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Research with Radiation and Healthy Children: Greater than Minimal Risk

by William L. Freeman

Like other IRBs across the country, the national IRB of the Indian Health Service confronts several questions when reviewing protocols involving children: What does "greater than minimal risk" mean in research with healthy children? Does research radiation pose greater than minimal risks to healthy children and newborns? Should healthy children and newborns be subjects of research that entails greater than minimal risk?

To help the IHS National IRB review a protocol recently, I did a survey of published research involving children and radiation. Unexpectedly, there were many articles about radiologic measurements of body composition or bone density of healthy children. I want to discuss three of the articles found, but first must briefly define some technical terms.

A millirem (mrem) is a measure of the amount of radiation absorbed by a body. Background whole-body radiation comes from cosmic rays and radioactive elements in the earth and body. It is about 95 mrem per year to each person.[1(p. 18)] Additional background radiation comes from radon. The average radon dose in the United States is 200 mrem; the actual dose depends on location, and ranges from 0 to more than 1,000 mrem. Because radon affects only the *lung* and has so much variability of dose, and because medical X rays affect multiple organs, radiation from medical X rays may best be compared with the *whole-body* background radiation of 95 mrem.

The dose for a chest X ray varies by size of patient: 20-40 mrem for adults, 2-5 mrem for infants. Major adverse effects of low-dose radiation include cancer, genetic damage, and mental retardation. I will discuss the risks only of cancer, because the dose to double the mutation rate (100,000 mrem) is much higher than doses reported in the articles, and mental retardation occurs following radiation during the first and second trimesters of fetal life, which is earlier than the research done.[1(p. 77, 356)] Two earlier articles in *IRB* give more details about the nature and measurements of radiation.[2,3]

Two radiologic procedures were used in the three articles I want to review here: quantitative computerized tomography (CT) and single photon absorptiometry. According to recent review articles about the procedures, quantitative CT of the upper lumbar spine delivers 100-1,000 mrem absorbed radiation to the target part of the body; single photon absorptiometry of the extremity delivers 2-20 mrem.[4,5] The dose to the gonads due to scatter is "as low as 10 [mrem]" for quantitative CT, and negligible for single photon absorptiometry.[4] These numbers do not include the dose from the routine localization or scout X ray, which is used in quantitative CT.4 In some photon absorptiometry studies, the actual dose delivered is 3 to 5 or more times the single-scan dose, due to reposition of the arm or repetition to average the results.[6,7]

To summarize the three articles:

In research reported by Gilsanz and colleagues,[8] the subjects were healthy normal children between 2.5 to 19.9 years old who were recruited for the research. The purpose of the study was to determine how vertebral bone density varied by age and race in prepubertal and pubertal girls. That purpose was part of a larger issue: to prevent osteoporosis in older women by understanding the process of maximal acquisition of bone when it occurs, during puberty, among European-Americans (who are at high risk to develop osteoporosis) and African-Americans (who are not at high risk). The method was quantitative CT scan applied to the first through third lumbar vertebrae. The researchers reported that their machine and method gave a local dose of 100 mrem radiation, and no gonadal exposure. No mention was made of the dose from the routine localization or scout X ray.

Pittard et al. conducted a study of newborns who at delivery had gestational ages from 29 (very low birth weight, very premature) to 40 weeks (normal age at delivery).[9] The premature and term newborns were otherwise normal. The purpose was to do "intrauterine" research about fetal bone acquisition by studying newly born premature infants, as shown by the following quotations: "Previous reports using photon absorptiometry have produced *intrauterine* values for both BMC [bone mineral content] and BW [bone width]"; "With the data collected at birth, an *intrauterine* curve of bone mineralization (for both BMC and BW) throughout *the last trimester of gestation* was constructed (Figs 1 and 2)." (Italics added.) The article

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made no claim that there was any clinical problem related to bone mineralization in these term and premature newborns, nor that the study was of vital importance to any clinical problem. The 3mm-wide single photon absorptiometry was applied to the distal third of the right radius. Five scans were taken per session, and 3 sessions were done at 2 days, 8 weeks, and 16 weeks after delivery. (Thus, total radiation was 30-300 mrem to the local site.)

