

MINIMAL RISK IN THE TRI-COUNCIL POLICY STATEMENT

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Scenario 1: An oncology researcher approaches the Research Ethics Board (REB) office of a Canadian institution to request guidance on an REB submission. The researcher, a neurosurgeon, intends to take part in a multi-centre trial of a new agent for the treatment of the intractable and fatal condition Glioblastoma Multiforme (GBM), a brain cancer for which currently available surgical, radiographic and chemotherapeutic approaches increase mean survival times to only 12-14 months. The experimental procedure involves implanting a device to deliver existing chemotherapeutic agents in a novel fashion; this implantation would take place during the surgical excision of the tumour in open-brain surgery, a treatment option that patients with GBM almost universally accept. The researcher points to Section C.1 of the Tri-Council Policy Statement and claims that his research project needs no more than expedited review. "The patients are all going to undergo brain surgery and chemotherapy anyway; clearly the risks involved in this procedure are minimal, as they are within the risks of daily living for people with GBM for whom undergoing brain surgery is normal – and that's how the Tri-Council Policy Statement defines 'minimal risk'." A month later, another neurosurgeon at the institution approaches the REB office with a research study for the same population: his procedure specifically targets the tumour as it reappears after initial treatment, and involves stereotactic surgery, which as a neurosurgical procedure is safer than the original surgery to excise the tumour. He points to the same Section C.1 of the Tri-Council Policy Statement and argues that his research proposal should receive expedited review; after all, the procedure is even safer than the craniotomy that

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such patients have already undergone, and the disease itself carries universal extreme morbidity and, for the patients eligible for his study, a very high likelihood of death within a matter of weeks or months. Hence, relative to the condition itself and the ordinary course of its treatment, the risks of his stereotactic surgery are well below the risks such patients face in the course of their lives.

Scenario 2: *A stem cell researcher approaches the REB office with a research protocol for an experimental neurosurgical intervention for the rare (and uniformly fatal) genetic condition called Batten disease. Children would undergo stereotactic brain surgery to implant neural fetal stem cells that are expected to provide the appropriate enzymatic activity to counteract the disease. The researcher is puzzled as to the correct interpretation of the restrictions the Tri-Council Policy Statement places on risk in research with children. "The Tri-Council Policy Statement says I can only do 'non-therapeutic' research with children that exposes them to minimal risk – I looked up Section C1 on minimal risk in order to understand what this restriction in Article 2.5(c) amounts to. That section seems to suggest that what I'm doing is minimal risk, because these patients already live with significant risk. But we've never implanted fetal neural stem cells into children's brains before – or adults, for that matter. The risks are significant indeed. When I looked at the Tri-Council definition, it seems to me that perhaps we've been far too cautious about our research all along. If your REB office just consults their risks of daily living – well, these are virtually certain death within a couple of years, even with our best medical care. There are much riskier procedures that fall within that range that I can take straight to human trials without so much time-consuming pre-clinical work with animal models!"¹*

How should a Canadian REB office respond to each researcher? Should it offer expedited review to the experimental neurosurgical procedures of Scenario 1? Does reference to the guiding ethical prin-

1 The technology described (but not the conversation with the REB) is in clinical trials with children. See R.A. Martin & J.S. Robert, "Is Risky Pediatric Research Without Prospect of Direct Benefit Ever Justified?" (2007) 7:3 *American Journal of Bioethics* 12 and I. Singec *et al.*, "The Leading Edge of Stem Cell Therapeutics" (2007) 58 *Annual Review of Medicine* 313 at 322.

principle of “Minimizing Harm” (“Context of an Ethics Framework” (C)) answer the question of the researcher in Scenario 2?

What if the second research protocol were for an adult group with a disease with a similarly bleak prognosis? If an experimental intervention is acceptable at all for a paediatric population, would that same procedure therefore be eligible for expedited review in an adult population?

*Are such questions to be settled solely by reference to the standards of practice indicated in regulatory documents such as the **Tri-Council Policy Statement**?*

An assessment of the risks posed by experimental interventions to research participants is central to research ethics review. Clinical research that poses significant risks to research participants may be undertaken if it meets (among other requirements) three important constraints: 1) it must provide *some* prospect of personal benefit to the research participant and/or a good prospect of significant benefit for future patients in the form of contributing to progress towards effective treatments in the future; 2) an REB must approve the research; and 3) the participants must give their free and informed consent for participation in the research. Not all research involving human subjects exposes participants to the same level of risk, however; furthermore, not all research can meet these conditions. In recognition of this, the *Tri-Council Policy Statement for Ethical Conduct for Research Involving Humans*² is committed to the principle of proportionate ethics review. Research that poses no more than minimal risk to research participants is permitted some leniency on these requirements. It may be permissible to use expe-

2 Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998 with 2000, 2002, 2005 amendments), online: Interagency Advisory Panel on Research Ethics (PRE)

<<http://pre.ethics.gc.ca/english/policystatement/policystatement.cfm>>
[*Tri-Council Policy Statement*].

dited procedures for its review, it may be permissible to allow it to proceed in populations that do not have the capacity to understand and consent to the research (“vulnerable populations”), where parents or others acting *in loco parentis* may give authorization for the participation of their children or incapacitated adults, and it may proceed where fully free and informed consent is impracticable or methodologically impossible. Hence, under the application of Canada’s *Tri-Council Policy Statement*, the designation of a study as “minimal risk” may have significant implications for the level of scrutiny to which an REB will subject it and hence for the protection afforded by such review to research participants. Judging a study to be minimal risk may even determine whether a study is possible at all when free and informed consent of its participants is not possible.

This article considers the adequacy of the *Tri-Council Policy Statement* definition of minimal risk to demarcate appropriate dividing lines for the various purposes it serves. *The Tri-Council Policy Statement* in effect asserts, as do regulations in many other jurisdictions, that only minimal risk studies should be allowed to proceed when they are incapable of satisfying the conditions of full and informed consent for research participants, and furthermore that minimal risk studies can be excused from full REB review. We shall see that in order to maintain this, the phrase “minimal risk” must assume an artificial definition bearing little resemblance to its ordinary meaning. Significant debate concerning this point has centered on the question of whether “minimal risk” is to be understood in an absolute or relative sense. The absolute interpretation has the support of numerous review and advisory bodies, and appears to be endorsed by the courts insofar as they have ruled on the question; however, regulatory documents, including the *Tri-Council Policy Statement*, persist in asserting a relative standard. In fact, we argue, those who advocate for an absolute interpretation nonetheless maintain an understanding of clinical equipoise that is formally similar to a relative interpretation of minimal risk for an important class of research – a class that captures much of clinical research activities with vulnerable populations. The result is that “minimal risk” is in fact a term of art, and research guidelines and regulations fail to specify the true nature of the higher standard of protection they intend to extend to vulnerable populations, offering little effective guidance to researchers and REBs in carrying out their responsibility to provide heightened protection to vulnerable research participants.

1. Purposes of the Minimal Risk Threshold

The *Tri-Council Policy Statement* states that “while all research must be reviewed adequately, proportionate review is intended to reserve most intensive scrutiny, and correspondingly more protection, for the most ethically challenging research.”³ To this purpose, the concept of minimal risk acts as a sorting mechanism to distinguish research that warrants full REB scrutiny and review from research that does not:⁴ “In accordance with the principle of proportionate review, research that exposes subjects to minimal risk or less requires only a minimal review process.”⁵ Thus, minimal risk studies, under the *Tri-Council Policy Statement*, may qualify for expedited, departmental-level, or other forms of delegated review.⁶ Accordingly, we call this first use of the concept of minimal risk the *proportionate review standard*. It should be evident that such a standard needs to be relatively non-controversial in its application: a standard that requires for its application the considered judgment of an entire REB would be inappropriate as a sorting mechanism for those studies that do and those that do not need to go before an entire REB.

The standard of minimal risk also operates in the *Tri-Council Policy Statement*, as it does in many ethics guidelines, as a threshold for the level of risk allowable for so-called “non-therapeutic” research involving vulnerable persons, such as children or decisionally incompetent adults.⁷ It is forbidden to enrol members of these populations in research projects that expose them to more than “minimal risk without the potential for direct benefits for them.”⁸ United States (U.S.) regulations allow for a “minor increase over minimal risk” in the case of non-therapeutic research with children,⁹ while the *Tri-Council Policy Statement* is more restrictive. U.S. regulations also al-

3 *Ibid.* at s.1(D1).

4 *Ibid.* at s.1(C1).

5 *Ibid.* at s.1(F).

6 *Ibid.* at s.1(D1).

7 U.S. regulations also name pregnant women and prisoners as vulnerable populations. See United States Department of Health and Human Services, *Protections of Human Subjects*, 45 C.F.R. 46 Subparts B & C (revised 23 June 2005), online: National Institutes of Health-Office of Human Subjects Research <<http://www.nihtraining.com/ohrsite/guidelines/45cfr46.html>> [*Protections of Human Subjects*].

8 *Supra* note 2 at Art.2.5(c).

