

Protections for Children in Research: Issues Arising Under Federal Subpart D

By Jennifer Kulynych, J.D., Ph.D. and Joanne Pollak, J.D.

Providers and institutions conducting research that involves children must navigate a complex, often ambiguous array of legal requirements, including federal regulations promulgated separately by the U.S. Department of Health and Human Services (DHHS) and the U.S. Food and Drug Administration (FDA); state laws governing medical consent, and, in some cases, research; and the requirements of state agencies when research will involve children under state care or supervision. In this article we summarize the special federal regulatory protections for child subjects, provide an overview of the interplay of federal regulations and state law, and explore certain elements of the federal regulations that present particular compliance challenges.

I. CONTEXT

The legality of much pediatric research turns upon often difficult judgments about concepts appearing in the federal regulations, such as the meaning of “benefit,” “condition,” “minimal risk,” and “minor increase over minimal risk.” With the exception of “minimal risk,” these terms are not defined in the applicable regulations and there is little federal agency guidance available to aid those who must interpret and apply them. Compliance with the federal regulations governing pediatric research is made more difficult by the fact that these federal standards advert to state medical consent laws that may also be ambiguous when applied to research, particularly research that does not involve medical treatment.

As if compliance alone were not a sufficient challenge, attorneys counseling clients engaged in pediatric research must also be mindful of the potential for such research to engender controversy and, potentially, legal and regulatory liability.

Such controversy surfaced, for example, in early 2005 surrounding the enrollment of HIV+ foster children in trials of antiretroviral drugs, and, perhaps most notably, in the wake of a 2001 lawsuit against the Kennedy-Krieger Institute, a leading pediatric research hospital, over a study of the relative effectiveness of several proven lead-abatement techniques in Baltimore housing stock.¹ Each case generated sharply negative publicity for the participating institutions, prompted legislative hearings, and inspired heated political rhetoric. Among the disputed issues in both cases was the proper interpretation and application of regulatory criteria for approving pediatric research.

Today, children are enrolled in studies that take place not only in academic medical centers, but also in community clinical practice settings, as when community providers participate in federally funded cooperative clinical trial groups or contract directly with industry to conduct clinical research involving pediatric subjects. The National Institutes of Health (NIH) and FDA now strongly encourage the inclusion of children in clinical trials, in response to concern that, despite evidence of increasing “off-label” prescribing for children of medications tested only in adults, insufficient data is available about the safety and effectiveness of many medications used in pediatric populations. NIH guidelines on the inclusion of

children in research actually require investigators who submit applications for federal grant funds to include children in all human subjects research, absent a legal or regulatory prohibition or an acceptable scientific justification for excluding child subjects.²

Research involving children spans a continuum of risks and benefits. Some pediatric research involves relatively low-risk procedures such as surveys or blood draws undertaken for studies (e.g., genetic marker studies) that may not benefit participants directly, but are expected to yield new knowledge about a disease or condition affecting children. Other studies involve high-risk procedures (e.g., the administration of very toxic investigational cancer drugs) that are permissible under applicable regulatory standards only when they offer ill children a potentially therapeutic option that is at least as good as the available alternatives.

Special regulatory protections for child subjects of research are a relatively recent development and reflect the recognition by policy makers that children are particularly vulnerable. The history of pediatric research through the first part of the twentieth century includes dismaying examples of the coercion and exploitation of children in medical and scientific studies.³ Responding to concern about the need for additional protections for child research subjects, DHHS, acting upon recommendations of the National Commission for the Protection of Human Subjects, promulgated in 1983 the specific protections for children that are found in 45 C.F.R. Part 46, Subpart D. FDA adopted its version of Subpart D in 2001.⁴

The implementation of Subpart D is a work in progress. As determined by studies and reports conducted by researchers and review bodies, including the Institute of Medicine of the National Academy of Sciences, many institutional review boards (IRBs), the entities charged with the approval and oversight of federally regulated research, do not interpret the pediatric regulations consistently, nor, in some cases, meet all the applicable requirements. Moreover, FDA regulations make investigators personally responsible for ensuring that the research is reviewed by an IRB that complies with applicable regulations—a task that is difficult when IRBs differ significantly in their interpretation and application of federal requirements for pediatric studies.⁵

