because the rate of blood flow to the skin and lungs is higher in children, topical and inhaled agents may be absorbed more rapidly in children than in adults. Consequently, when drugs have not been tested on children, doctors are likely to stick to older, less cutting-edge and perhaps less effective treatments for

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3 www.fda.gov – general information
children, while adults reap the benefit of innovative, tested medicines. Further, not only is the lack of child-specific pharmaceutical information risky, but although it is legal to use drugs off-label, the practice is deceptive because parents will assume that a drug on the market, prescribed by a physician, has gone through the rigorous three-phase FDA approval process and has proven safe and effective for the recipient.

Disincentives

This “pediatric gap” stems from numerous financial, legal and ethical issues that have served as disincentives to employing children as research subjects. To summarize, the financial disincentives are that: children are a smaller, less profitable market than adults because they are healthier; off-label prescriptions serve to bring in profits without the expense of conducting pediatric research; and pediatric studies present additional and substantial liability due to the tolled statute of limitations. The legal disincentives were that until the promulgation of Subpart D in 1983, the federal regulations providing additional protection for children involved as subjects in research, because only an adult can give informed consent, children’s role in research was legally uncertain. Ethically, the disincentives to conducting pediatric research remain immense: the validity of the child assent and parental permission proxy; defining the value and acceptability of Utilitarianism for this “vulnerable” group; delimiting an acceptable level of risk; and addressing rampant conflicts of interest within the Institutional Review Boards (IRB), with the referring doctor, and possibly with the child’s parent(s).

4 Groopman at 37.
Federal Regulations Governing Human Research

Against the backdrop of a history of ethical violations and abusive practices, from the torturous Nazi “experiments” abroad, to incidents such as the Tuskegee Study and the Willowbrook School incident in the United States, Congress authorized the Department of Health, Education, and Welfare (DHEW) to regulate research on children subjects. The Department created initial regulations in 1974, and following the National Commission’s Belmont Report on Human Subject Research, in 1981 the Department of Health and Human Services (DHHS), formerly DHEW, promulgated general regulations for the protection of human subjects in 45 C.F.R. § 46. Two years later DHHS issued Subpart D of the regulations: additional protections for children involved as subjects in research, 45 C.F.R. §§ 46.401-46.409. See attached Subpart D.

Congressional Encouragement of Pediatric Research

To combat the deeply entrenched, above-mentioned disincentives to conducting pediatric research in order to fill the pediatric gap, Congress recently enacted economic incentives to spur on pharmaceutical companies. The Food and Drug Administration Modernization Act (FDAMA) of 1997 and the Best Pharmaceuticals for Children Act (BPCA) of 2002, encourage pediatric research by granting a 6-month extension of monopoly privileges if the company provides the FDA with adequate pediatric labeling. Despite the substantial increase in the number of pediatric studies, one figure cites the increase in child participation in industry-funded trials as jumping from 16,000 in 1997 to 45,000 in 2001, the pediatric gap still exists and the legislation has created numerous concerns. One such concern is the resultant costly delay in the approval of generic drugs. A GAO report of 2001 on the issue of pediatric exclusivity stated,

7 Alice Dembner, Teddy Bears and Veiled Threats to Attract Children into Medical Experiments, Researchers increasingly Use “Incentives” and Appeal to Parents’ Deepest Fears, Boston Globe, (March 20, 2001).
FDA estimates that the delay in availability of generic drugs could increase national drug spending by … on average about $695 million per year over a 20-year period.\(^8\)

Further, the Acts are only voluntary and they do not address the issue of old drugs that have never been tested on children and for which there is no exclusivity extension incentive. Although the Pediatric Research Equity Act\(^9\) was passed in 2003, requiring drug companies working on a treatment for a disease that affects both adults and children to conduct pediatric studies, it has serious loopholes. Particularly, Congress did not set a timetable for the completion of those mandatory pediatric studies. Therefore, because of the 2007 “sunset,” drug companies may push their adult-approved drug to market, promise to conduct the child studies, but wait until the legislation expires or lapses and never conduct the pediatric studies.

