FEATURE ARTICLE

Pediatric Magnetic Resonance Research and the Minimal-Risk Standard
Matthias H. Schmidt, Jennifer Marshall, Jocelyn Downie, and Michael R. Hadsks

The Merits of Procedure-Level Risk-Benefit Assessment
Anna E. Westra and Inez D. de Beaufort

Researcher Experiences with IRBs: A Survey of Members of the American College of Neuropsychopharmacology
Katherine L. Wisner, Robert R. Conley, Stephan F. Taylor, Thomas Kosten, Mark Hyman Rapaport, and Lawrence S. Brown

LETTER

Pediatric Magnetic Resonance Imaging (MRI) research combines powerful electromagnetic forces and sophisticated electronic technology to provide privileged glimpses into the human body. These features make the field a proving ground for ethical debate on research risks. They also create practical challenges for research ethics boards (REBs) engaged in the review of protocols and charged with the task of ensuring the safety and well-being of participants. Determining the level of risk associated with any given protocol can be one of the most difficult tasks. Thus, it is not surprising that REBs’ risk assessment involving MRI studies has been inconsistent, ranging from minimal to high risk.1

While an accurate assessment of risk is always important, it is especially so in pediatric research. We have previously examined the risks associated with pediatric magnetic resonance neuroimaging research.2 Recognizing the pivotal nature of the minimal-risk standard, we now set out to determine under what circumstances pediatric magnetic resonance imaging research does or does not meet this standard. We did not address the issue of whether the physical, psychological, and other risks associated with incidental findings3 in MRI research exceed the minimal-risk standard. The complexity of this issue warrants thorough treatment in a separate paper.

The Minimal-Risk Standard

Although our primary emphasis is on the risk analysis of Canadian REBs, we considered the definitions of minimal risk offered by both the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS)4 and the regulations of the United States Department of Health and Human Services governing research with humans.5 Both definitions compare the risks that individuals would face by participating in research to the risks they normally accept in their day-to-day lives. Both definitions consider the probability as well as the magnitude of potential harm. However, the two definitions differ significantly in terms of their perspectives. Minimal risk is defined in the TCPS as “research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by participants in those aspects of their everyday life that related to the research.”6 According to

---


the TCPS, healthy children cannot be enrolled in studies that involve greater-than-minimal risk; pediatric patients may be enrolled in therapeu
tic studies that involve greater-
than-minimal risk, but such studies are not eligible for delegated review, and waiver of consent is not permis-
sible.7

The TCPS asks REBs to “at-
tempt to assess the harm from the perspective of the participants to the extent possible.”8 It also notes that REBs’ risk assessment should be informed by an understanding of the role of the culture, values, and beliefs of the populations to be studied.9 The TCPS recognizes that there are limits to REBs’ ability to assess harm from the participants’ perspective; thus, the TCPS tacitly accepts that members of REBs may be required to impose their own experiences and values on the process. Another interesting stipulation of the TCPS is that comparators drawn from everyday life should “relate to the research.” This stipulation challenges REBs to identify routine activities that sufficiently resemble the research procedures to serve as meaningful comparators.

According to the U.S. regula-
tions, 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.”10 This definition simplifies the analysis by removing the subjective viewpoints of REBs and of potential participants from consideration. Rather than insisting on comparators from everyday life that resemble research procedures, it allows REBs to consider also “routine physical or psychological examinations or tests.” Such comparators are easier to liken to biomedical and neuropsychological research procedures.

In our deliberations, we did not consider the specific socioeconomic, cultural, or religious context within which each and every potential participant might weigh the risks of research against those of everyday life. We also did not consider the special situation of pediatric patients, whose daily lives might routinely involve diagnostic MRI or other medical interventions. Although REBs operating under the TCPS need to consider this additional layer of complexity, we felt that our analysis required the generic perspective of the typical, healthy child as a practical starting point. Rather than focusing on subjective risk perception, we quantified risk, using actuarial and epidemiological data. In making comparisons between everyday risks and research risks, we attempted to identify situations encountered commonly by typical, healthy children and resembling essential aspects of MRI research. In so doing, we hoped to make our deliberations useful to REBs that operate under the TCPS and that cannot, therefore, use “routine physical or psychological examinations or tests” in their application of the minimal-risk standard.