Although Congress, federal agencies, and two federal advisory commissions, including the current DHHS Secretary's Advisory Committee for Human Research Protections (SACHRP), have deliberated issues arising under the pediatric research regulations, virtually no interpretive federal guidance has yet been proposed by DHHS or FDA.⁶

II. LEGAL REQUIREMENTS

A. Scope of Applicable Law and Regulations

Federal regulations for the protection of child subjects apply to research that is federally funded or conducted (through or by DHHS or other federal agencies that have adopted the regulations), or that involves an FDA-regulated product. In addition, some states have, to a greater or lesser degree, extended the requirements of federal human subjects protection regulations, including protections for child subjects of research, to all human research conducted within the state.

For example, Virginia law establishes certain required procedures and protections for all “human research,” including a limitation upon the extent to which parents and other legal representatives may consent to the participation of children in research; however, Virginia law exempts from state regulation research that complies with federal requirements.⁷ New York law similarly regulates human research, to the extent of requiring the consent of the Commissioner of Health for research involving children or other vulnerable populations.⁸ As does Virginia, New York exempts from this requirement research subject to federal regulation. Maryland law is perhaps most explicit in affirmatively requiring all research using a human subject to be conducted “in accordance with federal regulations on the protection of human subjects.”⁹

The intent of such state laws is to extend certain federal protections (or their state equivalents) including, in some cases, Subpart D, to research conducted by investigators and institutions within the state, even when the research is not funded with federal dollars and does not involve an FDA-regulated product. When considering the scope of these protections, it is important to remember that the term “research,” as defined in DHHS regulations for the protection of human subjects, encompasses not only clinical trials, but also any collection or use (through, for example surveys, blood draws, or medical chart reviews), of identifiable information or biological materials, if the primary purpose of the activity is to develop “generalizable knowledge.”¹⁰

B. Subpart D

The DHHS and FDA versions of Subpart D, found at 45 C.F.R. Part 46 and 21 C.F.R. Part 50, contain minor variations but are parallel (or, “harmonized”) in most material aspects. Generally, these regulations require the IRB to determine whether proposed research meets the criteria for one of the enumerated categories under which the IRB may approve the research.

HEALTH LAW ANALYSIS

The IRB must also determine whether child participants are of sufficient age and maturity that their assent must be obtained (in addition to the permission of their parents and guardians), and whether, for research offering the prospect of direct benefit (as described below), the research may be conducted without the assent of child participants. In all cases the IRB may not approve the research unless it also determines that adequate provisions are made for soliciting the assent of children and the permission of parents and guardians, as applicable.¹¹

When the research involves only minimal risk or offers the prospect of direct benefit (as described below), the IRB may find that the permission of one parent is sufficient; however, for research involving more than minimal risk and no direct benefit, permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the child. 45 C.F.R. § 46.408; 21 C.F.R. § 50.55.

1. Minimal Risk Research

The first category of approvable pediatric research comprises studies that involve no more than minimal risk to child subjects. 45 C.F.R. § 46.404; 21 C.F.R. § 50.51. Such research need not offer potential benefit to individual participants and is approvable under generally applicable standards for IRB approval of research at 45 C.F.R. § 46.111/ 21 C.F.R. § 50.109, provided that the IRB makes appropriate determinations (as described above) regarding assent and permission.

2. Research Offering Possibility of Direct Benefit

When research involves more than minimal risk but offers the prospect of direct benefit to individual child participants, the IRB may approve the research under the general standards at 45 C.F.R. § 46.111/ 21 C.F.R. § 50.109, provided that the IRB makes the appropriate determinations regarding permission and assent, and further, if the IRB determines (a) that the risks of the research are justified by the anticipated benefits, and (b) that the risk-benefit ratio is at least as favorable as that presented by alternatives to participation. 45 C.F.R. § 46.405; 21 C.F.R. § 50.52. This category of research is sometimes referred to as “treatment” or “therapeutic” research, although direct benefit studies depart in important ways from routine clinical care. IRBs may reach different conclusions about whether a treatment study may be approved under this regulatory category if the study protocol also includes procedures of more than minimal risk that offer no prospect of direct benefit.