Along with the increase in pediatric research have come increased numbers of ethical violations. According to one reporter, between 1999 and 2001, regulators cited more than three-dozen hospitals and universities for breaking research rules protecting children.\(^{10}\) Violations of Subpart D probably existed prior to the Congressional incentives, but with the increase in pediatric research, the legal and ethical uncertainties of Subpart D have become glaring. Contrary to its protective purpose, the regulations allow researchers great leeway to conduct perilous, ethically sketchy studies in the name of progress.

Deficiencies of Subpart D, applicable to all Human Research Subjects, Particularly Dangerous in Children: Money, Conflicts of Interest and Lack of Oversight

A. Money

There is nothing in the regulations that governs inducements. The AMA Ethics, however, give guidance, stating that researchers are not to receive money for referrals to studies. But doctors often profit from referring children to research protocols. According to the President of the

\(^8\) Karena Cooper, *Pediatric Marketing Exclusivity as Altered by the Best Pharmaceuticals For Children Act of 2002*, 57 Food & Drug L.J. 519, 528 (2002).


\(^{10}\) Dembner at 2
Alliance for Human Research Protection, “Physicians commonly earn fees of $2,000 to $5,000 per child they refer for clinical trials.”\textsuperscript{11} Similarly, Subpart D is silent as to whether money can be given to child research subjects. A survey by an NIH researcher, however, revealed that about 25% of pediatric studies in 1999 advertised some compensation for children or their parents – typically $200-$400, but sometimes up to $1,000.\textsuperscript{12} The problem with unregulated inducements is that they may persuade doctors to underestimate risks, making them more apt to recommend children as research subjects, and may undermine the objective decision-making process of parents and children.

B. Conflicts of Interest – The IRB, Doctors and Researchers

As for regulating conflicts of interest, only the general human subject regulations, not specifically Subpart D, address the issue. § 46.107 (e) states, “No IRB may have a member participate…in which the member has a conflicting interest…” But there is ample evidence of such conflicts. A 2003 Harvard Health Policy Institute survey concluded that, “The fact that almost half of all faculty IRB members serve as consultants to industry raises potential conflicts of interest.”\textsuperscript{13} Because the IRB plays the crucial role of overseeing the validity of informed consent (with a child, his assent and his parent(s)’ permission) and policing the level of risk in a study, those safeguards are compromised if and when the IRB members have a personal interest in the research.

Additionally, there is nothing within Subpart D, or elsewhere in 45 C.F.R. Part 46, which requires a special IRB membership for the review of child research. The federal regulations call for at least a five-member IRB with a non-scientist and a nonaffiliated member. But in practice, because only one member must be a non-scientist, the largely scientist composition of the IRB inevitably leads it toward approval of research more than if it were comprised of mostly laymen. Ethicist

\textsuperscript{11} Vera Sharav, \textit{Conflicts of Interest in Biomedical Research Harm children with and without Disabilities}, J. Disability Pol’y Stud. 50 (June 2004).
\textsuperscript{12} Dembner at 6.
\textsuperscript{13} Sharav at 7.
George Annas, though he would prefer all community members on the IRB, calls for a 1:2 ratio of community members to scientists for its composition. He states,

The question of what we can do to our fellow human beings in the name of science is a public question. And public members are the only people who can really speak to that.\textsuperscript{14}

While having all laymen decide the ethical issues of human subject research might be useful for evaluating the ethics of a protocol, because only scientists or medical doctors can understand and begin to predict the physical risks and effects of a scientific experiment, IRBs should remain at least equally composed of scientists and laymen.

When using children as research subjects, aside from having some non-interested, non-scientific point of reference to evaluate the ethics of the proposed experiment, the IRB should contain at least some specifically child-oriented members. The regulations, however, only permit for such specialists, but do not require them. §46.107(a) states in part,

\begin{quote}
If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children…consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these subjects. (emphasis added)
\end{quote}

§ 46.107(f) states,

\begin{quote}
An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB. (emphasis added)
\end{quote}

To ensure a thorough child-protective review as to the appropriateness of using this vulnerable category of subjects in research, Subpart D should specifically mandate that a Pediatrician and/or other child specialist review and vote on the inclusion of children in clinical trials.

