HUMAN SUBJECT RESEARCH INVOLVING SPECIAL SUBJECT POPULATIONS: FEDERAL REGULATIONS AND BEYOND

American Health Lawyers Association
Annual Meeting
January 26, 2007

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The Belmont Report, which forms the foundation for human research protection in the United States, recognizes that certain research subject populations are particularly vulnerable, and deserving of additional protections. Both the principle of respect for persons, which includes "the requirement to protect those with diminished autonomy," and the principle of justice, which requires that classes of research subjects not be "systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied," underlie much of the regulation related to special subject populations. See *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979. While there are legitimate ethical concerns whenever vulnerable populations are studied in research, research protocols may often be designed to study a disease or condition that exists only in a subset of the population or that can be effectively studied only in a particular setting. Both the U.S. Department of Health and Human Services ("HHS") regulations and the Food and Drug Administration ("FDA") regulations[2] describe certain subsets of research subjects for which special protections are required and for which special considerations must be reviewed before research involving such populations may be approved by Institutional Review Boards ("IRBs"). Counsel for institutions that conduct research studies involving any of these "special subject populations" must have a firm grasp of the various regulatory requirements to ensure that IRBs are appropriately reviewing and documenting their review of such protocols.

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[1] An earlier version of this paper was originally presented at the June 2006 Annual Meeting of the National Association of College and University Attorneys in Chicago, Illinois. The author gratefully acknowledges the assistance provided by Ms. Susan McCarthy, Paralegal, in the review and cite checking of this article.

[2] FDA regulations apply to any "clinical investigation," which is defined as "any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit." 21 C.F.R 50.3(c). A "test article" means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation" by the FDA. 21 C.F.R. 50.3(j).

This paper will provide an overview of both the HHS regulations and the FDA regulations applicable to special subject populations. Where those regulations differ, institutions must take particular care in crafting IRB policies and educating investigators about which regulations apply in which cases. The first step for institutional counsel in determining whether IRB policies are adequate is to review the institution's Federal Wide Assurance ("FWA"), and confirm whether the institution has agreed to apply the provisions of the Common Rule, 45 C.F.R. § 46, Subpart A, or the provisions of the common rule plus 45 C.F.R. § 46, Subparts B, C and D, which contain the additional protections for pregnant women, fetuses, and neonates, prisoners and children to all of its human subjects research regardless of the source of support, or whether the assurance only applies to Federally-support research. In addition, state law may place further restrictions on research involving some of these special populations. While by no means a comprehensive summary, some of these applicable state laws are reviewed below.

A. Pregnant Women, Fetuses and Neonates

Research interventions on a pregnant woman may have harmful effects on the developing fetus, presenting special ethical concerns. Where the research intervention holds out the potential to benefit the pregnant woman, but harm the fetus (or vice versa), competing interests must be weighed.[3] While the HHS regulations provide detailed guidance for IRBs in this complex area, review of state law is particularly key.

1. *The HHS Standards:*

The relevant HHS regulations are contained in Subpart B of 45 C.F.R. § 46, and apply to all HHS-supported research "involving pregnant women, human fetuses, neonates of uncertain viability, or nonviable neonates." 45 C.F.R. § 46.201(a). Understanding the definitions for each of these subject groups is key, and the definitions may or may not be consistent with your state law on abortion. First of all, pregnancy is defined as the time from "implantation until delivery," and pregnancy "shall be assumed" if the woman "exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery." 45 C.F.R. § 46.202(f). As a practical matter, investigators who are not intending to include pregnant subjects in their research are well advised to add a negative pregnancy test as an inclusion criteria for all female subjects who are not past menopause.[4] Viable neonates are defined as neonates that, after delivery, are able "to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration." 45 C.F.R. § 46.202(h). Again, local law or local medical practice may provide further detail about the ethically appropriate limits of "available medical therapy." In addition, while not separately defined, the regulations do recognize that there may be a neonate of "uncertain viability." A viable neonate is a child, and therefore the provisions of Subpart D of 45 C.F.R. § 46 will apply

[3] The provisions for "exempt" research (which are contained in 45 C.F.R.§ 46.101(b)) are equally applicable to pregnant subjects, without the need for any additional protections. 45 C.F.R.§ 46.201(b).

[4] Minors who are pregnant may only be included in research if both the requirements of Subpart B of 45 C.F.R. § 46 and the requirements of Subpart D, which governs involvement of minors in research, 45 C.F.R. § 46, are satisfied. This latter requirement may require both assent from the pregnant minor, and consent from her parents.

to research involving this category of subject. Nonviable neonates are simply defined as a neonate who "although living, is not viable." 45 C.F.R. § 46.202(e).

For proposed research involving pregnant women or fetuses, an IRB may approve a study if: 1) preclinical studies (if appropriate) and clinical studies on nonpregnant women are available and provide data for assessing risk; 2) the risk to the fetus is associated only with procedures or interventions that hold out the prospect of direct benefit to the woman or the fetus, or if no direct benefit is presented, risks are minimal and the research may develop important biomedical knowledge that cannot be developed through other means; 3) any risk presented is the "least possible;" and 4) informed consent is appropriately sought. 45 C.F.R. § 46.204(a)-(e). The nature of the informed consent will vary depending on the circumstances of the research. If the research presents minimal risk, or if it holds out the prospect of direct benefit to the woman or the woman and the fetus, the woman alone can consent. 45 C.F.R. § 46.204(d). If the research holds out the prospect of direct benefit to the fetus alone, consent of both parents is necessary, unless the father is unavailable or incompetent or if the pregnancy was the result of rape or incest. 45 C.F.R. § 46.204(e).

