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Ethics of PET Research in Children*

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Positron emission tomography (PET) technology offers clinical researchers the opportunity to gain unprecedented understanding of the neurobiologic correlates of pediatric illness. In contrast to other forms of functional neuroimaging, PET provides direct information on neurochemical activity, such as neurotransmitter function in the human brain (1). Such data may prove invaluable to the understanding of brain maturation and the development of novel pharmacologic treatments for children. However, because PET is a radionuclear medicine technique and children are classified as a vulnerable population requiring special safeguards, PET utilization in pediatric research is controversial. The involvement of healthy children in PET research is an especially contentious issue, and to date fewer than a dozen such studies have been conducted in the United States.

This chapter examines the ethics of pediatric PET imaging in the context of a hypothetical research study, as it is formulated and submitted to the institutional review board (IRB) for approval. First, issues that must be considered by the principal investigator (e.g., scientific significance and risk/benefit ratio) are addressed. Guidelines for minimizing risk to pediatric participants are reviewed. Next, the role of the IRB in determining the study's risk level and in protecting the children involved in medical research is outlined. Also discussed are the implications of recent case law concerning nontherapeutic research that poses greater than minimal risk, as well as IRB member liability.

The Role of the Principal Investigator

In our hypothetical study, we wish to investigate the neurobiology of attention-deficit/hyperactivity disorder (ADHD), a prevalent pediatric psychiatric disorder, with poorly understood neurobiochemical

*The views stated herein do not necessarily represent the official views of the National Institute of Mental Health, the National Institutes of Health, the Department of Health and Human Services, or any other agency of the United States Government.

etiology (2,3). We propose a methodology that involves PET with intravenous administration of raclopride, a radioligand used to measure the concentration of dopamine (D2) receptors in the brain. Proposed subjects for the first stage of the study are boys of ages 9 to 17 years (see discussion of inclusion criteria that follows). Two groups will be studied: individuals with ADHD and individuals with no psychiatric history. Before submitting the study to the IRB for review, it is essential (1) to establish scientific significance and evaluate scientific yield of the proposed methodology, and (2) to delineate the risk/benefit ratio to the participants involved. Potential ethical concerns should be addressed in the context of these two facets of the proposal.

Scientific Significance, Scientific Yield, and Ethical Considerations

Why is the proposed study scientifically significant? First, ADHD is a disorder that primarily affects children; it is the most prevalent psychiatric condition in the pediatric population (4). Recent statistics estimate a 3% to 10% prevalence rate of pediatric ADHD in the United States, and as many as 30% of children with the disorder either do not respond to or cannot tolerate the side effects of conventional (stimulant) treatment (5). Second, although ADHD has been found to be associated with altered dopamine function (6–8), the neurobiochemical mechanisms underlying such alternations are unclear. Therefore, this study is necessary to answer key questions regarding the postsynaptic functional integrity of the dopamine system in children with ADHD. Data obtained may aid in the design of more effective pharmacologic treatments for children suffering from the disorder.

Ethical concerns must be weighed against the scientific relevance and salience of the proposed study (9). Furthermore, the principal investigator should demonstrate that the study has been designed to maximize scientific yield and minimize risk to participants involved. Thus, it should be established that (1) PET is the only methodology that can be used to answer the scientific question, (2) the scientific question can be answered only in children, and (3) healthy controls are necessary for the interpretation of the findings.

Why PET?

When reviewing the study, IRB members may question why PET is proposed when less invasive functional neuroimaging tools are available. Functional neuroimaging methods, for example, PET, single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), and magnetoencephalography (MEG), differ in the nature of the recorded signal (e.g., radioactive counts for PET and SPECT, electromagnetic energy for fMRI and MEG), physiologic variables (e.g., cerebral blood flow for PET, SPECT, and fMRI; glucose metabolism and receptor density for PET and SPECT), temporal and spatial resolution, cost, and

associated risks (10). Positron emission tomography is the only technique that allows direct assessment of neurotransmitter function and thus can help to answer proposed scientific questions. It enables investigators to assess regional dopamine function and to parse out its different elements (e.g., presynaptic vs. postsynaptic). However, PET is associated with unique medical risks (delineated below) that raise ethical issues for its use in pediatric populations, especially when healthy children are involved.

Why Children?

Why must the proposed study involve children? A seemingly simple way to avoid ethical conflict would be to study adults with ADHD. However, findings from prior neuroimaging studies suggest that the developing brain is structurally and functionally distinct from the adult brain. In a review of 25 magnetic resonance imaging (MRI) studies of the developing brain, Durston et al. (11) cite age-associated volumetric changes in several brain structures. Although the basal ganglia decrease in volume with age, the amygdala and hippocampus increase in volume. Giedd et al. (12) found that these developmental changes in brain morphometry also vary according to gender. Amygdala volume increases significantly in males, and hippocampal volume in females. In addition, PET studies have revealed functional differences between the developing and mature brain. Chugani (13) reported that pediatric rates of cerebral glucose metabolism differ from those of adults, and that metabolism rates vary significantly throughout childhood. After birth, glucose metabolism rates rise steadily until age 4, when they are twice that of adults. Between the ages of 4 and 10, metabolism rates remain high, and then gradually decline to reach adult values by age 16 to 18. Additionally, Chugani found that metabolic rates in the developing brain differ by brain region. In newborns, glucose metabolism rates are highest in sensorimotor cortex, thalamus, brainstem, and cerebellar vermis, but as the infant grows, metabolic rates increase in occipital lobe, temporal lobe, and eventually frontal cortex.