3. No Direct Benefit Research with a Minor Increase over Minimal Risk

When proposed research offers no prospect of direct benefit to individual subjects but is likely to yield generalizable knowledge about the subjects’ “disorder or condition,” the IRB may approve the research under the general standards at 45 C.F.R. § 46.111/ 21 C.F.R. § 50.109, provided that the IRB makes the appropriate determinations regarding permission and assent, and further, if it determines that (1) the risks represent only a minor increase over minimal risk; (2) the intervention or procedures present experiences that are “reasonably commensurate” with the child’s actual or expected medical, dental, psychological, educational, or social situations; and (3) the intervention or procedures are likely to yield “generalizable knowledge” about the subjects’ disorder or condition that is of “vital importance” for the understanding or amelioration of the disorder or condition. 45 C.F.R. § 46.406; 21 C.F.R. § 50.53.

4. Research Not Otherwise Approvable

The pediatric regulations also define a fourth category of research that may only be approved by the Secretary of DHHS or the Commissioner of the FDA, as applicable. If the IRB finds that research not otherwise approvable presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children, the IRB may forward such research to DHHS for review by the Secretary (or to FDA for review by the Commissioner), who may approve the research after consultation with a panel of experts and an opportunity for public review and comment. 45 C.F.R. § 46.407; 21 C.F.R. § 50.54. The Web site for the DHHS Office of Human Research Protections (OHRP) lists seven studies that have been submitted for agency-level review (although several were withdrawn prior to an agency determination). An example of research approved under § 46.407 was a proposal to study diabetes risk in healthy children of Asian ancestry. The research could not be approved under § 46.406 because the study, which involved an intravenous glucose tolerance test, blood tests, and genetic testing, posed more than minimal risk and did not offer the prospect of direct benefit to the child subjects, whom neither the IRB nor the government viewed as having a “disease or condition.”¹²

5. Research Involving Wards

Under Subpart D, children who are wards “of the State or any other agency, institution, or entity” may not be included in research that involves more than minimal risk and no direct benefit unless the research is related to their status as wards, or the research is conducted in a set-

ting (e.g., a hospital) where the majority of children are not wards. 45 C.F.R. § 46.409; 21 C.F.R. § 50.56. If the IRB approves the enrollment of wards in such research, the IRB must also require the appointment of an advocate, not associated with the investigator, the research, or the guardian organization, who will act in the best interests of each ward for the duration of the ward's participation in the research.

The provisions of § 46.409/§ 50.56 received unprecedented attention this year following charges that institutionalized HIV+ foster children were given investigational medications without full adherence to the regulations.¹³ Critics alleged that the IRBs involved had failed to appoint advocates for the foster child subjects. Whether such advocates were required turned upon the question of whether the studies, undertaken with therapeutic intent but involving (at least in some cases) dose-determination procedures that could be regarded as non-therapeutic, were properly determined to offer the prospect of direct benefit to the child participants. At present, OHRP has made a determination of non-compliance for at least one of the institutions involved, citing a failure of the IRB to document that it obtained sufficient information to make necessary determinations regarding the process for consent and safeguards for foster children. OHRP has not yet determined whether advocates were actually required for foster children enrolled in the research.¹⁴

III. ISSUES IN INTERPRETING AND APPLYING THE PEDIATRIC REGULATIONS

A. Who Is a "Child"?

The federal Subpart D regulations apply to research involving "children," defined as persons who have not reached the legal age for consent to the treatment or procedures involved in the research under the applicable law of the jurisdiction. 45 C.F.R. § 46.402; 21 C.F.R. § 50.3(o). For any minor (as defined by the general legal age of consent under applicable state law) who is a potential research subject, the IRB and the investigator must determine whether that minor is a "child" under Subpart D.