Two additional key restrictions apply to this category of research. First, no inducements may be offered to terminate a pregnancy. 45 C.F.R. § 46.204(h). Second, no individual engaged in the research may have any part "in any decisions as to the timing, method, or procedures used to terminate a pregnancy." 45 C.F.R. § 46.204(i). This latter restriction, which is related to other federal regulations that prohibit the expenditure of federal funds for abortion,[5] make it a practical impossibility for an IRB reviewing an HHS-supported clinical trial of, for example, the morning-after pill, to approve such a study under subpart B.

Neonates of uncertain viability and nonviable neonates may be involved in research, provided that preclinical or clinical studies (where appropriate) provide data for assessing risk, where the person providing consent is fully informed as to the "reasonably foreseeable impact of the research" on the newborn, and where none of the research investigators are involved in the determination of the neonate's viability. 45 C.F.R. § 46.205(a). For neonates of uncertain viability, the IRB must determine either that: 1) the research may enhance the chance of the neonate surviving to viability, and the risk is the least possible for achieving that goal; or 2) the research will develop important biomedical knowledge which cannot be obtained by other means and there is no additional risk to the neonate. 45 C.F.R. § 46.205(b)(1). Either parent may give consent, or, if the parents are incapacitated or unavailable, either parent's legally authorized representative. Nonviable neonates may only be involved in research if the purpose of the research is to develop important biomedical knowledge which cannot be obtained by any other means, the neonate will not have its vital functions artificially maintained, the research will not terminate the heartbeat or respiration of the neonate, and there will be no additional risk to the

[5] Federal law prohibits the use of federal funds for "any research or experimentation, in the United States or in any other country, on a nonviable living human fetus ex utero or a living human fetus ex utero for whom viability has not been ascertained unless the research or experimentation – (1) may enhance the well-being or meet the health needs of the fetus or enhance the probability of its survival to viability; or (2) will pose no added risk of suffering, injury, or death to the fetus and the purpose of the research or experimentation is the development of important biomedical knowledge which cannot be obtained by other means." 42 U.S.C. § 289g(a).

neonate. 45 C.F.R. § 46.205(c). In this latter category, the consent of both parents is required, except in cases of rape or incest (where the father's consent is not required), or in the case of unavailability or incapacity of either parent. For this category, consent of a parent's legally authorized representative will ***not*** be acceptable. 45 C.F.R. § 46.205(c)(5).

If a proposed research protocol involving pregnant women, fetuses or neonates does not satisfy the above requirements, there is a mechanism, under 45 C.F.R. § 46.407, for HHS to approve such research. The IRB must first find that the research presents a reasonable opportunity to "further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates," and the Secretary of HHS, after consulting experts and allowing for public comment, determines that the research is ethically sound and informed consent will be appropriately obtained. 45 C.F.R. § 46.407(a) and (b). This mechanism has been little used, but it is analogous to the more common procedures for research involving children set forth under 45 C.F.R. § 46.407.

Finally, HHS regulations note that research involving the placenta, a dead fetus or fetal material may be subject to other federal and state laws. 45 C.F.R. § 46.206. The key federal law on use of this material is found at 42 U.S.C. § 289g-1. This law, which was enacted in response to earlier research in which fetal tissue was transplanted into the brains of Parkinson's patients, sets certain conditions on the use of human fetal tissue in federally funded human subject research. Among other things, no money can be paid for the tissue donation, informed consent must be obtained under specified conditions, and the donation cannot be made for the benefit of any specific recipient. This law defines "human fetal tissue" as "tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth." 42 U.S.C. § 289g-1(g).

2. *FDA Regulation and Other Federal Regulations*

As noted above, federal law prohibits the expenditure of federal dollars for certain categories of research involving fetuses. These laws would make it all but impossible for an IRB operating under the HHS Part B regulations to approve a protocol which, for example, compared the safety and effectiveness of the morning-after pill with surgical abortion. The FDA regulations are not nearly as restrictive. Aside from a specific requirement that informed consent documents indicate that "the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable," 21 C.F.R. § 50.25(b)(1), the FDA regulations do not specifically call for a separate review process for this category of research. Pregnant women are grouped into a general category of "vulnerable populations," for which the FDA requires IRBs to exercise special vigilance to ensure that subject selection is equitable. 21 C.F.R. § 56.111(a)(3). In addition, IRBs have an obligation to ensure that when "the subjects, such as . . . pregnant women . . . are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects." 21 C.F.R. § 56.111(b).

While the FDA regulations provide little concrete guidance to IRBs, a flat exclusion of women of reproductive age from a clinical investigation into a treatment for a potentially life threatening disease because of concerns about potential harm to reproductive organs or offspring may result in the FDA placing a clinical hold on the study. 21 C.F.R. § 312.42(b)(v). This

clinical hold would not be applicable to an exclusion based on actual pregnancy. In addition, in response to concerns that many women may take pharmaceuticals during pregnancy that have never been tested in pregnant women, the FDA has issued a draft *Guidance for Industry Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*, HFA-305, available at http://www.fda.gov/cder/guidance/5917dft.htm, to provide some guidance to investigators in designing such studies.