Finally, research by Namgung and coworkers involved single photon absorption in 55 "healthy newborns less than 3 days of age."[10] The purpose of the study was to determine if bone mineral content at birth was lower in winter-born infants than in summer-born, due to lower vitamin D and BMC among mothers in winter as reported by other research. The article did not claim any medical condition or disorder in these infants or relevance to their clinical care. The study was basic science, the effect of seasonal sunlight on fetal BMC physiology. Single photon absorptiometry was applied to the distal third of the radius, with at least three scans for each newborn. (Total radiation to the local site was 6 to 60 mrem.)

The researchers in all three studies obtained parental permission and their IRBs had approved the studies. On the basis of the published information (the articles may have omitted aspects of the protocol critical to the IRBs' assessments) how ought we to evaluate these studies in relation to our initial three questions?

Greater than Minimal Risk

The mandate of IRBs is to protect the rights, health, and welfare of research subjects. When considering proposed research involving children, IRBs must assess the amount of risk to the subjects of the intervention, and benefits and other burdens of participation. The IRB must then judge if the research should be approved, applying stricter standards than to research involving adults, because children are more vulnerable in terms of health, welfare, and rights.

Subpart D, "Additional DHHS Protections for Children Involved as Subjects in Research," of 45 CFR 46 gives the standards that IRBs must use. It is based on recommendations made by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[11] Subpart D defines four categories of research with children using answers to three questions the IRBs must ask in sequence. It lists the categories in order of increasing need to justify the research, as outlined in figure 1.

To understand the regulations' concept of "greater than minimal risk," one has to understand whether the concept is absolute or relative. "Greater than minimal risk" is relative in one aspect. DHHS had published for public comment an absolute definition of minimal risk that was tied to the risk encountered in the daily life of "healthy individuals." Following public comments, DHHS tied the definition to the risks encountered in the daily life or routine physical or psychological examinations or tests *of the subjects*.[12] The distinction is clearest when discussing "a minor increase over minimal risk": bone marrow aspirations for research purposes might be only "a minor increase" to an older child with leukemia who has had many, but would be more than a minor increase to a child of same age who has had none.[13] Thus, the concept is relative to the risks likely to be experienced by the research subjects themselves.

In section 46.404, "greater than minimal risk" is a *threshold* to provide more conditions or review. Section 46.404 asks IRBs to judge if the research is greater than minimal risk in any way. The section does not permit IRBs to keep the protocol under the 46.404 threshold if risk is only trivially greater than minimal. (To permit IRBs to do that, 46.404 would have included the phrase "a minor increase over minimal risk." IRBs are supposed to judge the degree of increase for those protocols reaching section 46.406.) This threshold, to move a protocol from the 46.404 category to a higher one, is absolute or categorical. "Greater than minimal risk" in 46.404 means "greater *in any amount or degree*," its meaning in layperson's English as well.

Is Radiation Greater than Minimal Risk to Children?

IRBs must assess risk—that is, the probability and magnitude of harm or discomfort.[14] As Richardson notes:

Figure 1. IRB Assessment of Risk Categories for Research with Children.

Answers			Require		45 CFR 46
Greater than minimal risk?	Directly benefits subject?	Meets 4 other requirements?*	Permission by	Other requirements and conditions	§
NO	—	—	1 parent	assent of child subjects	404
yes	YES	—	1 parent	risk-benefit ratio is as favorable as any available alternative approach *and* assent of child subjects	405
yes	no	YES (All 4 met)	both parents	assent of child subjects	406
yes	no	no (1 or more not met)	both parents	project will understand, alleviate, or prevent serious problem of children *and* approval by local IRB and DHHS-chosen panel of experts *and* assent of child subjects	407

* The risk is only a minor increase over minimal; *and* subjects must have the disorder of research; *and* the research is of vital importance for the understanding or amelioration of that disorder; *and* the research procedures are similar to the

> Age is the critical factor in determining radiation risk. Proliferating cells are more susceptible to the induction of cancer, and it is during fetal development and childhood that intense tissue generation and differentiation takes place.[15]

At the time of the IRB review, what was known about the risk of radiation to the subjects of the research in the articles?