If the research involves a medical procedure or intervention, the question under the federal regulations is whether any provision of state law grants the minor the power to consent to the treatment or procedure. For example, if state law permits minors to consent to treatment for drug abuse, it appears at this time (absent federal guidance to the contrary) that such minors would generally not be regarded as children under Subpart D with respect to research involving investigational treatments for drug addiction.¹⁵ Similarly, if state law permits minors who have attained a certain status (e.g., minors who are

married) to consent to their own medical treatment, those minors could presumably also consent to their own participation in research involving such treatment, rendering Subpart D inapplicable to the research.

Likewise, minors who have been fully "emancipated" by a court (in a jurisdiction that issues such decrees) and who therefore have the decision-making power of adults for all healthcare purposes, would not appear to be children for the purposes of any research protocol.¹⁶ Importantly, however, the IRB may impose any additional safeguards that it deems necessary to protect vulnerable subjects, and may elect to evaluate the proposed research under Subpart D even if it is uncertain whether the minor subjects are actually "children."

Because most states have not adopted laws that address the consent for research apart from medical treatment, it seems reasonable to assume that if proposed research does not involve medical treatment or procedures, the general age of consent in the state determines the application of Subpart D. The curious result is that minimal risk research could potentially be subject to Subpart D where research involving riskier interventions might not be. For example, although research involving investigational drug treatment for HIV+ adolescents may not be subject to federal Subpart D in a state where minor subjects of sufficient age may consent to such treatment, the same minor subjects could be "children" to whom Subpart D applies if the research involved only a survey or questionnaire, with no underlying treatment. In either cases, in the absence of federal guidance, and especially where no state law expressly authorizes consent by minors to the specific procedures or interventions involved in a research protocol, counsel and IRBs should be very cautious in determining that Subpart D does not apply to the research.

B. Who May Permit a Child to Participate in Research?

As described above, unless the research involves a medical procedure or intervention to which a minor may consent under state law, federal Subpart D requires that "permission" be obtained from a parent or guardian (in addition to the child's assent, where applicable). If a parent is available to provide permission, the IRB must then determine under § 46.408/§ 50.55 whether the permission of one parent is sufficient. When the IRB or federal regulations will require the permission of both parents, counsel may wish to provide guidance for investigators in the not-uncommon event that only one parent is readily available to participate in the informed consent process. In such a situation, the investigator may not rely solely upon the permission of the parent who is present unless the investi-

HEALTH LAW ANALYSIS

gator makes inquiries sufficient to determine that the absent parent is deceased, unknown, incompetent, or not reasonably available, or that only the parent who is present has legal responsibility for the child.

Authority to give permission under Subpart D, as well as consent under state law, may be unclear when a child subject is not in the care and custody of a parent. This situation arises, for example, when a child has been placed in foster care. Such children may be in the legal custody of the state or in placement with a foster parent, but the court-ordered guardianships that accompany such placements may be narrow in scope and may empower the foster parent or state agency to make only limited decisions with respect to the child's medical care.

Although parents may generally be viewed as having the authority to give consent and permission for "non-therapeutic" research (e.g., § 46.404, § 46.406, and §46.407 studies and their analogues under FDA regulations), it is unclear that foster parents or caseworkers would be similarly empowered, particularly if parental rights have not been terminated. State law and court practices will be relevant to this determination. Additionally, state and local agencies that oversee the foster care system may impose their own policies and requirements with respect to the review of research protocols. Researchers and institutions conducting studies in settings (e.g., metropolitan outpatient clinics) where foster children are likely to be among the population from whom participants are drawn should consider carefully the various issues associated with obtaining consent and permission from persons other than parents.