In addition to the HHS and FDA regulations, the Environmental Protection Agency ("EPA"), responding to a Congressional directive,[6] recently promulgated regulations that would prohibit, for research conducted or supported by the EPA, any research study that involved intentional exposure of any human subject who is pregnant to a potentially harmful substance. 40 C.F.R. § 26.203. For purposes of these regulations, a study is deemed to involve "intentional exposure" if the "exposure to the substance experienced by a human subject . . . would not have occurred but for the human subject's participation in the study." 40 C.F.R. § 26.203. While intentional exposure is prohibited in EPA sponsored studies, pregnant women may be enrolled in observational studies (which are defined as any study that does not meet the definition for intentional exposure), provided that the study complies with the requirements of the HHS regulations found at 45 C.F.R. § 46.204. 40 C.F.R. § 26.304. These same requirements also are extended to third party research that is conducted with the intent that the results be submitted to the EPA for consideration under the Federal Insecticide, Fungicide, and Rodenticide Act, or under Section 408 of the Food, Drug and Cosmetic Act. 40 C.F.R. § 26.1203.

3. *The Impact of State Law*

Research involving pregnant women or fetuses is often further complicated on the state level by restrictive laws aimed at regulating abortion. Under the Pennsylvania Abortion Control Act, any person "who knowingly performs any type of nontherapeutic experimentation or nontherapeutic medical procedure (except an abortion . . .) upon any unborn child . . . commits a third degree felony." 18 Pa. Con. Stat. § 3216(a). An "unborn child" or "fetus" is defined as "an individual organism of the species homo sapiens from fertilization until live birth." 18 Pa. Con. Stat. § 3203. The Pennsylvania Abortion Control Act further requires that fetal tissues or organs used in research or experimentation may only be obtained with the prior written consent of the mother. If the tissue is derived from an abortion, "such consent shall be valid only if obtained after the decision to abort has been made." 18 Pa. Con. Stat. Ann. § 3216(b). As the Abortion Control Act prohibits the person obtaining informed consent from "employ[ing] the possibility of the use of aborted fetal tissue or organs as an inducement to a pregnant woman to undergo abortion," the informed consent for the donation of the tissue for research purposes should be obtained separately from, and after, the consent is obtained for the abortion. No consideration of any kind may be offered to a woman to consent to donate fetal tissue, and the donor may not "designate the recipient of that tissue or organ." Finally, "[a]ll persons who participate in the procurement, use or transplantation of fetal tissue or organs, including the recipients of such

[6] While the most precipitating event was a Congressional directive included in the 2006 Department of the Interior, Environment, and Related Agencies Appropriations Act, Public Law No. 109-54, the regulations were preceded by public criticism of EPA in the wake of the *Grimes v. Kennedy Krieger Institute, Inc*., 366 Md. 29, 782 A.2d 807 (2001) decision, discussed below. A National Academies of Science report, solicited by the EPA, was released in February 2004 and provided additional guidance on the topic.

tissue or organs, shall be informed" as to the source of the tissue (e.g. abortion, miscarriage, stillbirth, ectopic pregnancy). 18 Pa. Con. Stat. Ann. § 3216(b)(4). Any protocol that involves an intervention derived from fetal tissue must include this information as part of the informed consent process.

Many other states have similar laws that may restrict research involving fetal tissue: see, e.g., Ohio Rev. Code § 2919.14 (making it a crime to "experiment upon or sell the product of human conception that is aborted"); or that may restrict non-therapeutic research on a fetus or embryo, see, e.g., Arizona Rev. Stat. Ann. § 36-2302(A) (making it a crime to "knowingly use any human fetus or embryo, living or dead, or any parts, organs or fluids of any such fetus or embryo resulting from an induced abortion in any manner for any medical experimentation or scientific or medical investigation" except for the benefit of the woman or fetus). The National Conference of State Legislatures maintains a useful chart of state laws (both current and pending) on its website, in this area. The chart, which is available at http://www.ncsl.org/programs/health/genetics/embfet.htm, also summarizes state laws relevant to human cloning.

B. Use of Prisoners in Research

Some of the most egregious cases of failure to protect human research subjects have involved prisoner populations. Indeed, the Nuremberg Code, one of the key documents on which modern research subject protection regulations are based, was drafted as a set of standards for judging physicians and scientists who had conducted biomedical experiments on concentration camp prisoners. Both federal regulations and state law must be consulted in evaluating protocols involving prisoners.

1. *The HHS Standards*:

Subpart C of the HHS regulations sets forth the federal requirements for IRB review of research involving prisoners. 45 C.F.R. § 46.301 et seq. An IRB should have policies to handle both research that expressly includes prisoners and research involving a subject who becomes incarcerated during the course of the protocol. The Office for Human Research Protections ("OHRP") has an informative guidance (the "Prisoner Guidance") on its website at http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm.

The IRB that reviews protocols involving prisoners must include at least one "prisoner representative." 45 C.F.R. § 46.304(b). This person may be a prisoner, former prisoner, advocate for prisoners, prison chaplain or prison psychologist. If a prisoner representative is subsequently added to an IRB, notice of the change in the IRB roster must be given to OHRP. Importantly, the regulations provide that, if the protocol is reviewed by more than one IRB, only one of the reviewing IRBs must satisfy the prisoner representative requirement. 45 C.F.R. § 46.304(b). As state law or local prison policy will likely require some type of prison board review of proposed research, it is possible that the IRB will be able to rely on the prisoner representatives on this board. In addition, before engaging in HHS funded research involving prisoners, your institution must certify to the Secretary of HHS (through OHRP) that the IRB has made the seven findings required under 45 CFR § 46.305(a). These seven findings require: 1) a permissible category of research (which is described more fully below), 2) a determination that

the advantages to the prisoner for participating in the research are not of such magnitude as to interfere in the prisoner's ability to weigh the risks, 3) the risks are commensurate with risks that a non-prisoner volunteer would accept, 4) the procedures for selecting subjects are fair and immune from arbitrary intervention by prison authorities or prisoners, 5) information is presented in understandable language, 6) adequate assurance is provided that participation by the prisoner in the research will not effect parole decisions (and the prisoner has been told this), and 7) if the IRB finds there is need for follow-up care, adequate provision for this follow-up care has been made. The additional findings required by 45 C.F.R. § 46.305 reflect the concern for the principle of justice in the Belmont Report. They also reflect the recognition that a prison setting is inherently coercive, so IRBs must be careful to avoid undue coercion in study design.