Available Guidelines

In Canada and the United States, federal guidelines are available to REBs faced with reviewing research protocols involving pediatric magnetic resonance imaging. Canadian guidelines include Safety Code 26, the Therapeutic Products Directorate under Health Canada, and the Panel on Research Ethics under the three national funding agencies (Canadian Institutes of Health Research, Social Sciences and Humanities Research Council, and Natural Sciences and Engineering Research Council). In the United States, the Food and Drug Administration (FDA) has established criteria for significant risk with respect to static magnetic field strength, specific absorption rate, rate of change of magnetic gradients, and sound pressure levels.11 It should be noted that the term “nonsignificant” risk is often used in the United States. However, nonsignificant risk and minimal risk are not equivalent terms. It should also be noted that “The risk determination should be based on the proposed use of a de-
vice in an investigation, and not on the device alone.”12 Thus, an REB might determine that research with a nonsignificant risk device exceeds the minimal-risk standard due to other aspects of the protocol. The U.S. Office for Human Research Protections (OHRP) has compiled a list of categories of research that may be eligible for expedited review, including MRI research that does not involve sedation or general an-
esthesia and does not exceed minimal risk.13 However, OHRP notes that “The activities listed should not be deemed to be of minimal risk simply because they are included on this list.”14

Nongovernmental agencies such as the Canadian Association of Radiologists15 and the American College of Radiology16 may provide useful information. These agencies are generally not concerned with risk classification or stratification but can provide important insights into the kinds of hazards that need to be considered, as well as suggesti

gions for best practices and risk management. However, these sources lack specific information pertinent to children. Such information often has to be compiled from the primary literature.18 Also, existing guidelines focus on physical risks of MRI and do not distinguish between clinical and research MRI practices. It should be noted that clinical and research MRI practices can differ in a number of noteworthy respects (e.g., risk-benefit ratio, safety and screening procedures, review processes). Additional risks, above and beyond the risks associated with MRI per se, also need to be considered if a protocol calls for the administration of drugs for
intravenous contrast enhancement or sedation.\textsuperscript{19}

**Risk of Physical Harm**

Physical harms of MRI relate to the effects of strong magnetic forces, induction of electrical currents, and deposition of radiofrequency energy. They include physical injury due to the "missile effect," displacement and/or malfunctioning of medical devices, and skin burns.\textsuperscript{20} Without adequate ventilation, asphyxiation can occur as a consequence of rapid cryogen release in the event of a "quench."\textsuperscript{21} Information about the magnitude of these risks can be gleaned from the FDA's Manufacturer and User Facility Device Experience (MAUDE) database. Reporting is voluntary, and it is estimated that only 1–10% of nonfatal injuries are reported.\textsuperscript{22} A review of the MAUDE database from 1995 to 2005 revealed 389 accidents: 70% due to burns, 10% due to projectile collisions, 10% due to implant damage, 5% due to acoustic injuries, 4% due to fires, and 2% due to internal heating.\textsuperscript{23} There were nine fatalities: three due to pacemaker failure, two due to insulin pump failure, and the remaining four due to implant disturbances, collision with a missile, and asphyxiation during installation.\textsuperscript{24} The number of MRI examinations performed each year has been increasing steadily at a rate of 5% per year, and 27.5 million MRI examinations were performed in the United States in 2007.\textsuperscript{25} Assuming that approximately 22.5 million examinations were performed in the United States from 1995 to 2005 and that the actual frequency of nonfatal injuries is 100 times the reported frequency, the risk of injury from all causes is approximately 17 per 100,000 examinations. The risk of death is four per 100 million examinations.