9 *Supra* note 7 at §46.406(a).

low for non-therapeutic research that poses a greater than minor increase over minimal risk, with heightened standards for review and transparency.¹⁰ Such “Section 407” research requires approval by the Secretary of the Department of Health and Human Services, after review by an expert panel and publication of notice in the Federal Register.¹¹ Whether research is or is not permissible for such populations will then depend heavily on how minimal risk is defined, as well as how the lines are drawn between “therapeutic” and “non-therapeutic” research.

The ethical solution to the dilemma of experimenting on children (as one example of a vulnerable group) was once resolved in favor of protecting them from any exposure to risk in experimentation. This solution was found unsatisfactory: no risk is avoided if the products of medical research are eventually applied to them in clinical practice, with no prior evidence of safety and efficacy for that population, or if research is simply not carried out on diseases of childhood. The creation of a category of ethically acceptable research with the vulnerable is a response to this problem. Tauer notes that in the past “children have been described as ‘therapeutic orphans’ because of the absence of adequate research on the treatment of children, especially the inadequate testing of drugs and biologics used in the treatment of children.”¹² In this context, the category of “minimal risk” is intended as a way of ensuring special protections to groups whose interests are represented by third parties,¹³ while preserving for these groups the possibility of fair

10 *Ibid.* at §46.407.

11 D. Wendler & S. Varma, “Minimal Risk in Pediatric Research” (2006) 149 *Journal of Pediatrics* 855 at 857; L.M. Kopelman & T.F. Murphy, “Ethical Concerns about Federal Approval of Risky Pediatric Studies” (2004) 113:6 *Pediatrics* 1783.

12 C.A. Tauer, “Central Ethical Dilemmas in Research Involving Children” (2002) 9:3 *Accountability in Research* 127 at 127.

13 *Supra* note 2 at Art.2.5(b), 2.5(c). See a discussion of this relationship to the scope of discretion for parental decision-makers in B. Dickens, “The Legal Challenge of Health Research Involving Children” (1998) 6 *Health Law Journal* 131; F. Baylis, J. Downie & N. Kenny, “Children and Decisionmaking in Health Research” (1999) 21:4 *IRB* 5; and F. Baylis & J. Downie, “An Ethical and Criminal Law Framework for Research Involving Children in Canada” (1993) 1 *Health Law Journal* 39 [“An Ethical and Criminal Law Framework”]. We will return to this below.

benefit from medical research.¹⁴ Although the assent of the vulnerable party is required for most of this research along with the authorization of the guardian, the guardian bears the bulk of the responsibility for understanding the harm-benefit trade-off in research participation. Hence this standard for acceptable risk bears some relationship to what guardians may or may not choose or authorize for their children or for incapacitated adults for whom they make decisions. We call this second use of the concept of minimal risk the *limit on research with the vulnerable*.

Sometimes it is not characteristics of the research population (their age or cognitive function, for example) that make fully free and informed consent difficult or impossible, but characteristics of the research study itself. There is, for instance, research in social psychology where revealing the true aim of the study would be detrimental to getting valid or reliable results; such information is deliberately withheld from research participants until debriefing at the end of the study. Milgram's famous experiment could only test obedience to authority by concealing the fact that such obedience was its object of study.¹⁵ In some situations, it is claimed that consent is so impractical that the choice is between waiving the requirement of consent and not doing the research, as with large databases¹⁶ or banked tissue samples.¹⁷ There is also clinical research that falls under this rule: research in emergency medicine may frequently involve scenarios where not only participant consent but also substitute decision-maker authorization is impossible.¹⁸ *Tri-Council Policy Statement* Article 2.1(c.i) stipulates that waivers or alterations to the requirements of consent are permitted only for studies that are minimal risk or less. Hence the designation of a study as minimal risk opens up the possibility that such a study may, where necessary, be permitted to proceed without fully free and informed consent. As in the case of the use of mini-

14 *Supra* note 2 at Art.5.1, 5.3. See generally H. Shirkey, "Editorial Comment: Therapeutic Orphans" (1968) 72:1 *Journal of Pediatrics* 119.

15 S. Milgram, "Behavioural Study of Obedience" (1963) 67 *Journal of Abnormal Psychology* 371.

16 G.E. Simon *et al.*, "Large Medical Databases, Population-Based Research, and Patient Confidentiality" (2000) 157:11 *American Journal of Psychiatry* 1731.

17 L.E. Wolf, "Untapped Potential: IRB Guidance for the Ethical Research Use of Stored Biological Materials" (2004) 26:4 *IRB* 1; K.S. Azarow *et al.*, "Ethical Use of Tissue Samples in Genetic Research" (2003) 168:6 *Military Medicine* 437.

18 M.C. Morris & R.M. Nelson, "Randomized, Controlled Trials as Minimal Risk: An Ethical Analysis" (2007) 35:3 *Critical Care Medicine* 940.

mal risk as a limit on research with the vulnerable, this use of the concept of “minimal risk” is intended to enable socially beneficial research that could not otherwise take place if the requirement for fully free and informed consent were considered an absolute. We call this third use of the concept of minimal risk the *limit on unconsented research*.¹⁹

Both the limit on research with the vulnerable and the limit on unconsented research as applied to emergency research depend for their application on the distinction between “therapeutic” and “non-therapeutic” research. This distinction is intended to separate research that tests a clinical intervention thought or hoped to be therapeutically efficacious for the individual research participant who receives the intervention, from research that has other aims or likely outcomes: e.g., testing of a diagnostic procedure, establishing safe dosage levels in a Phase I trial, or gathering basic knowledge about the natural course of a given condition. This is not, strictly speaking, a distinction between two different types of research: according to the “component analysis” approach to the assessment of research risk, a study

19 It may also be the case that “minimal risk” is intended to perform a fourth sorting: to divide social science and humanities research from biomedical research and distinguish appropriate standards for review that would protect academic freedom and avoid imposing an inappropriate biomedical paradigm for the former. Subsequent review processes have identified it as an inadequate tool for such a purpose. The Social Sciences and Humanities Research Ethics Special Working Committee (SSHWC) has argued that where minimal risk is the exception rather than the rule (i.e. in biomedical research), the concept may be appropriate for sorting studies that may receive expedited review from those that may not, but that where minimal risk is the ordinary course of affairs (as is the case, SSHWC claims, in social sciences and humanities research), a concept of “identifiable harm” would be more appropriate to distinguish research for which the REB may review and require changes from the majority of social sciences and humanities research that should be exempt from such review and revision. Social Sciences and Humanities Research Ethics Special Working Committee, *Giving Voice to the Spectrum. Report of the Social Sciences and Humanities Research Ethics Special Working Committee to the Interagency Advisory Panel on Research Ethics* (Ottawa: Interagency Advisory Panel and Secretariat on Research Ethics, June 2004), online: <<http://pre.ethics.gc.ca/english/workgroups/sshwc/SSHWCVoiceReportJune2004.pdf>> at 23. Burgess has recently argued that such an understanding would devalue the importance of social risks, such as those attached to HIV testing. M.M. Burgess, “Proposing Modesty for Informed Consent” (2007) 65 *Social Science & Medicine* 2284.

is typically “therapeutic” but may contain “non-therapeutic” components.²⁰ According to this approach, the risks inherent to research are balanced in relation to benefit in two distinct ways. Firstly, the “therapeutic component”²¹ of a research study (the experimental agent and all that belongs to its administration) must be justified by its standing in clinical equipoise with the current standard treatment.²² That is, for the experimental intervention to be suitable for clinical trial, it must (according to the concept of equipoise proposed by Fried²³ and developed by Freedman²⁴) offer at least as good a harm-benefit trade-off as that offered by the current standard treatment, if there is one, or the course of the untreated disease, if there is none. Secondly, the “research component” of the study involves extra testing to collect data for the purposes of establishing the study’s scientific hypothesis with validity – this may be as minor as filling out a questionnaire, or may involve extensive imaging studies, burdensome and intrusive monitoring over time, a lumbar puncture, or exploratory surgery. This component must have its harms minimized wherever possible and, in adult and competent populations, these harms must be justified by reference to the social and scientific value anticipated to result from the gathering of this information. The standard for vulnerable populations incapable of giving their own fully free and informed consent is higher: for these populations, no increase over minimal risk is allowed in Canada, and just a minor increase over minimal risk in the U.S., where such an increase in risk is to be justified in relation to the importance of the anticipated results from the study – and the possibility is

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- 20 C. Weijer, “The Analysis of Risks and Potential Benefits in Research” (1999) 9:2 NCEHR Communiqué 16 [Weijer, “The Analysis of Risks”]; C. Weijer, “The Ethical Analysis of Risk” (2000) 28:4 *Journal of Law and Medical Ethics* 344 [Weijer, “The Ethical Analysis of Risk”]; C. Weijer, “The Ethical Analysis of Risk in Intensive Care Unit Research” (2004) 8:2 *Critical Care* 85 [Weijer, “Risk in Intensive Care Unit Research”]; C. Weijer & P.B. Miller, “When Are Research Risks Reasonable in Relation to Anticipated Benefits?” (2004) 10:6 *Nature Medicine* 570 [Weijer & Miller, “When are Research Risks Reasonable?”].
- 21 It is, naturally, controversial whether an experimental intervention can be labeled as therapeutic absent the therapeutic misconception.
- 22 *Supra* note 2 at ss.1(C1) & 7(A).
- 23 C. Fried, *Medical Experimentation: Personal Integrity and Social Policy* (Amsterdam: North-Holland Publishing Co., 1974).
- 24 B. Freedman, “Equipoise and the Ethics of Clinical Research” (1987) 317:3 *New England Journal of Medicine* 141.

reserved that a greater than minor increase may be permissible when judged appropriate by national and transparent review. Hence “non-therapeutic” research, or the “non-therapeutic” component of a “therapeutic” research study, with such populations in Canada would be justified solely with reference to existing risks of daily living; the intention is that the permissible level for such risk would be lower than for non-vulnerable adults.