The federal regulations strictly limit the types of research that can be carried out with HHS funding involving prisoners as subjects. Basically, there are two broad categories of permitted research. One type is minimal risk studies related to criminal behavior, causes of incarceration and conditions of prisoners and prisons, 45 C.F.R. § 46.306(a)(2)(i) and (ii). The other type is greater than minimal risk studies on conditions "particularly affecting prisoners as a class," or research on practices "which have the intent and reasonable probability" of benefiting the health and well-being of the prisoner-subject, including placebo controlled studies. 45 C.F.R. § 46.306(a)(2)(iii) and (iv).

In this latter category of research, the Secretary of HHS must first approve the study, following consultation with medical, ethics and penal experts. In addition, in the case of studies on "conditions particularly affecting prisoners as a class," 45 C.F.R. § 46.306(a)(2)(iii), and in the case of "research on practices . . . which have the intent and reasonable probability of improving the health or well-being of the subject . . . [but which] require the assignment of prisoners . . . to control groups which may not benefit from the research," 45 C.F.R. § 46.306(a)(2)(iv), the study may proceed only after the Secretary has consulted with appropriate experts, and published notice, in the Federal Register, of his/her intent to approve such research. It is important that investigators understand that this latter approval is mandatory. The timing of such approval can sometimes lead to confusion by investigators, as generally the IRB will approve the protocol, contingent upon receipt of the final approval from the Secretary of HHS. Investigators may improperly begin to enroll subjects and collect data before the final approval is received from HHS.

2. *The FDA Regulations and Federal Bureau of Prisons*

Like the HHS regulations, FDA regulations recognize that prisoners are a vulnerable population, but the FDA requirements leave much discretion to IRBs as to how to ensure that protections appropriate to the population are in place. FDA regulations require that subject selection for an FDA regulated study be equitable, and that "the IRB take into account the purposes of the research and the setting in which the research will be conducted." 21 C.F.R. § 56.111(a)(3). Similarly, the FDA regulations recognize that prisoners are a subject population "likely to be vulnerable to coercion or undue influence," and therefore IRBs must ensure that "additional safeguards have been included in the study to protect the rights and welfare of these subjects." 21 C.F.R. § 56.111(b). The FDA regulations give no further detail on what those safeguards should include.

No doubt part of the reason for the scant detail provided by the FDA regulations is that many prison officials have adopted guidelines that would prohibit use of prisoners within their facilities for "medical experimentation, cosmetic research, or pharmaceutical testing." 28 C.F.R. 512.11(a)(3). This latter prohibition is taken from the regulations applicable to prisoners incarcerated in a facility under the jurisdiction of the Federal Bureau of Prisons. While this prohibition is clearly designed to avoid exploitation of this vulnerable population, other Federal Bureau of Prisons regulations are targeted as much to the security needs of the prison officials. For example, this agency further requires that researchers not provide any incentives to persuade prisoners to participate in research, except for "soft drinks and snacks to be consumed at the test setting." 28 C.F.R. § 512.11(a)(5). These regulations also detail the application process that must be followed by researchers seeking to receive approval to conduct research with the federal prison system. One additional, significant aspect of the Federal Bureau of Prisons regulations is the requirement for informed consent. In addition to the usual, expected elements, the researcher is also required to provide the prisoner-subject with a statement of exceptions to any guarantee of confidentiality. Specifically, "a researcher may not guarantee confidentiality when the subject indicates an intent to commit future criminal conduct or harm himself/herself or someone else, or, if the subject is an inmate, indicates an intent to leave the facility without authorization." 28 C.F.R. § 512.16(a)(9).

3. *The Application of State Law*

As with most special subject population regulations, the federal regulations expressly state that "compliance with the procedures set forth herein will [not] authorize research involving prisoners as subjects, to the extent such research is limited or barred by State or local law." 45 C.F.R. § 46.301(b). As prisons are, by design, highly regulated facilities, there almost certainly will be either state regulations or local prison board policy, or both, applicable to research involving prisoners.

In Pennsylvania, the Department of Corrections has issued Policy Statement 2.1.2 setting forth the conditions under which research involving prisoners in state prisons may be conducted. The Pennsylvania Policy Statement goes well beyond the HHS regulations and, like the Federal Bureau of Prisons, effectively bans the use of state prisoners in any medical experiments, cosmetic experiments, or pharmaceutical testing, with the exception for some testing involving treatment for AIDS and HIV infection. In addition, any research in Pennsylvania state prisons must be reviewed by the Research Review Committee. This IRB-type board does include prisoner representatives, so review by this Committee will satisfy the federal requirement.

Other states may have more liberal policies. For example, in Arizona, medical research, plasmapheresis and whole blood donation is permitted in the state prisons, provided that the program is first approved by the prison director. Ariz. Rev. Stat. Ann. § 31-322(A). The prison director may place conditions on research programs, and will issue the researchers a "revocable license" to enter the prison and conduct the research. Ariz. Rev. Stat. Ann. § 31-322(D). The prisoner-subject, in addition to giving informed consent, must have the written consent of the prison director and the chief of the prison health services to enroll in such research, and any compensation offered to research subjects must be paid into a trust fund. Ariz. Rev. Stat. Ann. §

31-321(A) and § 31-323(B). Ohio similarly permits prisoners to participate in medical research programs approved by the prison director. Ohio Rev. Code § 5145.28. Research subject compensation for such participation "shall be paid into the prisoner's aid fund to provide books and other educational materials for the inmates of the volunteer's correctional institution. *Ibid*.