Considering these structural and functional differences, the neuropathology associated with neurologic and psychiatric illnesses may also differ in the developing and mature brain. For example, studies of children and adults with ADHD reveal neurobiochemical differences between the two groups. Blood or cerebrospinal concentrations of the dopaminergic metabolite homovanillic acid (HVA) have been found to be abnormal in children with ADHD (14,15) but not in adults with ADHD (16,17). Cerebral glucose metabolism levels have been found to be abnormally low in adults with ADHD (18) but unaltered in adolescents with ADHD (19,20). Most significant are PET-based findings that children with ADHD exhibit different abnormalities in dopaminergic function than adults with ADHD (6,7). Such age-associated neurobiochemical changes may explain why certain psychiatric medications are effective in adults but not in children (e.g., tricyclic antidepressants for major depressive disorder) (21). Furthermore, they suggest that the

proposed scientific question cannot be answered based on inferences from adult data.

Another consideration is the age of the children. The younger the children who are subjects in a study, the more stringent are the safeguards. This is particularly important with regard to the capacity of children to assent to participate in a study. In our study, 9 years of age was selected as the inferior age limit because, by age 9, healthy children are believed to possess the cognitive maturity necessary to understand the research process and evaluate the risks involved in participation (22). However, there is much debate on this topic, with some arguing that the age of assent should be as high as 14 (23).

Why Healthy Controls?

Although there is some debate over whether it is better to enroll healthy or affected children in nonbeneficial research (24), PET studies of children with ADHD are generally more likely to receive IRB approval than studies of healthy children, who are less likely to benefit from participation (1). In previous pediatric PET studies, researchers have utilized several methods to mitigate ethical objections to the inclusion of healthy controls (25). The first is to scan healthy siblings of children affected by the condition under investigation. Siblings may indirectly benefit from increased knowledge of ADHD, a disorder with probable genetic etiology that may be inherited by their own children (26). However, the use of siblings as healthy controls can reduce the scientific yield if the siblings carry a common genetic vulnerability that influences brain function, even if behavioral symptomatology is not expressed. A second method, applied by Chugani et al. (27), is to study unaffected brain regions of children with transient neurologic disorders, such as epilepsy. This method is also suboptimal, because neurologic disorders may induce changes in cerebral function that increase variability and lead to results difficult to interpret. A third method, utilized by both Bentourkia et al. (28) and Chugani et al. (29), is to retrospectively select control children who had been scanned as part of a diagnostic evaluation, but whose results had been negative, indicating an absence of neurologic abnormalities. This method is also problematic because the medical or behavioral problems that prompted a diagnostic PET scan undermine these subjects' status as truly "healthy" controls. A fourth method is to study only children with ADHD and correlate PET results with symptom severity (30). However, this method reduces the investigators' ability to elucidate the neural mechanisms of the disorder because no comparisons can be made to the healthy brain. Thus, although these alternative methods may be more ethically feasible, the use of nonrelated, nonsymptomatic children as healthy controls remains the gold standard for optimizing scientific yield.

Once scientific significance is established, and issues related to scientific yield are addressed, the principal investigator must demonstrate that the study has a favorable risk/benefit ratio (i.e., the risks to the subjects involved are lower than or at least proportionate to the bene-

fits to the subject and society) (9,31). In addition, the investigator should demonstrate that the study design minimizes risks and maximizes benefits to participants involved.

Optimizing the Risk/Benefit Ratio

Risks

Risks for participants in pediatric PET protocols include (1) physical side effects associated with the venous line; (2) stress related to the procedure (e.g., possible claustrophobic reaction, difficulty lying still, anxiety provoked by medical environment); and (3) radiation exposure.

Risks related to the insertion of the venous line include transient redness, swelling, or bruising. A topical anesthetic such as eutectic mixture of local anesthetics (EMLA) cream can be used to numb the site of needle puncture, which tends to reduce discomfort and anxiety. Adequate preparation can significantly reduce stress related to the procedure. Before the scan, children should visit the room where the procedure will take place and ideally spend time in a PET simulator. Simulation can help to desensitize the subject to the medical environment. Furthermore, it can allow the research team to determine if the subject will have a claustrophobic reaction once inside the scanner. Optimal simulation should replicate any environmental elements (e.g., background noise, lights) that may be anxiety provoking for children during the actual scan. Children, especially those with ADHD, often have difficulty remaining still during a PET scan. Placing the child's head on an inflatable pillow and allowing him to watch a video can alleviate this problem.