Do we allow typical, healthy children to enter situations or environments associated with a heightened risk of injury and death in daily life? We encourage children to participate regularly in sports, the "leading cause of the pediatric injury burden."\textsuperscript{26} A systematic review of studies on injury rates in children under the age of 16 engaging in a wide range of sports and recreational activities found injury rates ranging from a minimum of four per 100,000 hours of participation in soccer to a maximum of 12,730 per 100,000 hours of participation in ice hockey.\textsuperscript{27} Assuming that the duration of an MRI examination is on the order of an hour, the risk of injury associated with an MRI examination (1.7 per 100,000) clearly falls within the lower end of this range. Many children are also regularly passengers in vehicles, which poses "the highest risk of mortality ordinarily encountered by healthy children."\textsuperscript{28} This risk ranges from six deaths per 100 million car trips for children aged 1–4 years and younger to 40 per 100 million for children aged 15–19 years.\textsuperscript{29} Thus, the risk of death from an MRI examination (four per 100 million) is clearly less than the risk of death from a car trip. MRI can therefore meet the minimal-risk standard from the point of view of physical harm. This, of course, presumes the use of known effective safety procedures. Just as we strive constantly to improve the safety of participating in sports and traveling in vehicles, it behooves us to continue to improve the safety profile of MRI. This can be a special challenge in the pediatric MRI environment, and specific risk management strategies in this special setting should be developed and used.\textsuperscript{30}

**Risk of Psychological Harm**

Participants in MRI research may experience psychological harm due to the need for prolonged immobility and confinement within the narrow, noisy bore of the scanner. In a study of 80 adults without prior history of claustrophobia, 25% reported at least moderate anxiety, and three were unable to complete their MRI scan.\textsuperscript{31} Children may actually be less vulnerable than adults. In a survey of children aged 10–18 years who were being scanned for a variety of clinical indications, 12% reported that they felt disturbed by the confined space, and 16% reported that they felt bothered by the noise.\textsuperscript{32} Only 1.2% of children were unable to complete their MRI scan due to claustrophobia.\textsuperscript{33} Another study, focusing on pediatric cancer patients, reported similar levels of discomfort with MRI scans.\textsuperscript{34}

Do typical, healthy children risk experiencing intense fear in daily life? A "top 10 list" of fear-inducing stimuli, based on the reports of parents of 160 children aged 4–12 years, includes: darkness (50%), spiders (49%), thunderstorms (46%), blood (28%), doctors (23%), dentists (19%), dogs (14%), and birds, heights, and elevators (each 8%).\textsuperscript{35} These stimuli are ubiquitous. Childhood fears are experienced intensely, based on interviews with children\textsuperscript{36} and parents.\textsuperscript{37} Indeed, in a sample of 290 school children aged 8–13, 49% of children reported fears associated with subclinical manifestations of anxiety disorders, while 22.8% met the full criteria of an anxiety disorder.\textsuperscript{38} The risk of some distress associated with MRI examinations (12–16%) is not dissimilar, and the risk of experiencing
full-blown symptoms of claustrophobia in the MRI scanner (1.2%) is relatively small. MRI can therefore meet the minimal-risk standard from the point of view of psychological harm. However, it should be noted that children who are aware of a phobia will make an effort to avoid the object or situation that triggers their fear. Likewise, children with known claustrophobia must not be included in MRI research. Some have advocated for use of claustrophobia questionnaires. These should be administered to children prior to participation in MRI research. Such questionnaires may not identify every child with latent claustrophobia, since most children will not have had prior experience of an environment as confining as an MRI scanner. Therefore, researchers must also continue to be alert to any unease shown by participants, and they must be prepared to terminate a scanning session at the first sign of claustrophobia.