C. Use of Minors in Research

One of the most common "special populations" in research is children. Children are a particularly vulnerable population because they lack the maturity and legal ability to give proper informed consent to participation in research. Inclusion of children in research is critical; however, as children's response to drugs and devices is often very different from adults, and because some important areas of research (for example, research into educational methods) require participation of minors. Both the HHS and FDA regulations reflect the need for close ethical review for studies involving minors.[7]

1. *The HHS Regulations*

Subpart D of 45 C.F.R. Part 46 sets forth the special protections that apply to research involving minors. 45 C.F.R. § 46.401 et seq. The federal regulations essentially allow for four categories of acceptable research, which are detailed below. These categories of research each have additional requirements, including that adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in 45 C.F.R. § 46.408. For purposes of these regulations, "children" are defined as those who have not attained the age of legal consent to treatment under the jurisdiction where the research is conducted. 45 C.F.R. § 46.402(a). In most states, that is a person under the age of 18.

Of the six categories of research that may be exempt from IRB review, one is not fully available if children are research subjects. 45 C.F.R. § 46.101 (b) (2) exempts research involving survey or interview procedures or observation of public behavior. Where children are involved, however, the research is exempt from review only if the investigator merely observes and does not participate in the activities being observed. Otherwise, the categories of research exempt from IRB review are available for research involving children. 45 C.F.R. § 46.401 (b).

IRBs may include children in non-exempt research in three broad categories. First, they may be included in minimal risk studies. 45 C.F.R. § 46.404. Second, they may be included in research involving greater than minimal risk, where the research holds out the potential for benefit to the child-subject. The risk must be justified by the potential benefit available, and the relationship of the risk to the potential benefit must be at least as favorable as the available alternatives. 45 C.F.R. § 46.405. The third category of research acceptable for children is research that is greater than minimal risk, and does not offer the prospect of benefit to the subjects, but which is likely to produce information about the subject's disease state or condition.

[7] A very thorough review of the legal and ethical issues inherent in involvement of children in clinical research may be found in Field and Berman, *The Ethical Conduct of Clinical Research Involving Children* (National Academies Press 2004), online version available at http://newton.nap.edu/catalog/10958.html.

In order to approve research in this category, the IRB must determine that the risk represents a minor increase over minimal risk, the research intervention presents the subjects with an experience that is "reasonably commensurate with those inherent" in the situation of other similarly situated children, and the research is likely to produce information that is vital in the understanding of the subjects' disease or condition. 45 C.F.R. § 46.406.

In addition to these three categories, the Secretary of HHS may approve research that does not fall into any of the above categories, but that nonetheless "presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children."[8] 45 C.F.R. § 46.407. Before granting this approval, the local IRB must determine that the research is appropriate for consideration under this category. The Secretary of HHS will then consult a panel of experts, and seek public comment on the protocol through notice in the Federal Register. Approval under Section 407 is appropriate if the research, in addition to presenting a reasonable opportunity to further understanding of, prevent or alleviate a serious problem affecting children, is also determined by the Secretary to be conducted in accordance with sound ethical principles, and appropriate permission from parents and assent from children is sought. 45 C.F.R. § 46.407(b).

OHRP has recently published a helpful guide for IRBs on the 407 approval process. The guidance, available at: http://www.hhs.gov/ohrp/children/guidance_407process.html, gives practical information on requirements for submission of a Section 407 petition, as well as a summary of the internal process OHRP will follow in processing submitted petitions. It is important to note that, where a study involves an intervention that is also subject to the FDA regulations, OHRP will defer to the FDA process for reviewing a Section 407 petition. OHRP also maintains on its website a listing of 407 petitions currently under review, and recently reviewed petitions, including determination letters and conditions placed upon approval. Again, this information can be of enormous practical use to IRBs in assisting investigators with their own Section 407 petitions.

Under any of the subsections of the HHS regulations permitting inclusion of children as research subjects, the IRB must provide for both permission [parents may not consent for children under 45 C.F.R. Part 46] from the child's parent or guardian (both parents must grant permission for research approved under §§ 46.406 and 46.407) and "assent" from the child.[9] Even for research approved under §§ 46.406 and 46.407, permission from only one parent will suffice if the other 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." 45 C.F.R. § 46.408(b).

Waiver of the requirement for parental permission may be permitted for some types of research where the subject population or the matter under study (e.g., sexually abused children) would make the requirement of parental permission unreasonable. 45 C.F.R. § 46.408(b). This

[8] HHS will only invoke this procedure for HHS funded research. If your institution has voluntarily agreed in its FWA to apply these regulations to all research, regardless of funding source, you may need to contact the agency that funded the research for further guidance.

[9] In determining whether the minor subjects of a study are capable of giving assent, the IRB should take into account the age, maturity and psychological state of the children involved.

provision is subject to any further restrictions in state or local law, so a careful review of those laws should precede approval of any such waiver. In addition, parental permission may be waived under the same circumstances that informed consent may be waived under the provisions of 45 CFR 46.116.

Children who are wards of the state are subject to further restrictions on their participation in research (as they are a doubly vulnerable population) and may only be enrolled in studies under §§ 46.406 and 46.407 if the research is either related to their status as wards or is carried out in an institutional setting (such as a school) where the majority of the other subjects are not wards. 45 C.F.R. § 46.409.