The most ethically concerning of these risks is exposure to radiation because of its association with genetic mutation and carcinogenesis. Three common misconceptions regarding this association may bias the evaluation of pediatric PET studies: (1) any radiation dose can produce cancer or genetic damage, (2) the severity of adverse effects is directly proportional to the radiation dose received, and (3) children are more radiosensitive than adults (32). Ernst et al. (32) conducted a comprehensive review of studies of low-level radiation exposure from various sources (background, occupational, and medical) to assess the health hazards of radiation exposure in the context of brain imaging research. Findings indicated that the incidence of cancer in individuals exposed to low-level radiation, defined as 10 to 20 rem (roentgen equivalents in man, the conventional unit for dose equivalent), cannot be detected above the incidence rate of cancer in the general population. Although the majority of the studies available for review did not include children, there were no definitive findings of higher risks associated with younger age (younger than 5 years old) following exposure to low-level radiation.

One possible exception is data from an Israeli longitudinal study conducted by Ron et al. (33), who tracked the incidence of thyroid tumors following childhood exposure to radiation. A total of 11,000 subjects

who had been treated with scalp irradiation for tinea capitis as children and 16,000 controls were followed between 1950 and 1972. Age at treatment ranged from 1 to 15 years, with a mean of 7.1 years. The authors concluded that an estimated thyroid dose of 9 cGy (9 rem) was linked to a fourfold [95% confidence interval (CI) = 2.3–7.9] increase of malignant thyroid tumors and a twofold (95% CI = 1.3–3.0) increase of benign thyroid tumors. In addition, younger age at exposure was found to be associated with higher risk, particularly in children younger than 5 years. In a more recent study, Juven and Sadetzki (34) examined the medical records of 4900 of Ron et al.'s subjects and also noted a possible association between childhood exposure to ionizing radiation and benign pituitary adenoma. An important limitation of both studies is the lack of a true measure of radiation exposure; radiation doses administered during treatment were estimated based on post-hoc measurements of representative exposures assumed to be analogous to the original exposures. In addition, although the mean radiation dosage was estimated to be 9.3 rem, dosage ranged from 4.5 to 50.0 rem. Thus, a proportion of the subjects were exposed to radiation dosages that significantly exceeded the low-level threshold. Therefore, it is problematic to draw generalized conclusions regarding exposure to low-level radiation based on the findings of these two studies.

Billen (35) examined the relationship between exposure to radiation and spontaneous DNA damage, and found that the biologic impact of low-level radiation at the cellular level is proportionally low in comparison to the frequency of daily spontaneous genetic mutations. Each day, an average of 240,000 genetic mutations spontaneously occur in the human body. Radiation exposure of a single rem adds approximately 100 mutations to this number.

In addition, research has provided evidence in support of hormesis, a theory that exposure to low-dose radiation may be beneficial. Studies conducted by Sanderson and Morley (36) and Kelsey et al. (37) demonstrated that previous low-level radiation can have a protective effect during subsequent high-dose radiation exposure by stimulating chromosomal repair mechanisms.

Despite these findings, many scientific questions remain to be answered before definitive conclusions can be made regarding the effects of low-dose radiation exposure during a PET scan. As relevant research evolves, the Food and Drug Administration (FDA) has developed vigilant guidelines to protect children, who may be more vulnerable to radiation exposure on account of smaller size and ongoing tissue growth. Currently, the FDA restricts the use of radioactive drugs in research involving minors to 0.3 rem in a single dose (or 0.5 rem cumulative annual dose) to the whole body, active blood-forming organs, lens of the eye, and gonads (32,38,39). This dose is one tenth of that mandated for adults. Furthermore, 0.5 rem is at least 20 times lower than the low-level exposure in the studies reviewed by Ernst et al. (32) (i.e., 10–20 rem). As of 1998, the highest research radiation dose used in imaging studies of healthy children 12 and older was 0.06 rem to the whole body (32,38,39).

As an additional safeguard, when large medical institutions conduct human research studies that involve exposure to non–medically indicated ionizing radiation, a local radiation safety committee (RSC) or radioactive drug research committee (RDRC) reviews the study prior to or concurrently with the IRB review. Members of these committees provide the principal investigator and IRB with an estimated percentage risk (in terms of increased likelihood for the development of fatal cancer) associated with participation in studies such as the one proposed here. If the maximum permitted pediatric radiation dosage is administered (0.3 rem in a single dose, or 0.5 rem cumulative annual dose), this increase in percentage risk is approximately 0.000025.