C. How Should Risk Be Evaluated?

Once the IRB has determined that one or more subjects of proposed research are "children" under Subpart D, the IRB must assess the risks inherent in the research. As the Institute of Medicine found in its 2004 report, several surveys of IRB members and analyses of IRB determinations have found a degree of variability in risk classification that raises significant ethical and practical concerns.¹⁷ In addition, even within a single risk category such as "minimal risk," there are wide differences of opinion as to what activities and procedures fall within the category.¹⁸

Some of these differences are attributable to the fact that "minimal risk" is defined in federal regulations as meaning simply that "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."¹⁹ Those IRBs that have adopted what is sometimes referred to as a "rel-

ative" standard for minimal risk apply a different risk baseline for those children (e.g., pediatric oncology patients) whose routine experiences include significant medical intervention. Under such an interpretation, a procedure such as a spinal tap could be deemed "minimal risk" for children who are patients (and who presumably undergo such procedures repeatedly during clinical care), yet the same procedure could be deemed "more than a minor increase over minimal risk" for healthy children. The result would be that a study under § 46.406/§ 50.53 offering no prospect of direct benefit could be performed in ill children but not healthy ones.

In a 2001 report to Congress, issued in compliance with a requirement of the Children's Health Act of 2000 (Pub. L. No. 106-310), the DHHS OHRP acknowledged that interpretation of the term "minimal risk" was a source of confusion, but concluded at the time that no consensus existed that would justify adoption of an "absolute" or uniform risk standard.²⁰ Because a relative standard for defining "minimal risk" could mean that ill or disadvantaged children might be subject to a higher level of risk, based solely upon their status, the Institute of Medicine recommended in 2004 that "minimal risk" be interpreted uniformly, with reference to the normal experiences of average, healthy children.²¹ The Institute of Medicine also recommended that risks be considered in relation to the age of the child subjects, and that the risk of each procedure or intervention be considered separately.²² DHHS has not yet endorsed or rejected these recommendations.

Not surprisingly, the regulatory term "minor increase over minimal risk" is a source of even greater confusion. Although the determination that research involves only a minor increase over minimal risk is critical, because such studies need not offer the potential for direct benefit to the participants, SACHRP, the federal advisory committee, has struggled to define the concept of "no more than a minor increase." According to transcripts of its most recent meeting, SACHRP is considering a subcommittee recommendation that IRBs require investigators to present evidence about the procedures, population, and qualifications of research personnel sufficient to demonstrate, for any § 46.406/§ 50.53 study, that the probability and magnitude of harm are only slightly more than minimal risk, that any potential harms are transient and reversible, and that the probability of severe distress is extremely small.²³

D. What Is a "Benefit," and When Is Benefit Required?

Under Subpart D, the IRB must assess the potential of research to provide benefit. Even research that is categorized as "minimal risk" must offer some general societal benefit, in that it must have the potential to generate knowledge of sufficient importance to justify even a mini-

mal risk to subjects, but the IRB need not find that such minimal risk research has the potential to benefit the child subjects personally. As described above, when the research risks represent only a *minor* increase over minimal risk, the research still need not have the potential to benefit child subjects personally. Such research must, however, offer a specific societal benefit in the form of a potential to yield “generalizable” knowledge that is of vital importance to understanding or ameliorating the subjects’ disorder or condition. The potential for research to provide a direct, personal benefit to subjects only becomes essential under Subpart D when the risks to subjects represent more than a minor increase over minimal risk.²⁴

The case of *Grimes v. Kennedy Krieger Institute, Inc.* illustrates the complex interplay between risk and benefit and the confusion that can result from ambiguity about what is a benefit and when a determination of direct benefit is necessary.²⁵ In the early 1990s, researchers at the Kennedy-Krieger Institute (KKI) in Baltimore, at the direction of the federal Environmental Protection Agency (EPA), designed a study to evaluate the effectiveness of various methods for partially abating the lead paint hazards in Baltimore City housing stock. These partial abatement methods, which were not in widespread use but had shown promise in earlier research, were of great interest to EPA and housing advocates because approximately 95% of the city’s inner city housing stock was built during the time when lead paint use was common,²⁶ yet full abatement of this hazard had proved cost-prohibitive for property owners.