While the distinction between trials of clinical interventions and other research is coherent, it is disputed whether this ought to be labelled a distinction between “therapeutic” and “non-therapeutic” research, and whether the “therapeutic” component ought to be described as “offering some possibility of personal benefit for the research participant.” The terminology has been criticized for its perpetration of the therapeutic misconception.²⁵ In all clinical research, the primary beneficiaries are future patients, and it is misleading to call administration of an unproven intervention a “therapeutic” act. This is particularly apparent in a randomized controlled trial of a novel intervention against placebo; a significant proportion of participants may receive no active substance at all, and to describe this situation as one in which they enjoy some possibility of personal benefit is particularly contentious. This concern also arises where areas of clinical research are compared with one another: the possibility of personal benefit for receiving an experimental intervention in a “therapeutic” trial may range widely, from close to zero to better than half, and the possibility of harm is often greater than for the standard intervention. In some cases, where trials aim to show equivalence with current treatments rather than superiority, it is also unclear why one would be licensed to speak of the chance at undergoing a new and unproven intervention that aims at (and may fall short of) equivalence as a benefit. The phrase “thought to be at least as good as current therapy,” when used as a summary of clinical equipoise, gives little prominence both to the very real possibility that the new intervention may be worse than the current standard of care, and to the fact that the basis on which it is thought to be “at least as good” is less secure than the basis for our belief in the current standard of care (evidence for the new intervention may be anecdotal, or take the form of case studies, or consist in trials in animal and other models).²⁶ Hence while the “minimal risk” standard sorts acceptable from

25 F.G. Miller & H. Brody, “A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials” (2003) 33:3 *Hastings Centre Report* 19.

26 L. Reid, “Equipoise and the End of Innocence” [in progress].

unacceptable research for vulnerable populations where the intervention in question, considered as the whole of the research trial or as a part of it, is not itself an unproven intervention of therapeutic intent, it articulates no standard whatsoever for acceptable levels of risk or risk-benefit trade-off for the unproven intervention itself. We will employ the terminology of “therapeutic” and “non-therapeutic” research to mark the intelligible distinctions between trials of clinical interventions and other research (diagnostic etc.), and between components of a given trial, and discuss the application of the concept of “minimal risk” under current regulatory standards, but employ quotation marks to emphasize the concern that it may be a distinction that perpetrates the therapeutic misconception.

In sum, the category of “minimal risk” is intended to serve three purposes: to mark off research studies that may receive expedited review from those that require full review, thus ensuring both that research participants are protected and that the process of ethics review is not unnecessarily cumbersome; to ensure special protections to vulnerable populations while preserving for these groups the possibility of fair benefit from medical research; and to control the level of risk to which research without informed consent may expose people. We have also seen that the desiderata of the boundaries of such a category vary by function. To mark off expedited from full review, a non-controversial algorithm may be most appropriate; to decide acceptable and unacceptable research for vulnerable populations or in the absence of consent, significant controversies may need to be considered and decided on a case-by-case basis.

2. Legal Status of Regulatory Definitions

In most jurisdictions in Canada, there is no legislation specifically governing the judgment of when medical research risk is and is not appropriate. Quebec is the exception: its Civil Code has specified since 1998 that a minor or someone incapable of giving consent “may not be submitted to an experiment if the experiment involves serious risk to his health.”²⁷ This appears to

27 Art. 21 C.C.Q., online: Civil Code of Quebec <<http://www.canlii.org/qc/laws/sta/ccq/index.html>>. Prior to 1998, research involving decisionally incompetent participants was in effect illegal, as research participation required the informed consent of the participant. See S. Magder & A. Lefebvre, “Obtaining Consent for Research Studies on Incompetent Subjects: The Quebec Experience” (2003) 29 *Intensive Care Medicine* 496.

be a tighter restriction than the general provision in the Civil Code Article 20, which stipulates that a person with capacity “may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated.” A capable person could agree to a serious risk if it is balanced by prospect of benefit for self or society; a decisionally incapable person could not participate in any high-risk research. Participation of decisionally incapable persons in moderate risk through minimal to no risk research must either promise a direct health benefit to the individual research participant, or promise results that will, in the future, benefit members of the same age group, or those with the same disease or condition, and it must be authorized by a court-appointed guardian and not (for instance) a family member who is acting as surrogate decision-maker.²⁸ It would appear that the Quebec Civil Code is both relatively permissive of research risk for vulnerable populations and relatively intolerant of experimentation in general. It allows anything short of serious risk for vulnerable populations, yet requires experimentation that involves minimal or no risk to meet the standard of either offering direct health benefit to the participant, or offering reasonable prospect of benefit to others in the participant’s condition or age group, whatever the decisional capacity of its participants – whereas the regulatory standard of the *Tri-Council Policy Statement* permits minimal risk research with capable adults to be excused review that weighs personal and social benefit. The effect of such a regulation is to say that if research can be undertaken using participants who are not minors and do not have the condition towards which the research is directed, then minors with a given condition should not be recruited to that research. The *Tri-Council Policy Statement*, likewise, permits research with vulnerable populations only where the research question cannot be addressed with others.²⁹

The lack of statute law addressing permissible research risk in the rest of Canada does not mean that the law takes no interest in the question:

28 Consent for decisionally incompetent adults can only be by legally appointed guardian – unless in an emergency situation where such legal appointment is impossible, where it may be given by a family member. This fact is not well-understood by patients, researchers, or REB members in Quebec. See G. Bravo, M. Paquet & M.-F. Dubois, “Knowledge of the Legislation Governing Proxy Consent to Treatment and Research” (2003) 29:1 *Journal of Medical Ethics* 44; G. Bravo *et al.*, “Quebec Physicians’ Knowledge and Opinions Regarding Substitute Consent for Decisionally Incapacitated Older Adults” (2004) 26:5 *IRB* 12.

29 *Supra* note 2 at Art.2.5(a).

through action for negligence, researchers and others involved in the research enterprise, including institutions that host research, their REBs, sponsors, funding bodies, and (arguably) professional bodies such as the regulatory colleges,³⁰ may be brought to account for decisions made about what is and is not acceptable in research risk.

Case law in Canada does not directly address the broad question of acceptable levels of risk in clinical research. *Halushka v. the University of Saskatchewan et al.*³¹ speaks to requirements of risk disclosure in relation to the standards of care that researchers owe research participants. An engineering student was recruited as a healthy participant to a study of a new anaesthetic (hence a “non-therapeutic” study), the risks of which were in fact unknown, and suffered cardiac arrest and subsequent brain damage as a result of his research participation. In this case, the courts faced the question of whether the standard of care owed a research participant by a researcher for risk disclosure was the same as that owed a patient by a physician. It is a common argument in the ethics literature that a researcher does not owe a research participant a duty of care since they are acting as researcher – that duty of care is something a physician owes a patient. The Saskatchewan Court of Appeal, on the contrary, did not reason that a researcher does not owe a duty of care. The concept of a duty of care and the correlate notion of standards for care extend beyond a specific professional role and rely on broad considerations about proximity and foreseeability: such a duty exists where “the relationship between two parties is sufficiently close that the harm suffered (by the plaintiff) is reasonably foreseeable” by the defendant.³² Accordingly, Justice Hall concluded in *Halushka* that researchers and their institutions do owe a duty of care to research participants, and furthermore that where a medical intervention is not for the benefit of the person undergoing it, the requirement of risk disclosure is higher than the standard for disclosure that a physician owes a patient.³³

30 S.V. Zimmerman, “Translating Ethics Into Law: Duties of Care in Health Research Involving Humans” (2005) 13:2&3 *Health Law Review* 13 at 16.

31 (1965), 53 D.L.R. (2d) 436 (Sask. C.A.) [*Halushka*].

32 *Supra* note 30 at 14.