Likewise, nothing throughout Part 46 or Subpart D protects the participant from a treating doctor’s conflict of interest in research that he is conducting. Thus unbeknownst to a potential

participant, his treating physician may have a stake in the research and may present a more positive risk-to-benefit analysis than if he had no interest. Subpart D should explicitly circumscribe fees given to physicians for child subject referrals and should at a minimum obligate full disclosure of the researcher’s conflicts of interest.

C. Ineffective Oversight

Despite a number of federal agencies which exist to oversee, punish and prevent the abuse of research subjects - OHRP, GAO, the Office of the Inspector General of DHHS - in addition to the role played by the National Bioethics Advisory Committee and the Institute of Medicine, the agencies have all reported “systemic weakness and ethical violations in the conduct of human research.”15 Between 1999 and 2000 alone, OHRP found twenty universities to be in substantial violation of the federal regulations governing human research.16 Subpart D should include a regulation setting out consistent, thorough oversight of research on children, which would help deter their misuse and abuse in experiments.

Child Assent/Parental Permission

A. Child Assent

Amongst the most significant deficiencies of Subpart D is the ambiguous, ill-conceived child assent/parental permission provision. Justice Cardozo enunciated the well-established right of every individual to the possession and control of his own body in 1914, declaring, “every human being of adult years and sound mind has a right to determine what shall be done with his own body.” 17 But because children can not “consent” in the legal sense – a term that implies full competence to make an independent, legally-binding decision for one’s self – the regulations call for a proxy system in which a child gives “assent,” an affirmative agreement to partake in research,

15 Sharav, at 2
17 Schloendorff v. Society of New York Hospital, 211 N.Y. 125, 105 N.E. 92 at 129.
and a parent/parents give “permission” for the child to participate. One problem is that Subpart D does not define an age at which child assent should be solicited. Within each of the types of permissible research, §§ 404-407, Subpart D states that, “…adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.” The wording is problematic because it indicates that the process of attaining assent/permission may be more important than the actual procurement of assent/permission itself. Conceivably, if the assent/permission procedure exists and is initiated, research can proceed without its completion.

Further, the regulations make clear that the decision of when to solicit child assent is left to the IRB’s discretion. §46.408(a) states,

> In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. (emphasis added).

Not only does the individual IRB determine when and if the child’s assent should be solicited, but the regulations specifically allow the IRB to waive the child’s assent depending on the child’s understanding, the benefit to the child, and an even broader, nebulous blanket waiver. §46.408(a) states,

> If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A. (emphasis added).

Subpart A allows for a waiver of consent in numerous situations: (1) if the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the
waiver or alteration; (4) and whenever appropriate, the subjects will be provided with additional pertinent information after participation. Several of those exceptions have disturbing implications for research subjects. For instance, the decision of when the waiver will not adversely affect the subject’s rights or welfare could vary vastly amongst IRBs. Some could consider any waiver of consent to adversely affect one’s rights and some could consider that a waiver of consent in a nontherapeutic experiment would not adversely affect one’s rights in light of the potential to gain knowledge useful for others. The exception that allows waiver because research could not practicably be carried out without it seems to permit any research to proceed without consent, prioritizing the quest for knowledge above protecting subjects. Lastly, how does permitting waiver of consent but providing additional pertinent information after participation serve to protect the research subject?

With such broad latitude to decide when assent should or should not be solicited and heeded when it is solicited, the IRB has absolute discretion to disregard and override the child’s willingness to participate in research. This dangerous power is in direct contradiction to the supposed “additional protection” offered to children in Subpart D.

B. Parental Permission

As for the role of the parent or parents in giving permission, the effectiveness of the regulations in protecting child research subjects is questionable because the parents’ interests can conflict with the child’s, the parents may be under-informed or coerced into a decision, there is the possibility that the court may limit parental authority because their permission for participation goes against the child’s best interest, and the level of parental permission, one or both, may serve as an obstacle to participation as opposed to a protective mechanism.
In general, parents are authorized to make medical decisions for their children because it is believed that parents will do so in the child’s best interest. A parent’s permission for his child to participate in an experimental research protocol is necessarily different than his permission for an established medical treatment because of the less-established risk-to-benefit ratio of research in comparison to treatment. However, if a research protocol is the only treatment option for a child and it holds out the prospect of direct benefit, it is clear that participation, even in the face of unknown risk, could be in the child’s best interest. But, in the case of a nontherapeutic experiment that holds out no benefit for the participating child, how can a parent’s permission be sufficient since participation clearly does not fall under the rubric of a child’s best interest?