2. *The Impact of State Law*

While counsel to IRBs should always be attentive to additional restrictions contained in state law, in the area of research involving children, careful review of state law is critical. HHS regulations define "children" as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted." 45 C.F.R. § 46.402(a). OHRP has interpreted this regulation to exempt from the provisions of Subpart D any study that involves ***solely*** procedures or treatments that the child may consent to under state law. [10] Typical areas in which state laws will permit a minor to consent to treatment would include pregnancy or sexually transmitted diseases. *See, e.g.* 35 Pa. Con. Stat. Ann. § 10103 (authorizing minors to consent for services to determine the presence of or to treat pregnancy "venereal disease and other diseases reportable" to the state department of health).

State law is also critical in determining who is the legal guardian of a child, with the authority to give permission for the enrollment of the child in a research study. In many states, for example, foster parents may not be authorized under state law to consent to the enrollment of children under their care in research studies, or even for the provision of medical treatment.[11] After studies sponsored by the National Institute of Allergy and Infectious Diseases ("NIAID") that enrolled numerous foster children in HIV/AIDs clinical trials sparked a media firestorm,[12] the House of Representatives Ways and Means Committee's Subcommittee on Human Resources held a hearing on the legal and ethical issues presented by such research on May 18, 2005. The testimony of the various constituencies represented at that hearing, available on-line at: http://waysandmeans.house.gov/hearings.asp?formmode=detail&hearing=409, shows the wide range of ethical perspectives on this difficult topic. The New York City's Administration for Children's Services subsequently requested that the Vera Institute for Justice further investigate the enrollment of over 500 foster children under that agency's care in the 1980's and

[10] *See* OHRP *Human Research Question and Answers*, Answer ID 1016, available at http://answers.ohrp.hhs.gov/cgi-bin/answers_ohrp.cfg/php/enduser/std_alp.php.

[11] In Pennsylvania, foster parents are not even authorized to consent to routine medical treatment. Depending on whether a child was placed voluntarily or involuntarily under the protection of Children and Youth Services, either parental or agency permission is required.

[12] While there were many articles, the AP story *AIDS Drugs Tested on Foster Kids, Researchers Tested Drugs on Kids Without Advocate Protection*, May 4, 2005, available on-line at: http://www.cbsnews.com/stories/2005/05/04/health/main692980.shtml is representative of the media coverage.

1990's in HIV trials. The regular quarterly reports of that investigation can be viewed on-line at: http://www.vera.org/project/project1_3.asp?section_id=5&project_id=79&sub_section_id=38.

While cases involving drugs and devices may attract media attention, a far more likely area where local law impacts research involving children is in the design and approval of research in the educational setting. Many school boards have adopted policies related to research conducted within their districts. These policies may limit the number of studies in a particular school at any one time, may require review by a school board IRB, or may limit the type of research that can be undertaken. *See, e.g. Guidelines for the Approval and Conduct of Research at Beaverton, Oregon School District*, available on-line at: http://www.beaverton.k12.or.us/pdf/dist_conduct_of_research.pdf, *Pittsburgh Board of Public Education, Request to For Clearance to Conduct Research*, available on-line at: http://www.pps.k12.pa.us/IRBForms.asp, *Application to Conduct Research in the Topeka Public Schools*, available on-line at https://www.topeka.k12.ks.us/pc/Learning/res_&_eval/Research_Committee(IRB).html. Smaller, less urban school districts may have less well-developed mechanisms for reviewing and approving research. In such cases, counsel for the IRB would be well advised to obtain written permission from the appropriately authorized school superintendent.

Grimes v. Kennedy Krieger Institute, Inc., 366 Md. 29, 782 A.2d 807 (2001), is one of the few reported appellate cases to address some of the state law issues that can arise in research involving children. In that decision, the Court of Appeals of Maryland found that the research institution could be held liable for harm caused to children enrolled in a study which was designed to compare various remediation techniques for lead-based paint in low income housing. The court reviewed the history of modern regulations regarding the protection of research subjects and likened the children from low-income families in this case to the Tuskegee airmen, prisoners in concentration camps, and victims of the Japanese military's plague bombs in World War II. The court was openly disdainful of the IRB, concluding that "the scientific and medical communities cannot be permitted to assume sole authority to determine ultimately what is right and appropriate in respect to research projects involving young children free of the limitations and consequences of the application of Maryland law. The Institutional Review Boards, IRBs, are primarily, in-house organs." *Grimes*, 82 A.2d at 817.

This attitude lead the court to reach out to decide an issue that was not squarely before it – whether parental consent to nontherapeutic research on behalf of minor children was permitted under Maryland law. The court concluded: "[w]hen it comes to children involved in nontherapeutic research, with the potential for health risks to the subject children in Maryland, we will not defer to science to be the sole determinant of the ethicality or legality of such experiments. The reason, in our view, is apparent from the research protocols at issue in the case at bar. Moreover, in nontherapeutic research using children, we hold that the consent of a parent alone cannot make appropriate that which is innately inappropriate." *Ibid* at 855. This case makes clear both the potential significant impact of state law in an area too often assumed to be purely a federal regulatory matter and the need to consider the basic ethical considerations underlying the Common Rule in approaching IRB policies.