33 *Supra* note 31 at 443-44. See D. Pullman, “Subject Comprehension, Standards of Information Disclosure and Potential Liability in Research” (2001) 9 *Health Law Journal* 113 at 114 *ff.*

Research Ethics Boards did not exist at the time of the *Halushka* case; the *Weiss v. Solomon*³⁴ ruling by the Quebec Superior Court in 1989 speaks more directly both to what is reasonable in terms of risk exposure (and not simply disclosure), and to what research institutions via their REB processes owe research participants in this regard. In this case, a research participant (Weiss) died as a result of his involvement in a “non-therapeutic” trial when an existing medical condition unrelated to the research caused him to have an anaphylactic reaction to the fluorescein angiogram administered as part of the research protocol. The Quebec Superior Court ruled that the investigators and hospital through its REB failed not only to ensure the communication of a particular risk, but to ensure that the exclusion criteria of the trial ruled out participation by those with a condition that would place them at (low) risk of significant harm.³⁵ The court noted that the same condition and concomitant risk would not exclude such a person from taking on that risk in their own therapeutic interests, but that where there is no such therapeutic interest, such persons ought to be excluded from receiving an intervention that poses such a risk to them. Again, the court reasoned that outside of the therapeutic context, the requirements for protection of research participants may in fact be higher than those for protection of patients, where there is no likelihood of benefit for the research participant as there is for the patient.³⁶

In order to ascertain the standards that govern this duty of care, courts have considered documents such as the World Medical Association’s Declaration of Helsinki³⁷ (in *Halushka*); presumably, the *Tri-Council Policy Statement* would serve to define the standard professional expectations of research-

34 (1989), 48 C.C.L.T. 280 (Que. Sup. Ct.).

35 The judgement in the *Weiss v. Solomon* case is controversial, as the harm for which the researchers and REB were held responsible was one whose possibility was unknown at the time it occurred. The decision was not, however, appealed, and so it stands as delivered. See B. Freedman, A. Fuks & C. Weijer, “*In loco parentis*. Minimal Risk as an Ethical Threshold for Research Upon Children” (1993) 23:2 *Hastings Centre Report* 13 at 17; B. Freedman & K. Glass, “*Weiss v. Solomon*: A Case Study in Institutional Responsibility for Clinical Research” (1990) 18:4 *Law Medicine & Health Care* 395.

36 *Supra* note 30 at 15.

37 World Medical Association, *Declaration of Helsinki* (1964, rev 1975, 1983, 1989) in Warren T. Reich, ed., *Encyclopedia of Bioethics* (New York: Simon & Schuster Macmillan, 1995) at 2765-67, online: <<http://www.wma.net/e/policy/b3.htm>>.

ers and others involved in the research enterprise towards research participants.³⁸ If standards of care were set exclusively by professional guidelines, it would seem that researchers and the granting agencies could define “minimal risk” however they please. This is not, however, the case. Guidelines are one of several possible indications of professional standards of care.³⁹ The courts must weigh guidelines against expert testimony about consensus in practice, given the precarious link between guideline publication and implementation.⁴⁰ Professional discretion in the application of guidelines to specific patients is respected by the courts.⁴¹ Furthermore, guidelines may be set for various purposes:⁴² to protect professionals from liability, for instance, or to protect the public. The courts do not abdicate their role in determining legal standards of care, but hold professionals to standards of reasonableness in their ability to foresee harm for others and their obligation to act to prevent such harms from occurring,⁴³ in the light of public expectations that they will do so.⁴⁴ In specific, guidelines for the conduct of research have a peculiar property that is not shared by many medical practice guidelines. While practice guidelines may serve a number of purposes, as Campbell and Glass argue, there is an assumption that the aim of such guidelines (whether achieved or not) is that they will ensure the best interests of patients; those who create and enact research ethics guidelines in the Canadian context, however, are organizations that primarily exist to fund and promote research. The primary purpose of the three major public research funding agencies in Canada who jointly enforce the *Tri-Council Policy Statement* is to promote research, not to protect and advance the interests of research participants; within many institutions, the REB is part of a research services office, whose primary goal again is to promote research within the institution.⁴⁵ To point out these differing primary interests is not to argue that

38 *Supra* note 30 at 17.

39 A. Campbell & K.C. Glass, “The Legal Status of Clinical and Ethics Policies, Codes, and Guidelines in Medical Practice and Research” (2001) 46:2 McGill Law Journal 473.

40 *Ibid.* at 478-79.

41 *Ibid.* at 484.

42 *Ibid.* at 477.

43 *Ibid.* at 480-81.

44 *Ibid.* at 487.

45 J. Downie, “Contemporary Health Research: A Cautionary Tale,” (2003) Special Edition 1 Health Law Journal at 11-17.

researchers and research institutions are in fact careless with or neglectful of research participant interests; there is nonetheless a significant tension in the fact that research practice guidelines are promulgated by agencies responsible for promoting research, while at the same time they bear the responsibility of offering protection to human research participants. The tight connection that exists between performing good clinical care and meeting a patient's best interests does not exist between doing good research and meeting a particular research participant's best interests.

Guidelines such as the *Tri-Council Policy Statement* become in effect legally salient, if not binding, through the role they play in articulating standards of care; at the same time, they are themselves subject to legal review. Although the courts are reluctant to replace professional medical judgment with legal judgment, they may rule that a given professional standard of care fails to meet the standards of the care that a reasonable person would be expected to exercise. We shall see below that the standard of what a parent or guardian may authorize on behalf of their children or dependent adults is a touchstone for the courts in considering reasonable research risk for vulnerable populations. Furthermore, Hadskis and Carver⁴⁶ argue that the actions and procedures of Research Ethics Boards are subject to the scrutiny of administrative law, given their role in carrying out a statutory mandate⁴⁷ and given their mandatory character for employees/researchers.⁴⁸ Recently, statutes and regulations have begun to make reference to required REB functions,⁴⁹

46 M. Hadskis & P. Carver, "The Long Arm of Administrative Law: Applying Administrative Law Principles to Research Ethics Boards" (2005) 13:2/3 Health Law Review 19.

47 *Ibid.* at 21-22. This applies both to research ethics review carried out in hospitals and universities, and to review carried out by the College of Physicians and Surgeons of Alberta (CPSA)'s provincial Research Ethics Review Committee, in accordance with a bylaw passed by the governing Council of the CPSA.

48 *Ibid.* at 22. This applies principally to research ethics review carried out by hospitals and universities.

49 *Ibid.* at 22-23; since the publication of *ibid.*, Newfoundland has adopted the "Health Research Ethics Authority Act," which references the *Tri-Council Policy Statement* as one of two named guidelines documents that may be applied by a research ethics board in reviewing research in the province of Newfoundland. *An Act to Establish a Health Research Ethics Authority for the Province*, N.L. 2006, (assented to December 12, 2006) c. H-1.2, online: <<http://www.assembly.nl.ca/legislation/sr/annualstatutes/2006/H01-2.c06.htm>>.

which contributes to the understanding that REBs are acting with statutory authority. Furthermore, the scrutiny to which such statutory exercises of power are subject under administrative law extend both to procedural questions of the fairness with which they operate and to substantive questions of the correctness of their claims to regulatory reach.⁵⁰ It is possible that questions could come before the courts about the fairness of rules that determine levels of review for research protocols, and about the claim that such review serves the public interest.

3. Definition of Minimal Risk

Whether the concept of “minimal risk” is appropriate for its three purposes in the *Tri-Council Policy Statement* hinges in part on how it is interpreted, and its definition remains controversial.⁵¹ According to the U.S. Common Rule:

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.⁵²

This definition of minimal risk offers two standards: one has reference to medical and psychological procedures, and the other has reference to daily living. These two standards are already quite distinct: Kopelman points out that the disrobing for a physical exam and revealing private information in the course of a typical physical or psychological exam are, from a privacy

50 Hadskis & Carver, *ibid.* at 20.

51 See for instance L.M. Kopelman, “Children as Research Subjects: A Dilemma” (2000) 25:6 *Journal of Medical Philosophy* 745 [Kopelman, “Children as Research Subjects”]; L.M. Kopelman, “Minimal Risk as an International Ethical Standard in Research” (2004) *Journal of Medicine & Philosophy* 351 at 367-368 [Kopelman, “Minimal Risk”]; L.M. Kopelman, “Moral Problems in Assessing Research Risk” (2000) 22:5 *IRB* 3 [Kopelman, “Moral Problems”]; P.B. Miller & C. Weijer, “Moral Solutions in Assessing Research Risk” (2000) 22:5 *IRB* 6 [Miller & Weijer, “Moral Solutions”]; D.B. Resnik, “Eliminating the Daily Life Risks Standard from the Definition of Minimal Risk” (2005) 31:1 *Journal of Medical Ethics* 35.

52 *Supra* note 7 at §46.303(d).

perspective, far from minimal risk and are uncommon acts in daily living.⁵³ The given standards are also vague, although the U.S. attempts to offer some guidance in the form of paradigmatic examples of minimal risk procedures. There is one specific dimension of vagueness in the “risks of daily living” standard that is our focus in this paper. The daily living standard may be understood as absolute or relative – the same for all people at all times, or dependent on context. As is often noted in the American debate, living in an affluent town in rural Connecticut, for example, involves certain risks of daily living; living in a public housing project in South Chicago involves others.