When designing pediatric PET protocols, the principal investigator should take all possible steps to minimize radiation exposure to the subjects involved. In a PET study of adolescent girls with ADHD, Ernst et al. (19) implemented several methodologic adjustments to reduce the amount of tracer injected: they lengthened the scan acquisition time, thus recovering image resolution lost due to the lower injected dose; and they allowed subjects to void during the study, thus removing the tracer from the bladder, which is the organ with the highest level of exposure during [18F] fluorodeoxyglucose PET scans. When possible, researchers should also utilize new developments in PET technology, such as the emergence of highly sensitive three-dimensional (3D) cameras that permit the use of lower doses of radioactive tracer.

Another important consideration for the investigator is to use a design that minimizes the number of subjects exposed to risks. In the proposed study, only male subjects are included in the first phase of the trial. This decision was made in light of evidence of neurobiologic differences between males and females (12) and the fact that ADHD is predominately a male disorder (40). Enrolling only males effectively reduces the number of subjects exposed to radiation, while maintaining scientific validity.

Benefits

What are the potential benefits for participants in the proposed study? King (41) defines three possible types of research benefits: (1) direct (benefit arising from receiving the intervention being studied), (2) collateral or indirect (arising from being a subject), and (3) aspirational (benefit to society or future patients arising from the results of the study). According to these definitions, only collateral and aspirational benefits are available to subjects in the proposed study because it is nontherapeutic. For children with ADHD, collateral benefits may include a free psychiatric evaluation, physical exam, and an opportunity to learn more about their disorder. Healthy controls may also benefit from free evaluations and examinations, as well as a sense of altruism gained from volunteering to help other children (38). Furthermore, participation in a research protocol can be a valuable learning experience. Not only will subjects gain exposure to a hospital setting, but they can also learn about how scientific research is conducted. Research teams may augment this learning experience by

engaging the child in the research process (e.g., explaining to a curious child how neuroimaging "works" or providing the child with an image of his or her brain and a certificate of appreciation).

The proposed study also has potential scientific benefits at large, as ADHD affects thousands of children in the United States and is associated with academic impairments, social dysfunction, poor self-esteem, and increased likelihood for substance abuse (5). Studies such as the one proposed are essential for elucidating the neurobiologic correlates of the disorder. Findings will likely assist in the development of safe and effective treatment. Furthermore, because the proposed study includes healthy controls, PET data collected can provide critical insight into dopaminergic function during normal development. Such information is critical to the understanding of plasticity of the maturing brain and may help to identify critical periods of neural vulnerability as well as potential compensation and opportunity for treatment.

After delineating these potential benefits and contrasting them to potential risks, the principal investigator concludes that the risk/benefit ratio for the study is favorable and submits the protocol to the IRB for approval.

The Role of the Institutional Review Board

The IRB is charged with two main functions, which are often conflicting. Although its primary goal is to protect individual participants in medical research, it is also expected to facilitate research that is critical to the evolution of medical care. The board's members are guided by Title 45, Part 46 of the Code of Federal Regulations (CFR) (42), which outlines ethical and legal obligations of persons and institutions conducting or supporting research involving humans. The CFR mandates that each institution conducting federally funded research adhere to the principles for the protection of human subjects set forth in the Belmont Report (43). These principles include (1) beneficence, which requires that researchers maximize benefits and minimize harm; this principle also entails that all approved protocols have a favorable risk/benefit ratio; (2) respect for persons, which recognizes the autonomy of individuals, while requiring protection for people with diminished autonomy (such as children); this principle is implemented via informed consent and assent; and (3) justice, which requires equitable selection and recruitment, as well as fair treatment of research subjects.

Beneficence and Risk Classification

The first objective of the IRB is to classify the risk level of the proposed study (e.g., minimal risk, minor increase over minimal risk, or more than a minor increase over minimal risk). Subpart D of the CFR ("Additional DHHS Protections for Children Involved as Subjects of Research") prohibits IRBs from approving pediatric research that poses more than a minor increase over minimal risk and does not offer the prospect of direct benefit to participants. The level of risk, as well as whether there is prospect of direct benefit to participants, determines the provisions necessary for the study to be approved and conducted,

as outlined in Figure 7.1. In subsection 46.102 (i), the CFR suggests the following definition for minimal risk:

> Minimal risk means 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.

Given that the study's risk classification determines its approval, this definition is a paramount guideline for IRB deliberations. However, the definition contains several ambiguities.

First, risks "ordinarily encountered in daily life" can vary significantly among children, depending on their age, socioeconomic class, and physical environment. In terms of the proposed study, it can be argued that children who routinely fly on airplanes or frequently receive medical x-rays "ordinarily" encounter risks of radiation exposure. In fact, a cross-country flight and a chest x-ray each contribute approximately 0.003 rem (44). Does this mean that these children should be permitted to participate in the PET study, whereas children who do not "ordinarily" encounter risks of radiation exposure should be excluded? Furthermore, "examinations or tests" that are routine for a child with a medical disorder such as ADHD may not be routine for a healthy child. This disparity raises the question of whether the study's risk classification should differ for patients and healthy controls. A child with ADHD who is accustomed to a clinical setting may tolerate certain procedures (e.g., psychiatric interviews) better than a healthy child. On the other hand, ADHD could render a child more vulnerable to research-associated risks (e.g., psychological stress from an inability to lie still in the scanner). Although there is some agreement that the minimal risk standard should be based on risks in the lives of the general population, the lack of a more specific definition produces unnecessary complications. Furthermore, IRB deliberations may be hindered by the fact that the CFR does not provide definitions for the terms *minor increase over minimal risk* and *direct benefit.*