The abatement techniques examined in the KKI study were not mandated or assigned by the researchers as part of the protocol, but were performed by landlords and contractors on an elective basis through a state-funded grant program. KKI researchers educated participants about various lead-reduction techniques (e.g., cleaning methods), and periodically took blood samples from children living in the houses to monitor blood lead levels.²⁷ The blood lead levels of these children were compared to those of similar children in a control group living in homes that had been abated comprehensively by the City of Baltimore in the decade prior to the study, or that were built after 1978, when a federal ban on lead in paint became effective.

In light of substantial evidence presented by the investigators that the partial abatement techniques under study could be expected to reduce preexisting lead hazards in the participants’ environment, the IRB reviewing the KKI study concluded that participation presented both minimal risk and the prospect of direct benefit to child subjects living in the homes to be partially abated.²⁸ The inclusion of a control group in the study design compli-

cated the risk-benefit assessment, because children in these control homes were presumed to no longer be at significant risk of lead poisoning through contaminated dwellings. If, however, the blood testing and educational interventions undertaken with these control subjects posed no more than minimal risk to these child subjects, the investigators would not be required to show that control subjects would receive a direct benefit from participation.

In 2001 representatives of several child participants in the study sued KKI, the IRB that reviewed and approved the study on behalf of KKI, and the investigators. The lawsuit alleged, *inter alia*, that researchers failed to warn participants of elevated blood lead levels and failed to obtain fully informed consent, and further, that the study design was unethical and should not have been approved under applicable regulatory standards.

Because the study procedures involving blood testing and educational interventions would not expose control subjects to more than minimal risk, under federal standards it was unnecessary for the IRB to find that the study offered the prospect of benefit to these subjects. But both the IRB and the Maryland Court of Appeals seemed to think otherwise. In a sweeping decision reversing the lower court’s grant of summary judgment for the defendants, the Maryland Court of Appeals characterized the entire study (both the groups in partially-abated homes and the control group) as “non-therapeutic” research, and castigated the IRB for what the court viewed as an attempt to help investigators evade the application of Subpart D protections.²⁹

Although a full discussion of the case is not within the scope of this article, it is interesting to note that the Maryland Court of Appeals cited and appears to have been influenced by correspondence between the IRB and the investigator, in which the IRB suggested that the investigator recast the control group as a comparison group for which investigators would measure the background level of lead present in the subjects’ blood due to environmental factors other than lead paint in the home. Redesigning the study in this way would have permitted investigators to argue that control subjects would also gain benefit from blood lead testing.

The *Grimes* court has caused concern in the pediatric research community, in part by questioning (in dicta within the *Grimes* opinion) whether even a parent may consent to “non-therapeutic” research involving more than minimal risk to a child subject. In the wake of *Grimes*, attorneys advising IRBs should provide materials that will assist the IRB in interpreting Subpart D, and should caution IRB members, most of whom are not lawyers, against communications with investigators that could be miscon-

HEALTH LAW ANALYSIS

strued as attempts to find a benefit when none is needed under the federal regulatory scheme, to overstate the benefits of proposed research when federal regulations require a finding of direct benefit, or to otherwise circumvent the requirements of the pediatric regulations.

E. What Is a “Condition”?

Under Subpart D, research that offers no prospect of direct benefit may expose child subjects to a minor increase over minimal risk if the IRB makes certain findings, including a finding that the research is likely to yield generalizable knowledge that is of vital importance to understanding or ameliorating the subjects’ disorder or condition. As OHRP recognized in its 2001 report to Congress, regulators have been asked to clarify the meaning of the term “condition.”³⁰

An important question that awaits federal clarification is whether healthy children may ever be regarded as having a “condition.” Arguably, the term “condition” is not synonymous with “disorder.” Absent federal guidance to the contrary, an IRB could find that otherwise healthy subjects have a condition that merits study, based upon factors such as evidence that the subjects belong to an ethnic group with a genetic predisposition to illness or to a demographic group whose members are known to suffer from a higher incidence of health problems or who are exposed to unusual environmental health hazards. Deciding to include social characteristics within the scope of “condition” does have ethical implications, because otherwise healthy children with such characteristics might then be exposed to a higher level of research risk. The Institute of Medicine supports defining the term “condition” to include social characteristics, but only where “an established body of scientific evidence or clinical

knowledge” has shown a link between the characteristics and health risks or negative health outcomes.³¹