On the question of whether daily living is understood in absolute or relative terms, regulations in the U.S. are at best ambivalent: 45C.F.R. §46.102(i) itself speaks of the risks of daily living without specifying whose daily living constitutes the standard, whereas the 1981 Preamble to 45C.F.R. 46⁵⁴ specifies that the relevant risks are the risks for the patient population being recruited to the research study in question. The Medical Research Council in the UK specifies minimal, low, and high risk both in terms of specific examples of procedures and general descriptions. Minimal risk procedures include, for instance, the non-invasive collection of saliva or urine; such procedures are described as not resulting “in more than a slight and temporary negative impact on the health of the person concerned.” Low risk includes, for example, a blood test, which “might cause no more than brief pain or tenderness, small bruises or scars, or very slight, temporary distress.” High risk procedures include, for instance, lumbar puncture, and these cannot be performed solely for research purposes with children but only with experimental diagnosis or intervention that

53 There is also debate about whether the “routine physical and psychological exams” standard is an instance of the daily living standard, or a separate allowable standard. See Kopelman, “Children as Research Subjects,” *supra* note 51 at 750-52; L.M. Kopelman, “Estimating Risk in Human Research” (1981) 29:1 *Clinical Research* 1 at 5 [Kopelman, “Estimating Risk”].

54 United States Department of Health and Human Services, *Final Regulations Amending Basic HHS Policy for the Protection of Human Research Subjects*, 46:16 *Federal Register* 8366 at 8373 (January 26, 1981), online: Office for Human Research Protection <<http://www.hhs.gov/ohrp/documents/19810126.pdf>>. For a discussion of the historical controversy attendant to this interpretation, see Kopelman, “Minimal Risk,” *supra* note 51 and *supra* note 12.

is intended to be beneficial to the particular child concerned – not solely future patients.⁵⁵

The Canadian *Tri-Council Policy Statement* explicitly adopts a relative interpretation of “risks of daily living:”

...if potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research, then the research can be regarded as within the range of minimal risk.⁵⁶

This statement appears to countenance labeling even more serious risks as “minimal” for certain research participants: it specifies not just the patient population in question as a subset of the general population (as the Preamble to 45C.F.R.46 does), but the subset of risks in those patients’ lives that are related to their disease and its treatment.⁵⁷ For some patients, these may be the harms and potential harms related to taking a mild analgesic, and for others the harms and potential harms related to brain surgery or imminent death from a terminal condition. This specification of minimal risk as relative to “those aspects of his or her life related to the research” is exclusive to Canada’s *Tri-Council Policy Statement*,⁵⁸ *pace* the assertion in the *Tri-Council Policy Statement* that this definition is common.⁵⁹ The U.S. regulations allow a similar relativization of research risk to the lives of the relevant patient population; the result is that both permit non-therapeutic studies to match the level of risk patients find in their daily experience of their medical condition. There is no evidence in practice that Canadian REBs have felt licensed by this terminological variation to approve riskier studies, although it may be the case that a study that would be approved as “minor increase over minimal risk” in the U.S. would be approved in Canada as matching that

55 Medical Research Council (UK), *MRC Ethics Guide: Medical Research Involving Children* (London: Medical Research Council, issued 18 November 2004; revised 24 August 2007), online: MRC <<http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430>> at 15. Further international comparisons may be found at Kopelman, “Minimal Risk,” *supra* note 51.

56 *Supra* note 2 at s.1(C1).

57 *Ibid.*

58 L.M. Kopelman, “Minimal Risk,” *supra* note 51 at 353, 369.

59 *Supra* note 2 at s.1(C1).

subset of risks of daily living that belong to the disease and its management in Canada.⁶⁰

Anderson and Weijer have claimed that the component analysis approach and the *Tri-Council Policy Statement's* relative interpretation of the minimal risk standard are mutually supportive.⁶¹ We draw a different conclusion from the close relationship between the relative interpretation of minimal risk (which governs “non-therapeutic” research) and the standard of clinical equipoise (which governs “therapeutic” research) asserted in Section 1(C1) of the *Tri-Council Policy Statement*. Section 1(C1) speaks specifically of high-risk experimental interventions:

In some areas of treatment (for example, surgery, chemotherapy or radiation therapy), the treatments themselves are known to pose considerable risks of harm. Such therapeutic risks may be regarded as within the range of minimal risks for patient-subjects, since they are inherent in the treatment that the patient will be undergoing as a part of his or her current everyday life. Adherence to the principle of clinical equipoise (see Section 7) requires that the fundamental ethical consideration in the decision to expose patients to experimental procedures derives from the premise that the interventions being tested are not different in terms of the anticipated balance between their harms and benefits. Hence, the idea that considerable anticipated therapeutic risks might also be within the range of minimal risks extends to the therapies in the trial.⁶²

Clinical equipoise is a standard for the acceptability of the fundamental risk-benefit ratio of any experimental clinical research intervention. A definition of minimal risk according to which any research that satisfies clinical equipoise *ipso facto* carries the same level of risk as minimal risk “non-therapeutic” research – i.e. a minimal level of risk – is obviously problematic. Equipoise is the standard for an acceptable risk level, and minimal-risk research ought to be a subset of acceptable-risk research. A standard that conflates accept-

60 Variation in actual application of the standard of minimal risk has been documented in, for instance, S. Shah et al., “How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research?” (2004) 291:4 *JAMA: the Journal of the American Medical Association* 476.

61 J.A. Anderson & C. Weijer, “Minimal Risk and Its Implications” (2001) 11:1 NCEHR Communiqué 15 at 17.

62 *Supra* note 2 at s.1(C1).

able risk in research with minimal risk in research – outside of those specific populations for whom it has been decided that only minimal risk research is acceptable – offers no useful guidance as to the meaning of minimal risk.

4. Criticism of the Relative Interpretation

The relative definition of the standard of minimal risk has provoked considerable debate. Kopelman has argued since 1981⁶³ that a relative standard is inappropriate and discriminatory, offering less protection from risky research to those who deserve equal if not greater protection. The U.S. National Bioethics Advisory Committee (NBAC) 2001 report unequivocally agreed with Kopelman and rejected the relative interpretation of risks of daily living, arguing:

A relative standard for minimal risk would allow ill participants to be exposed to greater risks than healthy participants. Such a standard would impose disproportionate burdens of research on the ill and provide weaker protections for them than for healthy individuals. This would violate the ethical principle of justice.⁶⁴

And three subsequent federal commissions have reached the same conclusion.⁶⁵ We will call this common critique the “justice critique” of the relative

63 Kopelman, “Children as Research Subjects,” *supra* note 51; Kopelman, “Estimating Risk,” *supra* note 53; Kopelman, “Minimal Risk,” *supra* note 51; Kopelman, “Moral Problems,” *supra* note 51 at 3; L.M. Kopelman, “When Can Children with Conditions be in No-Benefit, Higher-Hazard Pediatric Studies?” (2007) 7:3 *American Journal of Bioethics* 15.

64 National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, vol. 1 *Report and Recommendations of the National Bioethics Advisory Commission* (Bethesda, MD: The Commission, 2001) at 83, online: The President’s Council on Bioethics <http://www.bioethics.gov/reports/past_commissions/nbac_human_part.pdf>.

65 National Human Research Protections Advisory Committee (NHRPAC), *Children’s Workgroup Report* (Washington, DC, 2001), online: NHRPAC April 9-10, 2001 Meeting <<http://www.hhs.gov/ohrp/nhrpac/mtg04-01/child-workgroup4-5-01.pdf>>; Institute of Medicine (IOM) of the National Academy, *Ethical Conduct of Clinical Research Involving Children*, M.J. Field & R.E. Behrman, eds., (Washington, DC: National Academies Press, 2004), online: The National Academies Press <http://www.nap.edu/catalog.php?record_id=10958>;

interpretation of minimal risk. Fisher *et al.* have recently summarized the work of these commissions, and argued that the debate is over and that we have reached the moment for implementation.⁶⁶

It may appear that 45C.F.R.46.406 licenses a relative interpretation for “non-therapeutic” research that would encompass interventions that carry risk beyond anything that might be considered minimal or a minor increase over minimal for a healthy population, but that offers significant chance of providing vitally important insight into a given condition. Kopelman⁶⁷ and Fisher *et al.* argue on the contrary that the permissible relativized risk for vulnerable patient populations must in turn meet the minor increase standard. Fisher argues, summarizing the deliberations of several national commissions, that the relativization of the minimal risk standard to the risks found in the lives of particular patient populations is meant only as a stipulation that the risks involved in research participation must be within the experience of the patient and guardian population, so that they understand that to which they are assenting or giving authorization.⁶⁸ That is, it is not a standard that allows greater risk than for healthy vulnerable research participants, but a standard that says that where the vulnerable participants have medical conditions related to the research, the “non-therapeutic” risks to which it is permissible to expose them must be both no more than a minor increase over minimal risk and also must be within their experience, so that they may make a decision as informed as possible about assuming such risks.

In relation to its function as a *proportionate review standard*, it would seem reasonable to base the level of protection that the research ethics re-

United States Department of Health and Human Services Secretary's Advisory Committee for Human Research Protections (SACHRP), *April 18-19 2005, Meeting presentation and reports* (Washington, DC, 2005), online: Office for Human Research Protections

<<http://www.hhs.gov/ohrp/sachrp/mtgings/mtg04-05/mtg04-05.htm>>.