Considering the ambiguous nature of CFR guidelines, it is not surprising that risk categorization varies greatly among IRBs. Shah et al. (45) presented a series of hypothetical research vignettes to 188 randomly selected chairpersons of IRBs in the United States and asked them to categorize the risks and benefits involved for a healthy 11-year-old participant. Data collected demonstrated marked variability in the risk determinations. For example, when asked to designate the risk category of MRI (without sedation), 48% of IRB chairpersons surveyed selected minimal risk, 35% selected minor increase over minimal risk, and 9% selected more than a minor increase over minimal risk. Disparities were also noted in the categorization of direct benefits of participation. Only 60% of the chairpersons surveyed considered added psychological counseling to be a direct benefit of participation in a study. Furthermore, 10% considered participant payment to be a direct benefit, even though the IRB guidebook explicitly states that it should not be (46). McWilliams et al. (47) and Rogers et al. (48) demonstrate how variations in the categorization of risks and benefits can

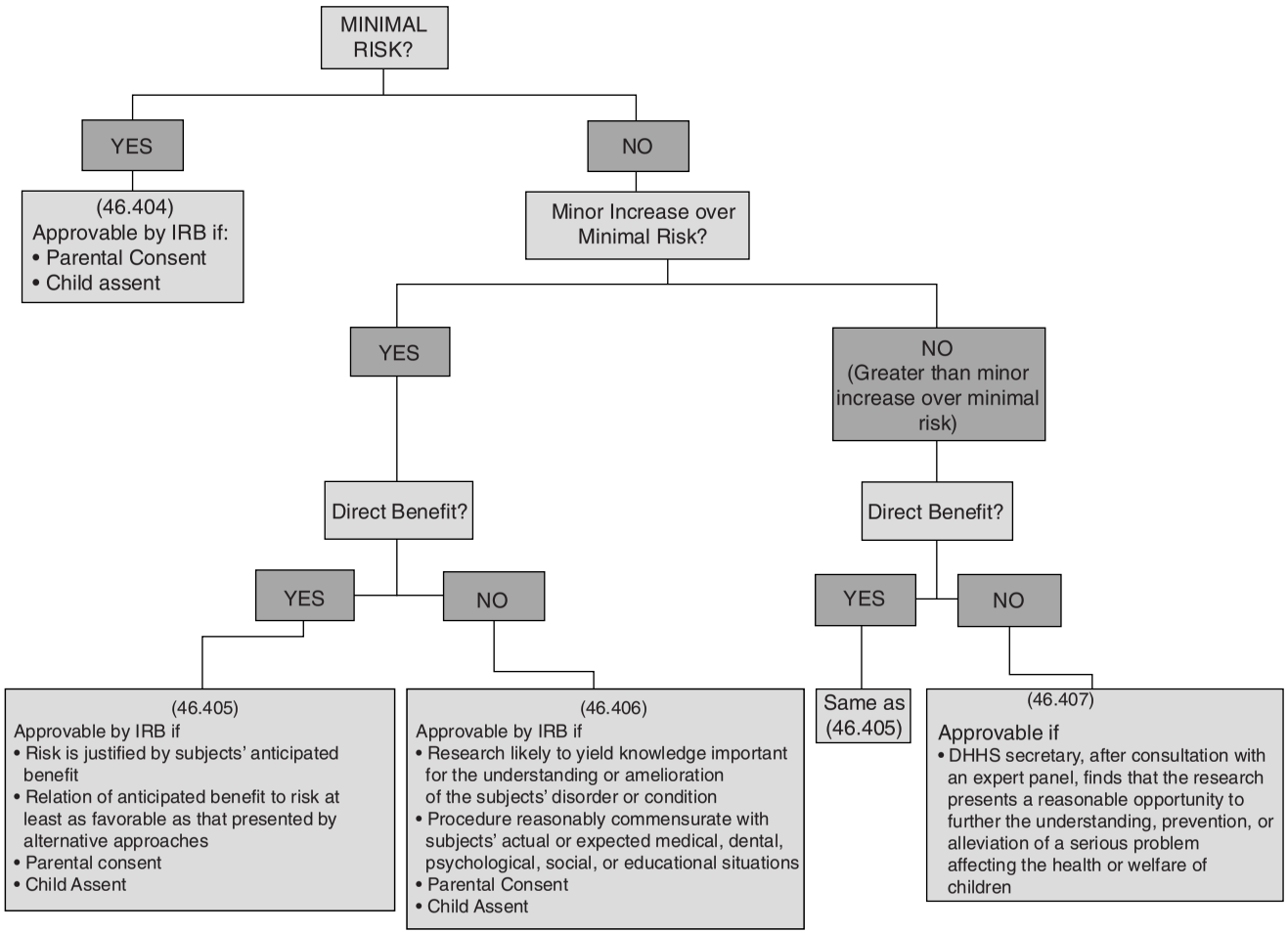

Figure 7.1. Institutional review board risk assessment flowchart. Based on CFR 46, Protection of Human Subjects, subpart D, Additional DHHS Protections for Children Involved as Subjects in Research.

complicate the review of multicenter protocols, which must be approved by the IRBs of each institution involved.