3. *The FDA Regulations*

The one area where FDA regulations and HHS regulations are most closely aligned is in the area of protections for children in research. The FDA regulations also contain a special subpart D that sets forth additional requirements for IRBs reviewing research involving children. 21 C.F.R. § 50.50. This subpart D contains provisions parallel to the HHS regulations. Minimal risk research involving children is permitted under the FDA regulations, provided that FDA procedures for seeking parental permission and assent of the children are followed. 21 C.F.R. § 50.51. For research that involves greater than minimal risk, but presents the prospect of direct benefit to the child/subject, the IRB may approve the research provided that "the risk is justified by the anticipated benefit" and "the relation of the anticipated benefit to the risk is at least as favorable" as available alternatives. 21 C.F.R. § 50.52(a) and (b). Finally, IRBs may approve clinical investigations involving a minor increase over minimal risk, that are "likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition." 21 C.F.R. § 50.53. The IRB must determine that the intervention presents an experience that is "reasonably commensurate" with the subject's actual or expected situation. *Id.* at (b). As with all such research, permission of the parents and assent of the children are also required. *Id.* at (c).

The Commissioner of the FDA may also approve a study, after consultation with appropriate experts and opportunity for public comment, that is not otherwise approvable under these regulations, provided that a reviewing IRB finds and documents (and the Commissioner agrees) that the study presents a "reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health and welfare of children," and the study will be conducted in accordance with appropriate ethical principles, and the permission of parents and assent of the children will be sought. 21 C.F.R. § 50.54. The FDA Commissioner maintains a standing Pediatric Advisory Committee that, in addition to other duties, advises the Commissioner on these types of studies. That Committee's past agendas, meeting transcripts, and briefing materials are available at http://www.fda.gov/oc/advisory/acoc.html and provides some insight into how the FDA approaches these types of studies.

On May 10, 2006, the FDA issued a Draft Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors on Process for Handling Referrals to FDA Under 21 C.F.R. 50.54, *available at* http://www.fda.gov/oc/gcp/draft.html. The comment period on this Draft Guidance closed on July 10, 2006. While still in draft form, this Guidance provides helpful information for IRBs preparing a protocol for referral to the FDA.

The FDA has worked to find appropriate, ethical incentives to motivate pharmaceutical companies to test their compounds in children. This has been a difficult task as, for some pharmaceutical companies, the safer course of action has been to receive approval only for an adult indication. Doctors may then prescribe the drug off-label for pediatric patients. In an effort to appropriately motivate the pharmaceutical industry, Congress passed the Best Pharmaceuticals for Children Act ("BPCA") in 2002. This law, which amended portions of the Food Drug and Cosmetic Act and portions of the Public Health Service Act, authorized the FDA

to identify drugs for which pediatric testing was lacking, but needed. The FDA, in concert with the National Institutes of Health ("NIH"), could then solicit first the company holding the marketing permit for that drug, and then third parties (including universities) to conduct on a contract basis the necessary testing for the drug in pediatric patients. 42 U.S.C. § 284m(b). BPCA also established a new office within the FDA, the Office of Pediatric Therapeutics, to coordinate all FDA efforts in this area. While BPCA represented a good faith effort to provide incentives (in the way of exclusivity provisions and fast track reviews), there was more carrot than stick in this law. In 2003, Congress again acted by passing the Pediatric Research Equity Act ("PREA"). PREA amends the Food, Drug and Cosmetic Act by adding a new section that requires entities submitting new drug applications or biologics licensing applications in several broad categories to include a pediatric assessment, unless a waiver is obtained. 21 U.S.C. § 355B. In certain cases, under PREA, the FDA may require that a pediatric assessment be submitted for drugs already approved for marketing. As PREA's provisions are mandatory, IRBs should expect to see an increase in pediatric drug protocols. Helpful information on the implementation of PREA is available in a draft guidance issued by the FDA in 2005, *How to Comply with the Pediatric Research Equity Act*, available at http://www.fda.gov/cder/pediatric/index.htm#bpca, posted September 7, 2005.

4. *The EPA Regulations*

Partially in response to the *Grimes* decision, the EPA commenced a rule making which culminated in new regulations released on February 6, 2006 that prohibit, in any research conducted or supported by the EPA, the intentional exposure of a child to a potentially harmful substance. 40 C.F.R. § 26.203. For purposes of these regulations, a study is deemed to involve "intentional exposure" if the "exposure to the substance experienced by a human subject . . . would not have occurred but for the human subject's participation in the study." 40 C.F.R. § 26.203. While intentional exposure is prohibited in EPA sponsored studies, children may be enrolled in observational studies (which are defined as any study that does not meet the definition for intentional exposure), provided that the study either presents minimal risk, 40 C.F.R. § 26.404, or the study presents greater than minimal risk, but holds out the prospect of direct benefit to the child or "is likely to contribute to the subject's well being." 40 C.F.R. § 26.405(a). The reviewing IRB must determine that the risk is justified by the anticipated benefit, and that the relation of the anticipated benefit to the risk is at least as favorable as the available alternative approaches. 40 C.F.R. § 26.405. Appropriate mechanisms must be employed for soliciting the permission of the parents and the assent of the children in such observational studies. 40 C.F.R. § 26.406. These same requirements also are extended to third party research that is conducted with the intent that the results be submitted to the EPA for consideration under the Federal Insecticide, Fungicide, and Rodenticide Act, or under Section 408 of the Food, Drug and Cosmetic Act. 40 C.F.R. § 26.1203.

D. Research Involving the Decisionally Impaired

1. *The Basic Premise of the Federal Regulations*

Although the federal regulations (both FDA and HHS) do not create a special subset of regulations for the decisionally impaired (as they do for children, prisoners and pregnant women), special consideration must be given to research involving decisionally impaired populations. Often, a study will include mildly impaired subjects (for example, a patient with early signs of Alzheimer's). As a general rule, all adults, regardless of their diagnosis or condition, should be considered competent to provide consent unless there is evidence of serious mental disability that would impair reasoning or judgment. This is a fundamental principle underlying the informed consent provisions of the Common Rule. Even those who do have a diagnosed mental disorder may be perfectly able to understand the potential risks and benefits of being a research volunteer, and they may be quite capable of consenting or refusing study participation. Mental disability alone does not disqualify a person from consenting to participate in research; rather, there should be specific evidence of the individual's incapacity to understand and make a choice before they are deemed unable to consent. (See Protecting Human Subjects, Institutional Review Guidebook, NIH). Protocols for such studies should address how the competency of these potential subjects will be assessed. Where a subject with some impairment is nonetheless competent to consent to participate in the research, no proxy consent should be sought.