66 C.B. Fisher, S.Z. Kometsky & E.D. Prentice, “Determining Risk in Pediatric Research with no Prospect of Direct Benefit: Time for a National Consensus on the Interpretation of Federal Regulations” (2007) 7:3 *American Journal of Bioethics* 5 at 7-8.

67 L.M. Kopelman, “Pediatric Research Regulations Under Legal Scrutiny: Grimes Narrows Their Interpretation” (2002) 30:1 *Journal of Law, Medicine & Ethics* 38 [“Grimes Narrows Their Interpretation”].

68 *Supra* note 66.

view process extends to research participants on the risks or harms inherent to the experimental intervention itself rather than on the health status and current treatment options of participants. By choosing the latter route, the relative definition of minimal risk treats the same risks as less serious and less worthy of review and oversight for the ill or disadvantaged than for the healthy and advantaged. Making the level of protection available to research participants sensitive to their health status is not in itself an injustice. We may think it reasonable that the vulnerable receive greater protection in the form of more rigorous research ethics review. Indeed, the *Tri-Council Policy Statement* states clearly as one of its guiding principles that “ethical obligations to vulnerable individuals in the research enterprise will often translate into special procedures to protect their interests.”⁶⁹ Moreover, the current *Tri-Council* PRE review process holds that “proportionate review is intended to reserve most intensive scrutiny, and correspondingly *more* protection, for the most ethically challenging research.”⁷⁰ The relative interpretation of minimal risk, however, specifically permits a *lowering* of the level of protection extended based on a group’s diminished health status or life circumstances. Justice requires that like cases be treated alike, and that differences in treatment be justified by relevant differences in the groups treated. By such a standard, it seems on the face of it that risky and invasive procedures for the patient with a terminal cancer diagnosis should receive at least as strong scrutiny and review before approval as risky and invasive procedures for patients who are healthier. Recall that the question here is not whether riskier proposals

69 *Supra* note 2 at “Context of an Ethics Framework” (C).

70 *Ibid.* at s.1(D1) [our emphasis]. The ProGroup reviewing the concept of minimal risk offers a mechanism for classifying such a case as warranting full review by proposing that we base eligibility for expedited review not solely on the level of risk involved in participation in the study, but also on the level of vulnerability of the research participant. See Subgroup on Procedural Issues for the *TCPS* (ProGroup): A Working Committee of the Interagency Advisory Panel on Research Ethics (PRE), “Refinements to the Proportionate Approach to Research Ethics Review in the *Tri-Council Policy Statement*” A Discussion Paper (December, 2005) 1 at 9, 12-16, 22-23, online: The Interagency Advisory Panel on Research Ethics (PRE) <http://pre.ethics.gc.ca/english/workgroups/progroup/Consultation_instructions.cfm>. This proposal is reasonable in itself, but as a solution to the problems of the relative definition of minimal risk it is an *ad hoc* solution to a problem created in the first place by the guideline’s artificial definition of “minimal risk.”

should or should not be approved for such populations: it is undoubtedly true that patients with terminal brain tumours, for instance, will face riskier experimental procedures than patients with the common cold. The question is what level of review such risky procedures should undergo. The proportionate standard asserts that greater scrutiny provides greater protection; we know of no argument that a procedure with (for instance) a 10 percent chance of death would deserve less *scrutiny* when offered to patients with terminal conditions than when offered to patients without – although such a procedure may well be permissible in the former case where it would not be in the latter. It may be thought that an experimental intervention for a terminally ill patient is especially time sensitive and that the patient cannot afford to wait for full review, but the case in which an experimental intervention is of such clear benefit to the individual research participant that its administration is “experimental” in name alone is the exception and not the rule. Indeed, it seems likely that for many terminal conditions, an especially high proportion of experimental interventions fail. Patients who already face terminal diagnoses or dangerous, invasive procedures – patients who therefore may be more vulnerable because of their circumstances – surely do not warrant lesser levels of protection than healthier research participants who face less risky procedures.

The debate around the definition of minimal risk has taken place largely in the context of discussion of its second purpose – the need to define a *limit on research with the vulnerable*, in pediatric research⁷¹ among other areas – and in relation to the *limit on unconsented research*, specifically in relation to emergency research.⁷² In such cases, the concern is with protection from excessive risk or harm where research must be done with the vulnerable, where not doing the research would deprive that group of the goods that come from research. These limits are supposed to be stricter than the limits on research with the non-vulnerable: the thought is that fully informed and capable adults ought to be permitted to take larger risks or accept greater burdens in the interests of scientific advance than children or other vulner-

71 See Freedman, Fuks & Weijer, *supra* note 35; Kopelman, “Children as Research Subjects,” *supra* note 51; L.M. Kopelman, “When is the Risk Minimal Enough for Children to be Research Subjects?” in L.M. Kopelman & J.C. Moskop, eds., *Children and Health Care: Moral and Social Issues* (Dordrecht, Netherlands: Kluwer, 1989) 89; *supra* note 12.

72 Weijer & Miller, “When Are Research Risks Reasonable”, *supra* note 20 at 572-573.

able populations – and the substitute decision-makers acting on their behalf. The justice critique, however, also applies to the use of minimal risk for this purpose. The same mechanism that preserves the ethical possibility of appropriate research with vulnerable populations by labeling that research “minimal risk” runs the risk of permitting exploitation of the vulnerable by the possibility it creates for reference to their greater risks of daily living to justify exposing them to risks to which the less vulnerable could not be exposed. The Willowbrook hepatitis experiments, where healthy children were deliberately infected in a context in which the disease was endemic, and the Kennedy Kreiger lead abatement study, where low-income families with young children were given incentives to live in houses with the hazard of lead paint to test biological effects of new removal methods, are frequently offered as examples of the danger of a relative interpretation.⁷³ Hence it seems that the relative interpretation of minimal risk as a *limit on research with the vulnerable* also fails by the standard of justice. The same factor that allows for necessary research with vulnerable populations also justifies more invasive or burdensome research for such populations, which is surely opposite to the intended goal of the minimal risk framework: to protect vulnerable groups.

The justice critique holds for the *limit on unconsented research*. For example, imagine a researcher seeking access to a large database of lifestyle and work history information about welfare recipients. Such recipients are routinely deprived of ordinary expectations of confidentiality; indeed, that could well be the reason such personal information about this population would be available. Does the very existence of the database prove that this group faces an unusual lack of expectation of privacy, and hence that a researcher has a lower level of obligation to seek their consent for accessing such information? Whatever inequities may exist in society, researchers may not replicate them by offering such research participants a lower level of informed consent than would be expected for those who are not routinely deprived of confidentiality.⁷⁴ Similarly, that prisoners have little or no privacy in many prisons should not justify practices giving researchers the same access to pris-

73 Kopelman, “Estimating Risk”, *supra* note 53 at 2; Kopelman, “Minimal Risk”, *supra* note 51 at 362-363; *supra* note 67.

74 Rothman summarized this concern neatly in 1982 in the context of observational studies as the danger of becoming accomplices rather than observers. D.J. Rothman, “Were Tuskegee & Willowbrook ‘Studies in Nature’?” (1982) 12:2 *Hastings Center Report* 5.

oners as prison guards, allowing them to proceed without ordinary requirements of informed consent. The prisoners' lack of privacy is functionally and pragmatically related to the goal of punishment and the realities of running a penal institution; a researcher entering the prison context has no such justification for any greater invasion of privacy than would be permitted with a non-incarcerated population without consent. The prior existence of a lack of privacy does not create justification for exploiting that situation.

5. The Persistence of the Relative Standard

Nonetheless, as we saw above, the Preamble to 45C.F.R.46 continues to embody a relative interpretation, and arguments are made in the ethics literature to defend this interpretation.⁷⁵ Indeed, on investigation it appears that defenders and critics of the relative interpretation share more in common than first appears. Those who defend the relative interpretation argue that other features of the regulatory framework rule out the kinds of exploitative research with which defenders of the absolute interpretation are concerned. For both parties, accepting that clinical equipoise governs acceptable risk for "therapeutic" research with vulnerable populations involves accepting a standard for "therapeutic" research risk that closely resembles the relative interpretation of minimal risk. In effect, both parties accept shielding the "therapeutic" component of a study from any requirement of greater caution for vulnerable populations. In this sense, both parties fail to consider the fundamental definitional inadequacy of the relative interpretation of minimal risk.

The proponents of the absolute standard argue that the minimal risk standard has to be understood in context, in the sense that the concerns about injustice raised in relation to the relative definition of minimal risk are dealt with by other principles in research regulation. For example, the requirement that risks be minimized, and the requirement that the benefits and burdens of research be equitably distributed are listed among the guiding ethical principles of the *Tri-Council Policy Statement* and seem applicable in relevant ways.⁷⁶ Before the question arises whether any risk is acceptable, risks must be minimized as much as possible; before the question of whether risks are

75 See, for instance, Miller & Weijer, "Moral Solutions," *supra* note 51; Freedman, Fuks & Weijer, *supra* note 35 for specific arguments against the absolute interpretation.