Variability in IRB review standards can be detrimental in two ways: either children may be subjected to undue risk, or potentially beneficial research may not be approved on account of inappropriate risk categorization. To prevent such consequences, more specific definitions for the terms *minimal risk, minor increase over minimal risk*, and *direct benefit* should be provided within the CFR. For example, Nicholson (49) provides a list of ordinary daily risks to which research risks can be compared to determine minimal risk (39). Furthermore, considering the fact that some IRB members lack clinical experience, neutral medical experts should be called upon to educate the committee when unfamiliar procedures (such as PET scanning) are proposed to ensure that risk categorization is not biased by misconception.

According to CFR 46.404, if the IRB categorizes the proposed study as minimal risk, it may be conducted as long as proper consent and assent is obtained. However, based on IRB classifications of comparable studies (45), our proposed study will likely be deemed greater than minimal risk, with no prospect of direct benefit to healthy subjects involved. If the study is categorized as a minor increase over minimal risk, CFR 46.606 (the subject condition requirement) should be considered by the IRB. This section permits research that is "likely to yield generalizable knowledge about the subject's disorder or condition." Thus, this section clearly sanctions the approval of the proposed study if children with ADHD are the only subjects included. How can this section be interpreted for the study of healthy controls? One could argue that the terms *disorder* and *condition* are ambiguous. For example, the IRB at the Children's Hospital in Los Angeles approved a computed tomography study of bone development in which 50 healthy girls were briefly exposed to 0.10 rem of radiation (50). Findings yielded increased knowledge on differences in bone density in developing African-American and Caucasian females. Can race be considered a "condition" in accordance with CFR guidelines? If so, what about childhood or adolescence? If the term is interpreted broadly, one could argue that in addition to elucidating the neuropathology of ADHD, including healthy control children will likely yield generalizable knowledge about the neurobiology of development, or the "condition" of immaturity itself.

Alternatively, if the proposed study is categorized as greater than minor increase over minimal risk, CFR 46.407 may be applicable. According to this section, the IRB may submit an unapprovable research study for higher review if it is believed to "present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children." Approval may be granted by the secretary of the Department of Health and Human Services (DHHS) after public review and consultation with an expert panel. In the 18 years following the 1983 adoption of 45 CFR 46, only two unapproved pediatric research studies were considered under section 46.407. However, in 2001 alone, the secretary of DHHS received 26 requests for higher review (51). Research proposals previously reviewed under CFR 46.407

are listed on the Web site of the Office for Human Research Protection (OHRP) (http://www.hhs.gov/ohrp/children/index.html#researchproposals). One protocol on this list, "HIV Replication and Thymopoiesis in Adolescents," is comparable to the proposed PET study because it involves healthy adolescents (ages 13 to 24) and radiation exposure (during a computed tomography scan and intravenous infusion of deuterium-labeled glucose solution). The OHRP recommended that the DHHS approve this study but stipulated that the risks involved must be clearly defined in the consent documentation (i.e., by including the specific amount of radiation to which each subject will be exposed and a statement that a CT scan is associated with more radiation exposure than a chest x-ray). The marked increase in pediatric protocols submitted under CFR 46.407 is likely a reflection of recent legal and ethical scrutiny of clinical research studies.

Issues Related to Informed Consent and Assent

After issues related to beneficence have been addressed, the IRB should ensure that the proposed study upholds the second principle set forth in the Belmont Report (43): respect for persons. Thus, the IRB must critically evaluate the proposed consent and assent process. According to federal guidelines, children under 18 must assent to participation in clinical research. In addition, their parents (or legal guardians) must sign consent forms for their child to participate (52). For the consent/assent process to be valid, participants must possess competence, knowledge, and a desire to participate in the study not influenced by undue coercion (38).