IV. CONCLUSION

Consistent with its charter, SACHRP, the DHHS advisory committee, has undertaken a thorough re-examination of Subpart D through a subcommittee appointed for this purpose. Thus far, the only final recommendations put forward to the Secretary of DHHS by this subcommittee concern the process for review of § 46.407 research at the agency level.³² DHHS is unlikely to provide formal guidance on Subpart D pending completion of the SACHRP process and internal agency review of the advisory committee’s final recommendations. Until such time, attorneys advising IRBs and investigators should be alert to the thorny issues of regulatory interpretation that may arise whenever research involves child participants.

Jennifer J. Kubynych, J.D., Ph.D., serves as counsel to the Institutional Review Boards for The Johns Hopkins School of Medicine. Ms. Kubynych worked previously as a National Institutes of Mental Health researcher, as regulatory counsel to the Association of American Medical Colleges, and as a health-care and research compliance attorney in private practice.

Joanne E. Pollak, J.D., serves as the Vice President and General Counsel for The Johns Hopkins Health System Corporation, The Johns Hopkins Hospital, and Johns Hopkins Medicine, a collaboration of The Johns Hopkins Health System Corporation and the Johns Hopkins University School of Medicine. Ms. Pollak has joint responsibility for providing legal advice to the School of Medicine Institutional Review Boards.

END NOTES

¹ See, e.g., John Solomon, *US Faults Testing of AIDS Drug on Foster Children*, THE BOSTON GLOBE, June 17, 2005 (www.boston.com); John Solomon, *Researchers Tested AIDS Drugs on Children*, CBS News.com, May 4, 2005 (www.CBSNews.com); Michelle M. Mello, David M. Studdert, and Troyen A. Brennan, *The Rise of Litigation in Human Subjects Research*, 139 ANNALS OF INTERNAL MED. 1, 40-46 (July 2003); Joanne E. Pollak, *The Lead-Based Paint Abatement Repair & Maintenance Study in Baltimore: Historic Framework and Study Design*, 6 J. HEALTH CARE L. & POL’Y, 90-110 (2002), available at www.hopkinsmedicine.org/Press_releases/2004/Pollak-Article.pdf.

² NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects (Mar. 6, 1998), available at grants.nih.gov/grants/funding/children/children.htm. The NIH policy defines “child” as an individual under the age of twenty-one years. See also FDA Web site “Special Ethical Protections for Pediatric Research Participants,” www.fda.gov/oc/opt (visited July 29, 2005).

³ BOARD ON HEALTH SCIENCES POLICY, INSTITUTE OF MEDICINE, *The Ethical Conduct of Clinical Research Involving Children* at 44-54 (Marilyn J. Field and Richard E. Behrman eds. 2004), available at www.nap.edu.

⁴ Food and Drug Administration, *Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products*, 66 Fed. Reg. 20589 (Apr. 24, 2001).

⁵ 21 C.F.R. §§ 312.60, 312.66.

⁶ FDA does explain Subpart D requirements in a draft Guidance for Industry and Staff: Premarket Assessment of Pediatric Medical Devices published by the Center for Devices and Radiological Health, (May 14, 2004), available at www.fda.gov/cdrh/mdufma/guidance/1220.pdf, but that document does not interpret the regulatory concepts discussed in this article. The preamble to the FDA’s pediatric research regulations states that FDA “anticipates” that certain enumerated pro-