76 *Supra* note 2 at "Context of an Ethics Framework" (C).

allowable for a given group, justice requires that the given group is not being used to conduct research that poses risks and burdens, and is of no benefit to that group but only of benefit to another group. Both these requirements – not to mention the overarching idea of a “subject-centred perspective” endorsed by the *Tri-Council Policy Statement* – would come into play for a case of researchers “shopping around” for a risk-burdened population to recruit to a risky research study. Kopelman’s concerns about exploitation arising through application of a relative standard would, on this view, be addressed by the guideline’s core principles unequivocally rejecting exploitation in research in general. Hence, Miller and Weijer argue, while the definition of minimal risk may not in itself ward off injustice, this does not imply that it is a standard that creates injustice, when it is taken in the context of the regulations of which it is a part.⁷⁷ The requirement of the *Tri-Council Policy Statement* that research only be undertaken with vulnerable populations where their participation is essential to answering the research question⁷⁸ rules out research being done with such a group for regulatory convenience, as does (by a different mechanism) the Civil Code of Quebec requirement that such research benefit the patient and age group to which the participant belongs.

Both proponents and critics of the relative definition of minimal risk accept the “clinical equipoise” determination of acceptable risk for “therapeutic” research, thereby placing a limit on “therapeutic” research risk for vulnerable populations that is not different from the limits for fully competent adults.⁷⁹ Anderson and Weijer cite the similarity of the minimal risk and clinical equipoise requirements; the *Tri-Council Policy Statement* asserts that a research intervention that achieves equipoise is therefore “minimal risk” in its relative sense of the term. In this sense, both proponents and critics of the relative interpretation agree in the case of “therapeutic” research to using the term “minimal risk” as what we might call a kind of “regulatory fiction.” The concept marks a limit on research with vulnerable individuals, while at the same time ensuring that vulnerable groups in the long run have access to the benefits of research – but it accomplishes this by counting research as “minimal risk” that is not, however, remotely consistent with

77 Miller & Weijer, “Moral Solutions,” *supra* note 51 at 10.

78 *Supra* note 2 at Art. 2.5(a).

79 Kopelman, “Grimes Narrows Their Interpretation,” *supra* note 67 at 46. See *supra* note 61 on complementary work of component analysis and minimal risk standard.

ordinary meaning of the phrase “minimal risk,” such as brain surgery or chemotherapy. For “non-therapeutic” research, the common view that Canadian guidelines are stricter in not allowing any increase over minimal risk is belied by the whole-hearted embrace of the *Tri-Council Policy Statement* of a relative standard, according to which “the idea that considerable anticipated therapeutic risks might also be within the range of minimal risks extends to the therapies in the trial.”⁸⁰ The level of permitted “non-therapeutic” research risk depends entirely on how risky diagnostic and monitoring procedures for a given population happen to be, rather than on a given standard of permissible risk.

It is possible that such complacency with this shared feature of the relative interpretation of minimal risk and clinical equipoise is related to the common mistake of understanding such research risk as substitutive. Freedman *et al.* have argued that research risks are substitutive rather than additive: the patient undergoing a risky novel procedure is undergoing that procedure instead of the risky standard procedure that patients would undergo off-trial.⁸¹ This is not true in the case of exactly the procedures that the minimal risk standard is intended to cover with vulnerable populations: the procedures that are extra to the experimental “therapeutic” intervention. These are procedures undergone both by active and control groups, in order to monitor the outcomes for research purposes; hence, they are exactly the procedures that patients would not undergo but for their research participation. It is also not true that risks are substitutive for the “therapeutic” component of the research study. Depending on the protocol, the research participant who receives the experimental intervention typically foregoes standard of care for it. But the requirement of equipoise cannot be that we in fact are confident that the risk-benefit trade-off of the new intervention is equivalent to or better than the standard of care: this is precisely what is unknown and the reason for carrying out the trial. In foregoing the standard of care, the research participant is not substituting one harm-benefit trade-off for an equivalent one, but foregoing a proven harm-benefit tradeoff of one intervention for a harm-benefit tradeoff that is relatively unproven. If the unproven does not work, as it may well not, the research participant may in some research be lucky to survive long enough and with little enough damage to be able to receive the standard of care after all. Where there is no stan-

80 *Supra* note 2 at s.1(C1).

81 Freedman, Fuks & Weijer, *supra* note 35 at 17.

dard of care, as in the stem cell research described by Martin and Robert,⁸² a risky research intervention again is not substitutive when compared with the natural course of the disease. The most likely outcome of such research, judging by the historical track record of research for this condition and of early human trials of novel biotechnology, is that the harms and burdens of the highly experimental research will be added to the harms and burdens of the disease.⁸³

Morris and Nelson⁸⁴ address this point when they propose to introduce clarity in emergency medicine research around the distinction between minimal risk research that may simply have consent requirements waived and research that may be permissible where patients cannot consent but must undergo national review and community input as heightened review standards. Randomized clinical trials that satisfy equipoise and randomize between two procedures that are both standard of care (in addition to satisfying the conditions that no standard of care offers a better harm-benefit trade-off exists, that “non-therapeutic” components are minimal risk, and that the protocol allows sufficient variation that clinical discretion in treatment is unfettered) would indeed be minimal risk in the sense that the risk of the intervention is substitutive. Hence it would seem reasonable that such research could be carried out with permission to waive informed consent requirements – under what we have in this paper called the standard for *limit on unconsented research*. Implicit in their proposed guideline is the recognition that where the trial protocol includes one treatment that is standard of care and one or more experimental interventions, such a trial is not “minimal risk” in the strict sense of the term; while such research may be permitted with the vulnerable, the same standard does not serve for the *limit on unconsented research* and the *limit on research with the vulnerable*.

An adequate definition must be neither too narrow nor too broad. While research ethics guidelines and regulations may need to specify more rigorous limits to “minimal risk” than the phrase carries in ordinary language, the relative interpretation defines these words such that what would not be labelled “minimal risk” in ordinary language would be labelled “minimal risk” in its technical sense. In other words, while we may need to make the boundaries of minimal risk more determinate for the purposes of research

82 *Supra* note 1.

83 *Supra* note 26.

84 *Supra* note 18.

ethics guidance, we ought not to set those boundaries at significantly different locations than they occupy in ordinary language. We accept that the law must determine more specific boundaries for adulthood than exist in common understanding, but it is not free to set the boundary at “between the ages of 3 and 60,” for instance. In invoking a risks of daily living standard, research guidelines have opted to adopt the perspective of the ordinary “person in the street” rather than the scientific specialist. It would be particularly inconsistent with the purpose of adopting such a perspective to then define “minimal risk” in a way that strays significantly from the ordinary use of the term. From this point of view, a relative interpretation of the phrase “minimal risk” fails in extension: the potential harms, actual harms, and burdens of chemotherapy would not in fact be ordinarily labelled as “minimal risk”; neither would a 90 percent probability of death within a one-year period – the “normal risk” in the life of a patient with Glioblastoma Multiforme – be considered a “risk of daily living.” To label burdens and harms faced by the extremely ill as “risks of daily living” is not plausible as a definition of minimal risk.

It could be the case that maintaining a relative definition of minimal risk as a “regulatory fiction” would be extremely useful; it would not be impossible for a term of art to elegantly pick out all and exactly the research that we would consider acceptable and necessary to pursue in order to ensure that the benefits of research flow for vulnerable populations. If that were so, objecting to this definition as failing to capture the ordinary language sense of “minimal risk” would not be a particularly strong argument against its adoption. However, the label of “minimal risk” for permissible research also embodies a claim about why that research is permissible: it sets a standard by which we justify research. It may lead us astray if it locates that standard in the wrong place. By turning our attention away from such standards as the likelihood of the research program to achieve success and the scientific rigour of the relevant preclinical studies of a new technology, for instance, and instead appealing to the risks and burdens of the disease in question and its current standard of care, we appeal to a measure that is inappropriate and potentially extremely permissive, in particular for research with conditions with high morbidity and mortality.

It would be a relatively simple empirical question to discover whether studies considered by researchers and REBs to be minimal risk, in the context of approving research with vulnerable populations where fully free and informed consent is not possible, would also be considered “minimal risk” by the general public employing ordinary language understandings of the term. There is some empirical research to back the claim that Institutional

Review Boards (IRBs) in the U.S. are in some cases less tolerant of risk than the minimal risk standard would allow them to be.⁸⁵ On the other hand, the very existence of therapeutic trials of novel and invasive procedures taking place under the claim that children and other vulnerable groups can benefit from the fruits of research without being exposed to more than minimal risk, or more than a minor increase over minimal risk, strongly suggests that these terms are construed more broadly by research ethics review than in ordinary language. Our definitional critique is that the minimal risk definition, combined with an understanding of clinical equipoise that does not distinguish an appropriate level of evidence for the belief of possible benefit, leaves the door open for high risk research with groups suffering from diseases with significant morbidity and mortality. It would be challenging to investigate empirically just how permissive REBs are with such research under the rubric of “minimal risk.” The interest of such an empirical investigation does not obviate the need we advance here for definitional clarity: how in fact should we operationalize the idea that, for certain populations, a lower tolerance of risk in research is appropriate? And is it in fact possible to enact such a differential standard and not deprive these populations of the fruits of medical research?