One group of subjects was premature newborns. It was known that intrauterine whole-fetus radiation due to diagnostic, pregnancy-related X rays caused a measurably increased rate of cancer in childhood, with a relative risk of about 2 and an absolute increase of about 1.2 cancer *cases* per 10,000.[16,17] There was no plausible biological reason to believe that the risk of radiation to a premature newborn is any less than to a fetus of the same gestational age. The other subjects were newborns and young children. Federal (FDA) regulations were that, "[f]or research subjects under 18 years of age, the limits shall not exceed 10 percent of those listed for adults."[3] (The FDA's limits for infants and children were more conservative than for adults for at least two reasons. First, infants and children have greater susceptibility to radiation damage. Second, the yearly risk of developing radiation-caused cancer does not decrease to zero following many years post-exposure, but remains finite; that is, the total, cumulative lifetime risk to develop radiation-caused cancer increases the longer one lives. Thus, the longer life expectancy of infants and children puts them at greater lifetime risk to develop radiation-caused cancer than adults, irrespective of greater sensitivity.)

It has recently been determined that the risk is greater than previously estimated, due to revised estimates of the radiation dose received by the survivors at Hiroshima and Nagasaki and to a longer follow-up of survivors for excess cancers.[1,18] Intrauterine exposure of radiation from the atomic bombs in Japan caused an increased rate of all cancers, with the incidence increasing as dose increased.[19] For 100 mrem exposure to the whole body at 5 or 15 years of age, about 1.4 excess cancer *deaths* per 10,000 people would occur.[1(p. 175)]

Some may argue that because the radiation used in the articles was trivial in relation to background radiation the subjects experience, it was not "greater than minimal risk." I disagree. First, the choice of the comparison—usually one year's background—is arbitrary. The choice could just as well be background for the duration of the exam. (The examinations in the articles lasted no more than 30 minutes, during which .006 mrem of background radiation would have been absorbed.) Second, the purpose of the comparison to yearly background is to communicate the relative amount of the radiation, not to argue that the added radiation has no risk. Third, if the research-added dose is 30 mrem to a target site, the risk from 125 mrem total to that site is 30 percent greater than the minimal risk from *whole-body* background radiation that year (or 325 mrem, 10% greater than the 295 mrem total of background including average radon dose to the lung).

Research radiation is additive to the background; the total is greater than only background. Thus, the total risk for adverse effects due to research radiation is greater than the risk experienced without the research. In an article published shortly after the National Commission's report *Research Involving Children* was released, Albert Jonsen, a member of the commission, supported this interpretation:

> "Minor increase" over minimal risk refers to risks of harm or discomforts greater in probability and magnitude than those encountered in the normal life of children but that pose no significant threat to the child's well-being. Thus, a biopsy, a spinal tap, or *the dose of an acceptable level of a radioisotope*, while surpassing the risks of daily life, are unlikely to cause any serious harm.[20] (Italics added.)

Dr. Jonsen understood that the risk of additional radiation, even if only a minor increase over minimal, moved the research to a more stringent category than 46.404. This interpretation is similar to the commonsense lay meaning of risk of radiation. Adding research radiation to background increases the total radiation and hence increases the chance for adverse effects.

How could IRBs consider radiation added to background as not presenting a risk additional to that presented by background, and thus in total greater than minimal risk? Another IRB's experience may help. It reported about a protocol involving two CT scans of the upper arm of young adult women of no benefit to the subjects:

> [The IRB had difficulty in] evaluating the risk of X-rays. . . . Some individuals are highly concerned about exposure to X-rays; others are willing to accept higher levels of exposure. *Familiarity may breed contempt. X-rays are accepted as routine procedures within many areas of health care.*[21] (Italics added.)

This article has two implications. First, some medical professionals and researchers may be too familiar with radiation, and thus ignore true risks. Second, the protocol would be even more problematic if the subjects had been young children or newborns. Their radiation risk is greater, they cannot give informed consent, and they have special protection by regulation.