Risks Associated with Intravenous Contrast Enhancement

For some kinds of MRI examination, it is necessary or desirable to inject a contrast-enhancing agent intravenously. Most children find venipuncture both painful and frightening. Indeed, fully 33% of pediatric oncology patients found venipuncture to be the most distressing aspect of their MRI scan. MRI contrast-enhancing agents can also be associated with symptoms such as fever, headache, flushing, rash, itching, nausea, vomiting, diarrhea, mild shortness of breath, mild slowing of the heart, and transient elevation of liver enzymes. The frequency of such symptoms ranged from 4-6% in children in 11 studies that used three different contrast agents. Rarely, MRI contrast-enhancing agents have much more serious side effects. These include nephrogenic systemic fibrosis (NSF), a potentially painful, crippling, and even fatal multisystem illness that can occur in persons with renal failure. The true risk of NSF is currently unknown but is estimated, based on limited available evidence, to lie between 1.5 and 3% in patients with renal failure. Serious allergic reactions to MRI contrast-enhancing agents can occur, including anaphylaxis. The risk of any acute allergic reaction in children has recently been reported to be 4.5 per 10,000 doses, while the risk of anaphylaxis is 7.5 per 100,000 doses.

Are typical, healthy children exposed to venipuncture, intravenous drugs, and their side effects? It would almost seem axiomatic that the answer should be “no.” However, we decided to look at MRI contrast-enhancing agents alongside vaccination because this is a comparable procedure carried out routinely in healthy children. Of course, vaccination involves no means a daily occurrence, and we recognize that this comparison strains the definition of “everyday life.” However, vaccination involves a subcutaneous or intramuscular injection. While this is technically not the same as venipuncture, the distinction is likely not significant from a child’s perspective. With varicella vaccination, local inflammation at the injection site occurs in 10-20% and rash occurs in 1-5% of children. Following measles/mumps/rubella (MMR) vaccination, parotitis occurs in 1% and malaise, fever, rash, swollen glands, stiff neck, and joint pains occur in 5% of children. Thus, the risk of local and minor systemic reactions from MRI contrast-enhancing agents (4-6%) is comparable to the risk of similar reactions following routine vaccination. The risk of anaphylaxis following MMR vaccination is 1.53 per one million doses, while the risk of anaphylaxis following any vaccination is on the order of 0.65 per one million doses. Thus, the risk of anaphylaxis from MRI contrast-enhancing agents (7.5 per 100,000 doses) is higher than the risk of anaphylaxis from vaccination. MRI with contrast enhancement therefore does not meet the minimal-risk standard.

Risks Associated with Sedation

Protocols for sedation are too varied to consider individually. Sedation can range from light to deep. Different oral and intravenous agents can be used alone or in combination. Following sedation, delayed complications include prolonged drowsiness, paradoxical hyperstimulation, gastrointestinal upset, and motor imbalance. Delayed gastrointestinal complaints may occur in 18-37%, restlessness and agitation in 23-29%, and motor imbalance in 66-85% of children. Serious hazards encountered during sedation include respiratory and cardiovascular compromise. The risk of hypoxia may be as high as 11% in children sedated with oral chloral hydrate and 17% in children sedated with intravenous pentobarbital.

Do typical, healthy children receive sedative/hypnotic medication in everyday life? The closest comparison might be over-the-counter cold medications, since these have sedating properties and may be given to typical children with minor symptoms. However, the use of such medications in infants and young children is in fact discouraged by both Health Canada and the American Association of Pediatrics. More to the point, medications used purposely for sedation are far more potent than over-the-counter medications at normal therapeutic doses. Both their therapeutic effects and their side effects fall well outside the realm of normal experience. We therefore do not think that MRI with sedation can meet the minimal-risk standard.
Conclusion

In our analysis of the minimal-risk standard in pediatric MRI research, we considered the risks of physical harm and psychological harm associated with the MRI procedure and the risks involved with the use of contrast-enhancing agents and sedation using the TCPS definition requiring consideration of risks "encountered by participants in those aspects of their everyday life that relate to the research." Regarding the physical and psychological risks that can attend the MRI procedure itself, we found that they do not exceed the minimal-risk standard, provided that all such reasonably foreseeable hazards are identified and that all reasonable steps are taken to prevent harm. However, we concluded that the risks of contrast enhancement exceeded those of the most comparable situation (vacation) encountered by typical, healthy children in everyday life. We also concluded that sedation surpassed the minimal-risk threshold, as it could not be related meaningfully to the everyday experiences of typical, healthy children. We did not draw conclusions with respect to whether the risks of incidental findings take MRI beyond minimal risk.