Some studies will nonetheless involve potential subjects who do not have the capacity to give informed consent to their participation in the study.[13] Federal law provides that a potential research subject's "legally authorized representative" may provide the requisite informed consent to participate in a research study on behalf of the subject. See the OHRP regulations at 45 C.F.R. § 46.116 and the FDA regulations at 21 C.F.R. § 50.20. The issue of who is the "legally authorized representative" generally turns on state law, as HHS regulations define this term as "an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." 45 C.F.R. § 46.102(c).

2. *The Interpretation and Application of State Law*

The issue of whether proxy consent can be sought in a particular study depends on state law. Many states have specific statutes on this topic, although it is important to note that statutes that allow for proxy consent for medical treatment may not be applicable to medical research. Within the past several years, OHRP has focused on this issue, and questioned IRBs closely on whether they have accurately determined who may provide proxy consent under state law. As an example of this increased scrutiny, the University of California-San Francisco ("UCSF") was the subject of an OHRP finding that UCSF had obtained proxy consent for patients in an experimental breathing support study in violation of California state law, and, by extension, the Common Rule. Under California law, proxy consent for research may only be given by the court-appointed guardian for an incapacitated person. California Health & Safety Code, §§ 24170-24179.5. An exception may be permitted for proxy consent only where the research is

13 Note that this discussion does not address "emergency research," for which a waiver of informed consent may be appropriate. OHRP's Guidance on Waiver of Informed Consent for such research may be found at: http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc97-01.htm.
The FDA regulations on this topic may be found at: http://www.fda.gov/oc/ohrt/irbs/except.html.

"related to maintaining or improving the health of the human subject or related to obtaining information about a pathological condition of the human subject." *Ibid* at § 24175. The OHRP determination letter in this cases is available at http://www.hhs.gov/ohrp/compliance/letters/2002.html#Apr. It appears to accept the UCSF argument that, since the study involved the comparison of two medically acceptable treatments, UCSF could rely on provisions of California law that allowed relatives or next-of-kin to consent to medical treatment on behalf of an incapacitated person. OHRP encouraged this IRB, and all other IRBs, to consider having a third party observe the informed consent process as an additional safeguard.

This is a developing area of law, and the law has developed differently in various states. In Oklahoma, there is a specific state statute authorizing proxy consent for enrollment in research of incapacitated persons by a set hierarchy of persons. See 63 Okla. Stat. 3102A. The Oklahoma law gives the following order of persons who may give proxy consent: legal guardian, attorney-in-fact with health care authority, or family member in this order – spouse; if no spouse, adult child; if none, either parent; if none, adult sibling; if none, relative by blood or marriage.

Virginia also has a statute expressly authorizing proxy consent, but only where the research involved is therapeutic research or nontherapeutic research involving no more than a minor increase over minimal risk. 5.1 Va. Code § 32.1-162.18(A) and (B). Virginia also sets forth a hierarchy of persons who may give proxy consent, but the hierarchy is different from the Oklahoma list. First is parent of a minor, then agent under advance medical directive, legal guardian, spouse, adult child, parent where subject is an adult, adult sibling, then "any person or judicial or other body authorized by law or regulation to consent on behalf of a prospective subject to such subject's participation in the particular human research." 5.1 Va. Code §32.1-162.16.

In Pennsylvania, persons who have been adjudicated under Pennsylvania law as "incapacitated" may not be enrolled in research by their court-appointed guardian unless the court order appointing the guardian specifically states that the guardian has authority to consent to the enrollment of the person in "any experimental biomedical or behavioral medical procedure or participation in any biomedical or behavioral experiment." The guardian otherwise cannot give consent for the enrollment of that person. 20 Pa. Con. Stat. Ann. § 5521(d)(3).

In studies that are anticipated to include such decisionally impaired subjects, the protocol should address how the investigators will ensure their compliance with state law on this issue. In states where the issue has developed through case law, or court interpretation of conflicting state regulations, the issue is even more unclear. See e.g., *T.D. v. New York State Office of Mental Health*, 165 Misc.2d 62, 626 N.Y.S.2d 1015 (1995). Here again, it is important that IRBs document carefully how the determination of decisional impairment will be made, and ensure that investigators are advised properly on who may give proxy consent.

As OHRP has made the issue of proxy consent a focus of review in several recent audits, counsel may wish to reconfirm the status of state law on the issue and make sure that IRBs and investigators understand the distinction between proxy consent for treatment and proxy consent

for research. If the state allows proxy consent, investigators must understand that there may be a hierarchy of persons from whom consent may be sought. As the term "decisionally impaired" spans a very broad spectrum, IRBs should also be careful to ensure that, where the impairment arises from a temporary or correctable condition, allowance is made for investigators to obtain the assent of such subjects to their continued participation in the research, if those subjects regain adequate capacity during the course of the study.

Research involving special subject populations requires special attention and oversight by IRB counsel, to ensure that appropriate policies are in place to capture the myriad federal and local regulations that may apply. IRBs should also be diligent in documenting their determinations regarding these protocols, to ensure that there is an accurate written record of the necessary findings required under federal and applicable state regulations.