Healthy Children in Greater than Minimal Risk Research

Research involving children that presents "greater than minimal risk" can be approved by the local IRB alone only under 46.405 or 46.406. The procedure or intervention that presents greater than minimal risk must *itself* either likely benefit directly each individual child subject (46.405), or likely yield generalizable knowledge about the "subject's disorder or condition" (46.406). Thus, approval under 46.406 requires that the children subjects have a "disorder or condition."

The research reported involved healthy children; some were healthy young children, others healthy term newborns, and others premature newborns without medical problems. Because the children were healthy, they could receive no direct benefit from the procedure. Thus, 46.405 could not apply. Did 46.406 apply, i.e., did they have a "disorder or condition"? Subpart D does not define "disorder or condition," but the comments in the proposed rule-making do make clear what is intended:

> [Greater than minimal risk research without direct benefit] must be related to the disorder or condition affecting those subjects who are involved. Such research *cannot*, by its very nature, *be conducted on normal subjects*. [The] limited circumstances [that permit approval under 46.406] are commensurability of experience, likelihood of yielding generalizable knowledge about the subject's disorder, and importance of that knowledge for understanding or

treating such disorder.[22] (Italics added.)

The National Commission also understood that "disorder or condition" excluded healthy children.[11(pp.145-54)]

Subpart D's prohibition of research that entails greater than minimal risk from being done on healthy children "makes[s] it difficult to develop normal control data for examinations and other procedures"[13] such as test validation, and placebo-controlled trials with invasive placebos or evaluation measures.[23] Difficult, but not always impossible; research should use "procedures already being performed on the subjects for diagnostic or treatment purposes."[24] For example, an earlier study by Gilsanz and colleagues determined bone density of normal controls who were "previously healthy subjects (age 2 to 21 years) undergoing CT examination . . . because of acute abdominal trauma."[25]

Some may argue that, in spite of the quotation from the *Federal Register*, "commensurability" permits healthy children to be included in 46.406. The argument would be that the X rays in the articles were commensurate with the risks healthy children experience in daily life from dental X rays, as research blood draws of healthy children are commensurate with their frequent experience of draws. I disagree that research radiation is equivalent to research blood draws. Blood drawn is a temporary loss and replenished; cancer from radiation is rare but permanent. The pain and suffering of blood draws are commensurate with the minor pain and suffering experienced in life in general, and are as temporary; the pain and suffering of radiation's effects can be severe. The few children who in fact have severe pain and suffering with blood draws can object, i.e., demonstrate their dissent; radiation is painless at the time of delivery.

Similarly, the argument that research radiation in healthy children is commensurate with screening dental X rays in clinical care fails to distinguish between injurious and minor harms. The harm of needlesticks is so small that one need not justify it by appeal to clinical benefits. However, dental X rays may cause benign meningiomas and parotid gland cancers in adults, and malignant and benign brain tumors in older children.[26-28]

The harm of dental X rays is actively debated, and *is justified only by the X rays' clinical benefit*. To argue that dental X rays justify research radiation in healthy children is to argue that research that forces healthy children to fall off bikes would be justified under 46.406 because most children experience bike falls.

Others may argue that prematurity itself is a "condition" and thus that the second study met the regulations. I disagree. First, the risks were not commensurate with tests experienced by the subjects, because *healthy* premature infants are not routinely X-rayed. Second, the risk of radiation is highest for the fetus and hence the premature infant. Third, subjects included healthy term newborns without any disorder or condition. Fourth, 46.406 requires that the research be "of vital importance," but the article did not claim such importance.

Once again, the intended meaning of the regulations is also the meaning in lay English. The term "disorder or condition" does not include healthy children; research involving them cannot be approved under 46.406 if it is greater than minimal risk.

IRBs in Society

In summary, only 46.405, 46.406, and 46.407 could apply to the research reported in these three articles, because "greater than minimal risk" is a categorical threshold in 46.404 and the research radiation was greater than minimal risk. Neither 46.405 nor 46.406 could apply, because the subjects were healthy children. Thus, the studies could be approved only under 46.407, that is, by a special panel of experts chosen by the Secretary of Health and Human Services. None of the articles claimed such approval.