Competence implies that the participant has the cognitive ability to arrive at a rational decision to participate in the study. In a review of literature assessing assent by minors, Leikin (22) concludes that by age 9, healthy children have sufficient cognitive capacity to make a valid decision as to whether to participate in a research study. In accordance with these findings, the minimum age for subjects in the proposed study is 9 years. However, there is ongoing debate on this topic, with some investigators proposing a more stringent age cutoff for assent (23), and IRBs varying widely in their requirements (53). Until the federal regulations explicitly include a minimum age, it is likely that this debate will continue. Regardless, it is critical that the investigator use age-appropriate language when providing an explanation of the purpose of the study and the procedures involved. Psychiatric disorders, often associated with characteristics such as paranoia, apathy, and impaired insight, may hinder a child's cognitive processing and ability to provide informed assent. Considering comorbidity of pediatric ADHD and psychiatric disorders such as anxiety, depression, and oppositional defiant disorder (54), subjects should receive a complete psychiatric interview before the PET scan. Furthermore, if the presence of a psychiatric disorder (other than ADHD) is suspected during the consent process, the principal investigator should carefully question the child to ensure that his or her motivation to participate in the study is psychologically sound.

Knowledge entails that the participant has been fully informed of the protocol methodology as well as all possible risks and benefits involved in participation. In its 2001 report on improving informed consent for research radiation studies, the NIH Radiation Safety Committee provided model language to clearly inform subjects of potential radiation-related risks (55). The template includes disclosure of the effective radiation dose to be administered before the PET scan and a comparative estimation of typical radiation exposure from natural background sources. Furthermore, it recommends disclosure of the estimated amount of risk associated with the research-related radiation exposure in terms of increased possibility of fatal cancer. The NIH Radiation Safety Committee provided the following sample clause as a guideline for informing research participants of the risks of low-dose radiation exposure comparable to that which would occur during a PET scan:

> One possible effect that could occur at these [radiation] doses is a slight increase in the risk of cancer. Please be aware that the natural chance of a person getting a fatal cancer during his/her lifetime is about 25 percent. The increase in your chance of getting a fatal cancer, as a result of the radiation exposure received from this study, is [insert percent increase calculated by Radiation Safety Committee]. Therefore, your total risk of fatal cancer may increase from 25 percent to (25 + calculated increased risk). This change in risk is small and cannot be measured directly. Compared with other everyday risks, such as flying in an airplane or driving a car, this increase is considered slight.

The IRB should ensure that consent documents for the proposed study adhere to these recommended guidelines to guarantee that participants are fully informed with regard to potential risks.

It is the responsibility of the investigator to ensure that the child's decision to participate in the study is completely voluntarily and not unduly influenced by financial need, parental pressure, or psychological coercion. The compensation of minor participants in medical research studies is a controversial topic frequently debated by IRBs. Major ethical questions include whether to compensate the parent or the child, whether to consider the economic status of the family when determining compensation, and whether the compensation should be correlated with risk involved (38). If compensation is provided for the child, its perceived value may differ based on the child's age, cognitive abilities, and socioeconomic status. Regardless, financial motivation should never preclude the child from carefully considering the risks involved in participating in a PET study. If there is any concern that compensation may be an undue influence, a neutral observer should monitor the consent/assent process to counterbalance investigator bias. Also, after parental consent is obtained, investigators should meet with the child alone to discuss his or her motivation for participation and ensure that there is no undue parental coercion before assent is elicited. There is some debate over whether researchers should meet with the child before the parent rather than after, but both processes are reasonable and should be left up to the individual investigator to decide.

Furthermore, it is critical that the child understands that he or she can withdraw from the study at any time without providing a reason and without loss of any previously attained benefits or financial compensation. Throughout the course of the study, the research team should strive to facilitate feelings of autonomy in the child participant. This can be accomplished by asking children how they feel about the prospect of a PET scan, having them fill out feedback forms, and having them make simple procedural decisions (e.g., which seat they want to sit in, which snack they would like to eat after completing the scan). Such simple steps increase the likelihood that the child will share concerns and questions with the research team, thus remaining a willing participant in the PET study.

Justice

The third ethical principle set forth in the Belmont Report is justice, which compels the IRB to monitor the selection of research subjects at two levels: the individual and the social (43). To uphold individual justice, the IRB should ensure that subjects for the proposed study are not preferentially selected or excluded on the basis of race, ethnicity, or socioeconomic class. For example, the proposed study includes only boys, which may be considered unjust if the principal investigator had not provided a scientific rationale, or stated intentions to include girls in subsequent phases of the study. According to the Belmont report, social justice "requires that a distinction be drawn between classes of subjects (e.g., adults and children) that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens." In the past, children have been excluded from research studies because they are considered less able to bear the burden of potential risks involved than adult subjects. However, excluding children from medical research precludes them from its benefits and could potentially cause them harm. For example, if research studies are not conducted to elucidate the neurobiochemical etiology of ADHD in children, it will be difficult to develop novel treatments for the disorder. Furthermore, attempts to extrapolate data from adult studies may lead to the development of treatments that are unsafe or ineffective for the pediatric population (9). Such consequences seem to be in conflict with the concept of "fairness in distribution" of the benefits of research, an ideal also included in the Belmont Report's definition of justice.