REBs faced with the evaluation of research protocols involving children and MRI may wish to use our discussion as a springboard for their deliberations. Assuming no sedation or contrast enhancement will be involved, REBs should consider: 1) the extent to which researchers have addressed risk management, 2) participant characteristics that might affect risk assessment, 3) aspects of the protocol that could move the study from minimal risk to greater-than-minimal risk, and 4) whether the physical, psychological, and financial risks that can attend incidental findings exceed the Canadian and U.S. minimal-risk standard. We urge researchers and REBs to collaborate in the ongoing effort to minimize the risk of harm and discomfort associated with pediatric MRI research.

Acknowledgments

The authors gratefully acknowledge the support of the Canadian Institutes for Health Research through a CIHR New Emerging Team Grant. The authors also wish to thank Liane Patterson of the NRC Canada Institute for Scientific and Technical Information for compiling MRI injury statistics and members of the Neuroethics NET for helpful discussion and insightful comments on earlier drafts of this paper.

Matthias H. Schmidt and Jennifer Marshall contributed equally to this article and share first authorship.

Matthias H. Schmidt, MD, FRCP, is Associate Professor in the Department of Radiology, Dalhousie University, Halifax, NS, Canada; Jennifer Marshall, MSc, is a PhD student in the Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada; Joecelyn Downie, LLB, LLM, SJD, is Canada Research Chair in Health Law and Policy and Professor, Faculty of Law and Medicine, Schulich School of Law, Dalhousie University, Halifax, NS, Canada; and Michael R. Hadashik, LLB, LLM, is Assistant Professor, Faculty of Law, and Faculty Member, Health Law Institute, Schulich School of Law, Dalhousie University, Halifax, NS, Canada.

References

3. Illes J, Kirschen MR, Edwards E, et al. Incidental findings in brain imaging research: What should happen when a researcher sees a potential health problem in a brain scan from a research subject? *Science* 2006;313:783-784. The authors define incidental findings as "observations of potential clinical significance unexpectedly discovered in healthy subjects or in patients recruited to ... imaging research studies and unrelated to the purpose or variables of the study," p. 783.
6. See ref. 4, TCPS 2010, Chapter 2, Section B.1.
7. See ref. 4, TCPS 2010, Articles 4.6(b) and 3.9(d); Article 2.9 and associated "Application" commentary; and Article 3.7(a).
8. See ref. 4, TCPS 2010, Chapter 2, Section B.
9. See ref. 4, TCPS 2010, Chapter 2, Section B.
10. See ref. 5, 45 CFR 46.102(d).
15. See ref. 14, OHRP 2010.
18. See ref. 5, Schmidt and Downie 2009.
19. See ref. 5, Schmidt and Downie 2009.
Misunderstanding, Period

To the Editor: We find it ironic that an article entitled "(Mis)Understanding Exploitation" ( Erik Malqvist, March-April 2011) is based on a parent misunderstanding of the position that it criticizes. Malqvist argues that the “nonexploitation” framework developed in a series of articles by Miller and Brody and by Buchanan and Miller misunderstands exploitation because the framework permits research subjects to be exposed to any level of risks as long as these risks are outweighed by benefits to others. Malqvist misreads these authors as taking the position that “excessive risks are risks that are not sufficiently outweighed by benefits to others.”

However, the articles cited by Miller and Brody and by Buchanan and Miller each make clear that subjects should not be exposed to undue or excessive risks, where the acceptable risk threshold sets a limit of reasonable risks beyond which subjects should not be exposed regardless of compensating benefits. Indeed, Malqvist quotes Miller and Brody as writing that “risks that are not compensated by medical benefits to participants should not exceed a tolerable threshold.” The author’s misreading of our position on excessive risks is puzzling; also puzzling is how this misreading survived peer review.

Howard Brody
University of Texas Medical Branch, Galveston
David Buchanan
University of Massachusetts
Franklin G. Miller
National Institutes of Health