These articles suggest that some IRBs may interpret the regulations differently from what was intended by the National Commission and the regulations themselves, and from the meaning in lay English. If so, such interpretations show a serious discordance of values between some IRBs and researchers and the National Commission and lay public. They may also show a serious discordance between how some IRBs fulfill their responsibilities and how the National Commission and lay public expected them to fulfill those responsibilities.

After three decades of revelations of research run amok, from the Jewish Chronic Disease Hospital to Tuskegee, matters were put to rest in the late 1970s. The National Commission and the regulations were in effect a social compact with the research community: "if you do your research within these rules, then society will not interfere with your studies."

Some may believe that Subpart D restricts research too much. (For instance, Subpart D does not reflect that the risk of radiation varies, from high for the fetus and premature infant to low for the older adolescent, or that the ability of legal minors to understand and assent improves as they grow older. Nor does Subpart D reflect what some researchers believe, that the radiation in some of these articles was only a "trivial" or "negligible" amount above background.) If so, the solution is not to ignore or misinterpret the regulations and thus override the compact. For any protocol not approvable under 46.404, 46.405, or 46.406, a short term solution is 46.407—the procedure to review such research at the federal level. A longer term solution is extended public discussion about revising the regulations themselves.

Overriding that compact may put the research endeavor at risk. Worse, however, it may put vulnerable child research subjects at risk.

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Does Radiation Research in Healthy Children Pose Greater Than Minimal Risk?

William J. Freeman reviewed three studies where X rays were taken of healthy children as part of IRB approved research studies ("Research with Radiation and Healthy Children: Greater than Minimal Risk," this issue). He concluded that using X rays should not be approved for research in healthy children because it represents greater than minimal risk. In one of the studies cited by Dr. Freeman, which was approved by our IRB, Gilsanz performed quantitative computerized tomography (QCT) on 150 children, aged 2 to 20 years (estimated radiation dose approximately one chest X ray).[1]

Dr. Freeman stated that the studies did not fit the criteria of 45 CFR 46.404, 46.405, or 46.406, but "could be approved only under 46.407, by a special panel of experts chosen by the secretary of the HHS." However, under 46.407, the regulations indicate that research may be approvable if

> (a) the IRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children; *and*
>
> (b) the Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment has determined either that the research satisfies the conditions of 46.404, 46.405 or 46.406; *or* that the research presents a reasonable opportunity to further the understanding of a serious problem affecting the health or welfare of children.

Gilsanz's study was designed to further the understanding of the "differences in the prevalence of osteoporosis and the incidence of vertebral fractures" among white and black *women*. His research did not intend to further the "understanding of a serious problem affecting the health or welfare of *children*." Based on these arguments, the study could not be approved under 46.404, 46.405, 46.406, *or* 46.407.

Our IRB determined that Gilsanz's study proposed research that was designed to develop or contribute to generalizable knowledge regarding osteoporosis and so could be approved under 46.102(d). His study resulted in information that may help to explain why certain groups of women are at higher risk for osteoporosis than others, and may add to the understanding of the mechanisms of osteoporosis in women.

Our IRB also determined that the research involved no greater than minimal risk, which is defined in 46.102(i) as "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." Many children can reasonably expect to receive an X ray in the course of their normal medical examinations during childhood. Although the risk of radiation exposure from one QCT scan is unknown,[2,3] it is believed to be small.[2,4,5] Our IRB thus concluded that the protocol was in keeping with 46.404.

Freeman argues that "minimal risk" can be understood by its meaning in lay person's English. However, Janosky and Starfield found wide disagreement among chairs of pediatric departments on what constitutes "minimal risk" in research on children.[6] IRBs across the country cannot be expected to, and do not, assess risks to common protocols in a uniform manner with uniform results. If one IRB approves a study that another might reject, it does not necessarily imply that the first IRB was wrong and the second right. For ex-