There are numerous scenarios in which a child and parent’s interests can conflict and in which the parents do not act in accordance with the standard of the child’s best interest. Examples which the court has reviewed and noted as contrary to the child’s best interest include: the case of a seven-year-old girl with no evidence of a mental disorder whose parents hospitalized her in a psychiatric ward because of their disapproval of her older boyfriend; parents who overmedicate children because of their difficult behavior; parents who make “wrong” treatment decisions because of financial, emotional, marital or family interests which conflict with the child’s best interest. One can perhaps more readily sympathize with a parent’s inability to focus on a child’s best interest because of emotional, marital and family stress than because of financial interests. But, since financial inducements are a factor that convince doctors to recommend child participation and children to act as participants, inducements are certainly a factor for some parents who permit their children to participate in research. Payments may lead parents to underestimate risks in order to

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gain monetary benefit, and may even cause them to ignore risks that develop once the child is in the protocol so that they can continue to make money.\textsuperscript{20}

A situation in which there is often a glaring conflict of interest between the parent and the child is with organ or bone marrow donation from one child to a sibling. Although being a donor is not akin to being a research subject, it is useful to consider the parent’s authority in giving this permission in comparison to a parent’s role in giving permission for a child to participate in nontherapeutic research. In the case that parents want child A to donate bone marrow or an organ to another child in the family, child B, the parents are acting in the best interest of child B. The donor, child A, will not receive a physical benefit, although some posit a psychological, altruistic benefit.\textsuperscript{21} Rather, the donor will undergo an invasive, potentially risky procedure that may be rationalized because there is a high likelihood of direct benefit to child B. However, when parents give permission for their child to act as a research participant in a protocol with no direct benefit but which may help gain knowledge about the child’s condition or a condition which the child does not have but which affects other children, the potential beneficiary is an unknown, future entity.

In \textit{Curran v. Bosze}, 141 Ill.2d 473, 566 N.E.2d 1319 (1990), the Illinois Supreme Court denied a father’s petition to compel his three and one-half year old twins to submit to bone marrow harvesting for the benefit of their half brother who suffered from leukemia. The court explained that a parent could only consent in such a case when to do so would be in the minor’s best interest. The factors the court considered were: if the parent was informed of the risks and benefits to the child; if there was emotional support to the child from the parents; and if there was an existing, close relationship between the donor and the recipient. Although one of the factors which weighed against allowing the father’s consent was that the mother objected to the procedure and would not


be supportive to the twins, the case largely hinged on the fact that the twins and their half sibling did not have a relationship with each other. Because of the lack of a relationship, the court reasoned that even though the half brother would likely die, the invasive procedure was not in the best interest of the twins.

While Subpart D sets out the parameters of nontherapeutic child research, in light of Curran, it is difficult to imagine a court upholding a parent’s authority to consent to any nontherapeutic research of their child as being in the child’s best interest when there is no relationship, let alone a close one, with the purported recipient of the research subject’s goodwill. As written by the Supreme Court,

Parents may be free to become martyrs themselves. But it does not follow they are free, in identical circumstances, to make martyrs of their children before they have reached the age of full and legal discretion when they can make that choice for themselves.22

Although the regulations, at § 46.116, require consent forms to be presented in language understandable to the potential participant, numerous studies indicate that the readability of the forms may be too advanced for the average research participant and that this may adversely affect a parent’s ability to grant permission. One study demonstrated that consent forms of hospitals required an undergraduate or graduate reading level.23 Another study revealed that informed consent forms for pediatric biomedical research were written for a graduate student reading level.24 Given the weight of a parent’s permission to allow a child to participate as a research subject and their intended role as protector of the child’s best interest, consent forms need to be easily comprehensible and elucidate the risks, not obscure them. Further, because data indicates that

parents who give permission for their children to participate as research subjects may be less educated, parental permission is not always the protective mechanism it was intended to be.25