In 1998, two policy initiatives were introduced to ensure that children are not unnecessarily excluded from the benefits of research (56). First, the NIH mandated that children be included in all human research conducted or supported by their institution unless there are sound scientific and ethical reasons to exclude them (57). Second, in response to the fact that 70% of all medications do not include sufficient data for use in children (45,58), the FDA developed the Best Pharmaceuticals for Children Act, which provided patent extension incentives to drug companies that tested their products in children (52). Although such initiatives promote the approval of the proposed

study, they should not preclude a careful consideration of the risks involved.

Recent Case Law and Implications

There is currently no known case law involving PET imaging in children. However, in the past 5 years, three highly publicized legal cases have raised controversial questions regarding human research studies involving greater than minimal risks and whether individual IRB members can be held legally liable for approving such studies if injury occurs. Challenges to the integrity of clinical research made during these three cases are especially likely to influence IRB review of ethically controversial pediatric research studies, such as the one proposed here.

The first case involved a lead abatement research study conducted by the Kennedy-Krieger Institute (KKI) (59). Between 1993 and 1995, researchers monitored dust lead levels in three groups of homes in a low-income Baltimore neighborhood, each treated with a different lead abatement method. Blood lead levels of children living in the homes were periodically sampled, and parents were reimbursed $15. In 2000, two families involved in the study filed suit against KKI, claiming that they had not been fully informed of the risks involved in the study and were not advised when their children's blood lead levels rose (60). In response, the Maryland Court of Appeals issued the following opinion:

> It is not in the best interest of any healthy child to be intentionally put in a nontherapeutic situation where his or her health may be impaired, in order to test methods that may ultimately benefit all children (61).

Thus, the court ruled that a parent or guardian cannot consent to a child's participation in nontherapeutic research in which there is any risk of injury or damage to the child's health (i.e., minor increase over minimal risk) (60). In addition, the court criticized the "IRB's attempt to manufacture a therapeutic value" for the KKI study (61). Two months later, the court clarified its ruling, seeming to conform again to federal regulations (62). And in 2002 the Maryland legislature essentially nullified the court's objections, allowing all research that is consistent with the federal regulations, which includes studies involving a minor increase over minimal risk (63). Nevertheless, the case instigated public and legal challenges to the integrity of pediatric research and the role of the IRB.

In 2001 *Robertson v. McGee* (64) set legal precedent by including 12 members of the University of Oklahoma IRB as defendants. The case involved a cancer vaccine trial that was suspended after an audit cited inadequate protections for human subjects. The OHRP was called to investigate, and concluded that the IRB had failed to "ensure that additional safeguards were included in the study" to protect subjects, many of whom were terminally ill. Based on these allegations, negligence counts were filed against the IRB members in the legal suit that followed (65).

In the aftermath of these cases, IRB members are likely to be increasingly cautious when reviewing studies such as the one proposed. Positron emission tomography imaging may be classified in a higher risk category, and the inclusion of healthy controls is unlikely to be approved. Furthermore, the IRB may be more likely to submit the study (under CFR 46.407) to the DHHS for higher review to avoid legal liability issues. And although there are no known examples of successful lawsuits against bioethicists or IRB members, the possibility of such a lawsuit may make individuals hesitant to provide advisory services to IRBs or serve on the committee. These circumstances threaten both the future of clinical studies and the welfare of research participants.

Conclusion

Pediatric PET research presents novel opportunity for scientific discovery, as well as unprecedented ethical issues warranting careful evaluation. Several conclusions can be drawn from the hypothetical PET study presented in this review: First, we have established the unique utility of PET to study neurobiochemical function, such as the mechanisms of dopamine modulation in children with ADHD. Second, because developmental differences mitigate any extrapolation from adult data, PET studies such as the one proposed here must be conducted in children. Third, including healthy children is the only way to maximize scientific yield and learn about normal neurobiologic development. Fourth, pediatric PET studies are associated with considerable potential risks, as well as significant collateral and aspirational benefits to participants. The principal investigator should take all possible procedural steps, including those outlined in this review, to optimize this risk/benefit ratio. It is hoped that these four conclusions may serve as a guideline in the design of future PET studies.

This chapter also yields several suggestions regarding the IRB evaluation of pediatric PET research. First, it is essential that board members be accurately informed of the risks associated with pediatric PET, especially in terms of radiation exposure. Second, the definition of *minimal risk* should be clarified and definitions should be provided for the terms *minor increase over minimal risk* and *direct benefit* within the CFR so that IRB deliberations are not clouded by ambiguity or misconception. Third, the IRB should ensure that risks associated with PET are fully disclosed in the consent documentation, as outlined by the NIH Radiation Safety Committee. Fourth, in accordance with the principle of justice, children are entitled to benefit from advances in scientific research, such as those that may be gained by conducting the proposed study. Therefore, it is critical that recent case law not bias the IRB's evaluation of the risks and benefits of pediatric PET studies. The IRBs are charged with the vital responsibility of protecting individual children while allowing research needed to improve overall pediatric medical care. It is hoped that the recommendations outlined in this chapter will aid in the ethical considerations needed to fulfill this responsibility.

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