- cedures, such as clean-catch urinalysis or oral temperature readings, might be viewed as minimal risk. See *FDA, Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products*, *supra* note 4, at 20593.
- 7 VA. CODE ANN. § 32.1-162.16 et seq. As specified in § 32.1-162.18.B, a legally authorized representative may not consent to “non-therapeutic research” that involves more than “a minor increase over minimal risk.” This standard tracks the federal limitation upon “permission” for research that does not involve the prospect of direct benefit to the child subject.
- 8 N.Y. PUB. HEALTH LAW § 2442(1) et seq.
- 9 MD. HEALTH-GEN. ART. § 13-2002.
- 10 45 C.F.R. § 46.102(d).
- 11 The federal regulations use the term “permission” when referring to the granting by a parent or guardian of what is typically referred to under state law as “consent” for the child’s participation or treatment.
- 12 See OHRP Web site at www.hhs.gov/ohrp/pdjay/hhsdetr.pdf.
- 13 See Solomon, *supra* note 1.
- 14 Letter from Karena Cooper, Division of Compliance Oversight, DHHS Office of Human Research Protections, to Harvey R. Colten, M.D., Vice President and Senior Associate Dean, Columbia University Medical Center, and Laura L. Foresese, M.D., M.P.H., Vice President and Chief Medical Officer, New York Presbyterian Hospital, May 23, 2005 < [/www.hhs.gov/ohrp/detrm_lettrs/YR05/may05c.pdf](http://www.hhs.gov/ohrp/detrm_lettrs/YR05/may05c.pdf)>.
- 15 For example, Maryland law permits minors to consent (but not to withhold consent) to treatment for drug abuse. MD. HEALTH-GEN. ART. § 20-102(c)(1).
- 16 See, e.g., provisions regarding the emancipation of minors in the CAL. FAM. CODE, §§ 7123, 7050.
- 17 See IOM Report, *supra* note 3, at 120.
- 18 See David Wendler, Leah Belsky, Kimberly M. Thompson, and Ezekiel J. Emanuel, *Quantifying the Federal Minimal Risk Standard*, 294 JAMA 7, 826 (Aug. 17, 2005).
- 19 45 C.F.R. § 46.102(i); 21 C.F.R. § 50.3(k).
- 20 See DHHS OHRP, *Protections for Children in Research: A Report to Congress, in Accord with Section 1003 of P.L. 106-310, Children’s Health Act of 2000* (May, 2001), at iv. The recent JAMA article by Wendler et al., *supra* note 18, would challenge this interpretation.
- 21 See IOM Report, *supra* note 3, at 5.
- 22 *Id.* at 5-6.
- 23 See transcript of SACHRP meeting, April 18, 2005, at 38-50, and meeting presentation materials, *available at* www.hhs.gov/ohrp/sachrp/mtgings/mtg04-05/mtg04-05.htm.
- 24 Note, however, that under the general standard applicable to all research, an IRB may not approve research unless it also finds that the risks are reasonable in relation to the importance of the knowledge that may reasonably be expected to result. 45 C.F.R. § 46.111(a)(2); 21 C.F.R. § 56.111(a)(2). Thus even a minimal risk study would not be approvable if it offered no potential to produce valuable new scientific knowledge.
- 25 *Grimes v. Kennedy Krieger Inst., Inc.*, 782 A.2d 807 (Md. 2001), *reconsideration denied*, (Oct. 11, 2001).
- 26 See Pollak, *supra* note 1, at 93, citing statistics of the U.S. Census Bureau.
- 27 *Id.* at 97-103.
- 28 Pursuant to an affiliation agreement, the KKI study was reviewed and approved by The Johns Hopkins Joint Committee on Clinical Investigations, a predecessor to the Johns Hopkins Medicine IRB that now oversees human subjects research at the authors’ institution.
- 29 See *Grimes*, *supra* note 25, at 6-7.
- 30 See OHRP Report, *supra* note 20, at 10.
- 31 See IOM Report, *supra* note 3, at 6.
- 32 See letter to the Hon. Tommy G. Thompson, Secretary of Health and Human Services, from Ernest D. Prentice, Ph.D., Chair, Secretary’s Advisory Committee on Human Research Protections, July 8, 2004, *available at* www.hhs.gov/ohrp/sachrp/commsec.html.

NOW AVAILABLE

To purchase go to: www.healthlawyers.org
or call AHLA Member Service Center
(202) 833-0766

© 2005, Cornerstone Series
Item: WB200502
Members \$110/Non-Members \$130