Although the Supreme Court has not decided a case indicating whether it would overrule a parent’s ability to give permission for his child’s participation as a research subject, two state court cases indicate that courts are willing to limit the authority of parents to allow their children to participate in nontherapeutic research. In a 1996 New York case, patients who were involuntarily hospitalized at psychiatric facilities and had been adjudicated mentally incapable of giving or withholding consent to participating in medical research brought an action challenging the Office of Mental Health (OMH) regulations governing research.26 On appeal, the New York Supreme Court held that OHM did not have authority to promulgate regulations governing human research and that the regulations violated due process. For purposes of child research, the court found the OMH regulations allowing the minor’s parent or legal guardian to consent to the child’s participation in greater than minimal risk nontherapeutic research invalid. The court explained,

We are not dealing here with parental choice among reasonable treatment alternatives, but with a decision to subject the child to nontherapeutic treatments and procedures that may cause harmful permanent or fatal side effects. It follows therefore that a parent or guardian, let alone another adult who may be a member of the child’s family, may not consent to have a child submit to painful and/or potentially life-threatening research procedure that hold no prospect of benefit for the child and that may have the same result as a denial of necessary treatment.27

More recently, in the now infamous lead paint abatement research conducted by the Kennedy Krieger Institute, in 2001 the Maryland Supreme Court held that a parent or other legal guardian cannot consent to a child’s participation in nontherapeutic research that posed any risk (the court clarified “any risk” in stating that, “…the context of the statement was a nontherapeutic study that

27 Id. at 192.
promises no medical benefit to the child whatsoever, so that any balance between risk and benefit is necessarily negative.”) of injury to the child. 28 The opinion states,

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 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. 29 (emphasis added).

While these New York and Maryland cases are not binding on other states, they suggest that parental permission alone is insufficient to safeguard a child’s vulnerability as a research subject and will not immunize research from court intervention on behalf of a child’s best interest.

Lastly in regard to parental permission, the regulations are inadequate in protecting children as research subjects in varying the level of parental permission in accord with the risk-to-benefit ratio of the proposed research. As will be discussed below, § 404, which presents no greater than minimal risk to the child subject and § 405, which involves greater than minimal risk but presents the prospect of direct benefit to the child, require the permission of only one parent. But § 406, in which research involves greater than minimal risk and no prospect of direct benefit to the child, but is likely to yield generalizable knowledge about the subject’s disorder or condition, and § 407, which has no limit on the level of risk and no direct benefit to the child subject but presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, require the permission of both parents. It is unclear that more than one parent’s input translates to more protection for child research subjects. In some families one parent is the primary decision-maker and requiring permission of the other parent may be little more than an obstacle as opposed to an additional safeguard. Further, since more than half of American children spend time in a single-family home whether because their biological parents never intended to live together,

29 Id. at 853.
one died, or they got divorced, requiring both parents to give permission may intrude upon the autonomy of the primary caregiver and may interfere with the family’s privacy.\textsuperscript{30}

The Specific Risk Designations: §§ 404-407

As for §§ 404-407, there are numerous grave problems with these designations. The “no greater than minimal risk” section, § 404, is the most lenient of the regulations. The study can proceed so long as it presents no greater than minimal risk and the IRB finds adequate provisions for soliciting child assent and a parent’s permission. Because the definition of minimal risk is broad and subjective, it can be manipulated at the expense of the child. Subpart D does not define minimal risk. Rather the National Commission’s report defines minimal risk as:

The probability and magnitude of physical and psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.

This definition does not sufficiently delimit permissible risk because the amount of risk a child may encounter in his daily life or in a routine examination can vary widely. For instance, if a child is exposed to a grave risk of violence, disease, and psychological harm in his daily life, should the IRB take that into account in determining minimal risk? Is it conscionable for an IRB to determine that a great risk to an “overprotected” child would be a minimal, permissible risk, for one accustomed to daily dangers?

A telling example of an IRB’s elastic interpretation of minimal risk comes from an obesity experiment in which 100 obese and 92 normal weight children ages 6 to 10, endured a two-day overnight hospital stay and were subjected to,

Insertion of an intravenous line for 18 hours; a battery of intensive measurements of metabolic rates; a two-hour hyperglycemic claim study involving a second IV line for two hours; blood sampling at five minute intervals; a three-hour hyperinsulemic

clamp study for two hours with two IV lines; and infusion of glucose and insulin for two hours.\textsuperscript{31}

The experiment was investigated by OHRP and later suspended. The IRB justified its unanimous approval of this “minimal risk” research in stating,

> Several members of the committee explored the meaning of minimal risk and what a child might encounter in a visit to the doctor or while playing in traffic. It was felt that \textit{spending several hours in the clinical center in a clamp experiment would be safer than playing actively on sidewalks and streets.}\textsuperscript{32}(emphasis added)

As that explanation demonstrates, the IRB can infuse their highly imaginative concept of the child’s daily experience with lurking dangers in order to justify the risk level of a proposed experiment.

Further, § 404 permits any research, so long as the risk is within this “low” level. But as mentioned earlier, is it ethical to subject the child participant to even a minimal risk - is it in his best interest - if the research presents no direct benefit to him? In the above-mentioned obesity experiment, should 92 normal weight children have been poked, prodded, clamped and monitored for two days, enduring great discomfort if not lasting harm, solely to function as a control group? For a sick child, is even a minimal risk too much if the research has no prospect of direct therapeutic effect or even a promise to glean information concerning his condition?

The “Greater than minimal risk, but direct benefit” category, § 405, raises numerous issues. Preeminent amongst them: is there a limit to acceptable risk? How much greater can “greater than minimal” risk be? It appears that extremely risky pediatric research could be justified so long as existing treatments are ineffective and the potential benefit, even though unlikely, would be positive if it did actually occur. Although any medical procedure entails a risk-to-benefit analysis, in the context of research, since the experiment serves numerous interests - those of the funding company,

\textsuperscript{32} Id. at 4
the researcher, and perhaps the institution itself - there is real opportunity for the IRB to underestimate risk and overstate a potential benefit.

Moreover, § 405 requires only one parent’s permission. If having permission from both parents does indeed protect the child, as it is intended to do, then because the level of risk in § 405 is not circumscribed as it is in § 406, which only allows a “minor increase over minimal risk,” how is the child protected when in the former only one parent need give permission and in the later both must give permission?

Under § 406, although the research will not have a therapeutic benefit for the participant, because the risk is circumscribed, the research is permitted in the hopes of gaining knowledge about the participant’s condition. Aside from the dangers of allowing those who cannot give informed consent to serve a Utilitarian role, the problem with this section is that the level of permissible risk is vague and may be too high. § 406(a) limits the risk level to “a minor increase over minimal.” This adds another level of ambiguity to the already subjective designation of minimal risk in § 404. How does one quantify “minor increase?”

Another issue in § 406 is the broad list of experiences to which the experiment should be commensurate. It states,

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.

But using familiarity to delineate risk level is of little assistance because there is such a range of personal experiences and levels of pain and risk within these perhaps “normal” situations. For instance, the IRB could imagine a scenarios in which a child who is presently not getting adequate dental care will in the future endure painful tooth extractions and develop gum disease. The IRB could rationalize that the extractions and the gum disease will be very risky because of the risk of infection and increased incidence of heart disease. They could then decide that a proposed
experiment’s risk level is within the acceptable range, “a minor increase over minimal,” because it is commensurate with this imagined future scenario.

Additionally, even though the section states that the research involves no prospect of direct benefit to individual subjects, (c) states that it is,

… likely to yield generalizable knowledge about the subjects’ disorder or condition which is of vital importance for the understanding or amelioration of the subjects’ disorder or condition. (emphasis added)

The wording is deceptive, suggesting that the generalizable knowledge will be directly applicable to the subject himself. To more accurately reflect the selfless, utilitarian purpose of § 406 research, the regulation should read, “…likely to yield generalizable knowledge…for the understanding or amelioration of a disorder or condition, which may in the future benefit those with the condition or disorder.” Again, there is the overarching question of whether we want children to act for the utility of others, especially since here the participant already has a disease or condition.

The last-resort section, 407, is the most perilous of Subpart D research categories, reserved for “research not otherwise approvable.” Although the drafters have added additional procedural hurdles for granting research approval, almost any conceivable experiment could be rationalized so long as the inquiry applies to “a serious problem affecting the health or welfare of children.” The opportunity for abuse is immense and the rationale, an unbridled research imperative, is questionable. Whereas sections 404-406 attempt to (unsuccessfully) delineate a permissible risk level, this section contains no limit on the level of risk. The United States stands alone in allowing this type of research – no limit on risk and no prospect of direct benefit for the participant.33

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33 Loretta Kopelman and Timothy Murphy, *Ethical Concerns about Federal Approval of Risky Pediatric Studies*, Pediatrics 1783 (June 1, 2004).
Although § 407 has existed for over two decades, only a few reviews have been completed. Historically, this high risk/low personal benefit section was designed in light of the polio epidemic of the 1950s and 1960s. One of the Commissioners who participated in the National Commission report stated that although the general policy objective was to protect children, the Commissioners rationalized that a great threat, such as polio, might sometimes justify higher risks. But since the regulation is so ambiguous, while it may be useful to combat a serious threat, it would also allow for non-urgent, ethically suspect research.

One obvious issue with § 407 is that there is no definition of a “serious problem affecting the health or welfare of children.” How many children must it affect? Would a deathly illness that affects only a miniscule percentage of children qualify? Would a painful, fatal disease that afflicts only ten in one million, five to ten year-old girls with both parents of Chinese origin justify § 407 approval? Another pitfall is the inclusion of the term “welfare” in addition to “health.” Almost anything could be said to affect the health and welfare of children. Where are the limits? Could social issues, for instance a proclivity to violence or coming under the influence of peer pressure, be investigated under § 407 under the rubric of understanding, preventing, or alleviating a serious problem affecting the welfare of children? Additionally, the regulation does not differentiate between sick or healthy participants. It falls to the individual IRB and the panel of experts to apply their morals to this unwieldy question.

Perhaps most importantly, while the section mandates increased procedures to attain approval, the procedures have no teeth. Whereas §§ 404-406 only require IRB approval, §407 requires both IRB approval and that the Secretary of DHHS give approval after consulting with a panel of experts and allowing for public review and comment. The regulation does set out examples of the fields of experts to be consulted – science, medicine, education, ethics, and law. But just as

34 Id.
35 Id.
an IRB’s approval is shaped by its membership, so too would a panel of experts’ decision. The regulations do not specify that there be any particular number or mixture of experts. One can imagine that an expert panel of all scientists, or all corporate attorneys would not be an asset in deciding an essentially moral issue: when should a child be allowed to participate in an unlimited risk study that will have no personal benefit whatsoever? Additionally, if the composition of experts changes with each review, there will be no consistency in deciding what is approvable.

As for the public review and comment provision, it is a weak addition. Probably only those directly involved with the proposed research will know to read the Federal Register to participate in the review and comment; the general public will be largely unaware. Further, the regulations do not elaborate on what is to be disclosed for review, how thorough a revelation of risk is required, or for how long. In sum, these procedural approval additions are little more than cosmetic.

Suggestions

While Congressional efforts to spur on pediatric research were well intended in light of the paucity of pediatric pharmaceutical information, the surge in pediatric research under the current ambiguous and elastic Subpart D regulations is cause for concern. We should redraft Subpart D to: better define and limit the permissible levels of risk; necessitate that approval review is more standardized amongst IRBs; mandate that IRBs include child specialists; include child advocates who will participate in the assent/permission solicitation and help ensure the exposure of conflicts of interest and a realistic presentation of risks and benefits; eliminate waiver of a child’s assent and require child assent in any research so long as the child is competent; ensure that parental permission is in line with a child’s best interest - in other words, only permit parental permission for research which has the prospect of direct benefit to the child or if not, only presents a truly minimal risk; prevent inducements to doctors, parents and children; and eliminate § 407 altogether except in the case of grave public health emergencies that would affect 25% or more of children.
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