Furthermore, it is not clear that the definition of minimal risk can be re-fashioned to serve this one purpose when it also serves another regulatory purpose. It is not plausible to use the same standard both for expedited review and for permitted research with the vulnerable. To accept the same relative definition of minimal risk for both purposes is to suppose that any procedure that would be acceptable in paediatric oncology patients (for example), would be one that, when done with an adult oncology patient, would not need more than expedited review. Conversely, to accept a robust absolute standard of minimal risk, one appropriate for sorting studies needing full review from those for which expedited review is acceptable, would likely make clinical progress for vulnerable populations impossible by imposing a uniform and low threshold for permissible risk on a wide variety of medical conditions and experimental approaches.⁸⁶ It is both unlikely that the standard for each of these should be the same level of risk and benefit, and that the standard should be of the same kind in its character and ease

85 *Supra* note 60.

86 Hence the concern about the lack of flexibility for an absolute standard in Miller & Weijer, “Moral Solutions,” *supra* note 51 at 9.

of employment. A “checklist” standard would be appropriate for sorting expedited from full review; considerably more judgment would be appropriate for distinguishing the permissible risk level for a pediatric clinical trial.

To accept a solution to the problem of research with vulnerable populations that sets “minimal risk” as a standard but defines it as a regulatory fiction raises the question of whether the public and the courts are likely to, or ought to, accept such a redefinition of the phrase. They may, rather, accept researchers at their word that they consider more than minimal risk research to be unacceptable with children (for instance) and unnecessary for medical advance, but reject the research community’s specific interpretation of minimal risk in given cases. Indeed, to date, where U.S. courts have ruled on cases involving the concept of minimal risk, they have adopted an absolute interpretation; in their rulings, they draw on considerations about what it is permissible for guardians and/or parents to authorize on behalf of their children or on behalf of decisionally-compromised adults for whom they have substitute decision-making authority.⁸⁷ They have also asked first whether a study offers reasonable prospect of benefit and reasoned from that to whether the study may be considered “therapeutic,” rather than reasoning from the nature of a study as a clinical trial of an intervention intended to have therapeutic benefit to the understanding that the trial offers potential personal benefit for research participants. This suggests that the courts may view a trial of an intervention for a condition that has seen thirty or more years of clinical trials providing little or no benefit for research participants (for instance, Glioblastoma Multiforme) as fundamentally different from a trial of an intervention for a condition for which research trials do generally offer even odds for individual benefit to research participants. The courts may well consider the former “non-therapeutic” research and the latter “therapeutic,” despite the fact that, from a research design perspective, one describes both as therapeutic trials insofar as they are both trials of what are hoped to be therapeutically effective clinical interventions.

6. Minimal Risk in the U.S. Courts

U.S. courts, as Canadian courts, have accepted the argument that researchers owe a duty of care to research participants, and have made reference to standards of care articulated in regulatory documents and research ethics guidelines. The U.S. courts, unlike the Canadian courts, have reviewed cases

⁸⁷ Resnik, *supra* note 51.

relating specifically to the determination of a research study as minimal risk, in one case involving children and one involving the decisionally incompetent. In both cases, a relationship is drawn between the court's interpretation of the standard of care as delineated by the regulatory document, and the court's assessment of the level of risk to which those acting *in loco parentis* may agree to expose their charges. That is to say, the courts do not accept researchers' regulatory documents as the sole relevant standard for determining acceptable research risk for vulnerable research participants, but make reference to other social and legal standards.

a. *Grimes v. Kennedy Krieger*

The Kennedy Krieger Institute (KKI) conducted environmental studies from 1993-1995 to test the efficacy of a new and less costly method for lead abatement for low-income housing in inner-city Baltimore with the aim of reducing lead levels for children living in such housing.⁸⁸ For two years researchers periodically collected blood, dust and water samples to measure contamination across five groups of housing, two of which included control groups:⁸⁹ for one control group, extensive repairs had eliminated all lead hazards from the residences in question, while the other lived in houses built after 1978, when lead paints were outlawed for residential construction.⁹⁰ For the purposes of the study, KKI researchers assisted landlords in securing public financing for eliminating lead from their properties and encouraged – and in one case even required – them to rent the premises to families with young children.⁹¹ KKI

88 For description of this case and the controversy surrounding it, see D.R. Buchanan, "Justice and Fairness in the Kennedy Krieger Institute Lead Paint Study: The Ethics of Public Health Research on Less Expensive, Less Effective Interventions" (2006) 96:5 *American Journal of Public Health* 781; M. Spriggs, "Canaries in the Mines: Children, Risk, Non-therapeutic Research, and Justice" (2004) 30:2 *Journal of Medical Ethics* 176.

89 *Grimes v. Kennedy Krieger Institute Inc*, 366 Md. 29, 782 A.2d 807 (Md. 2001) at 18-19, 22 [*Grimes v. Kennedy Krieger*].

90 *Supra* note 67 at 38; R.M. Nelson, "Nontherapeutic Research: Minimal Risk and the Kennedy Krieger Lead Abatement Study" (2001) 23:6 *IRB* 6 at 8.

91 T. Lewin, "U.S. investigating Johns Hopkins study of lead paint hazard" *The New York Times* (24 August 2001 late edition) A11, online: <<http://query.nytimes.com/gst/fullpage.html?res=9405E1DF1331F937A1575B00A9679C8B63>>; Spriggs, *supra* note 88 at 176.

also encouraged families with children who were already living in houses designated for study to remain in them.⁹²

Two of the mothers of children enrolled in the study filed lawsuits of negligence against KKI on behalf of their children, alleging that the investigators did not fully inform them of the risks and hazards involved in the study,⁹³ and that they were not warned in a timely fashion when elevated levels of lead dust in their homes were measured⁹⁴ – information that they claimed (and the courts agreed) would have affected their willingness to have their children continue in the study.⁹⁵ The lower court agreed with KKI's argument that the investigators' research relationship with subjects did not give rise to a duty to warn of potential dangers found using an experimental technique⁹⁶ but the Maryland Court of Appeals reversed the trial court's decision on this point, ruling (consistent with U.S. precedents) that the researchers owed a duty of care to research participants in such situations⁹⁷ and went so far as to condemn the research as inappropriate, unethical, and illegal.⁹⁸

The Court ruled on two questions related to the minimal risk standard in coming to the conclusion that the research was unethical and illegal. The first was the question of what level of risk parents may consent to on behalf of their children.⁹⁹ The second was the question of whether the research in question complies with the standard of care owed to research participants as defined (at least in part) by the Common Rule. In respect to the first question, the Court of Appeals in *Grimes v. Kennedy* concluded:

92 *Supra* note 89 at 1-3.

93 Spriggs, *supra* note 88 at 176.

94 D. Wendler, "Risk Standards for Pediatric Research: Rethinking the Grimes Ruling" (2004) 14:2 Kennedy Institute of Ethics Journal 187 at 188.

95 *Supra* note 89 at 63.

96 *Supra* note 94 at 188.

97 In *Whitlock v. Duke University*, 637 F. Supp. 1463 (M.D. N.C. 1986), *affirmed by*, 829 F.2d 1340 (4th Cir. 1987), the United States District Court for the Middle District of North Carolina accepted that researchers owe a duty of care to a subject of non-therapeutic experimentation, and referenced 45 C.F.R. section 46.116. *Id.* at 1471 to establish the standard of care owed.

98 *Supra* note 89 at 7-8, 13-14, 75-76, 85, 89, 93.

99 *Ibid.* at 44.

We hold that in Maryland a parent, appropriate relative, or other applicable surrogate, cannot consent to the participation of a child or other person under legal disability in nontherapeutic research or studies in which there is *any risk* of injury or damage to the health of the subject.¹⁰⁰

More particularly, the court ruled that:

In our view, otherwise healthy children should not be the subjects of nontherapeutic experimentation or research that has the potential to be harmful to the child. It is, first and foremost, the responsibility of the researcher and the research entity to see to the harmlessness of such nontherapeutic research. Consent of parents can never relieve the researcher of this duty. We do not feel that it serves proper public policy concerns to permit children to be placed in situations of potential harm, during nontherapeutic procedures, even if parents, or other surrogates, consent.¹⁰¹

This ruling speaks directly to the permissible interpretation of minimal risk as a standard for “non-therapeutic” research with vulnerable populations, and appears to require of researchers a higher standard of protecting individual research participants than the standard of parental authorization. On the relative interpretation, what otherwise would pass as greater than minimal risk for the average population, i.e. some degree of exposure to an environmental toxin that has been eliminated from the environment for the average American child, could be justified as minimal risk for a study that recruits socioeconomically disadvantaged research subjects whose risks of daily living may include such exposure. The defense in this case argued for such a relative interpretation, claiming that half of the residences were occupied prior to the study, and the other half were occupied *after* the study commenced by “inner city families who likely had no choice but to rent non-abated properties....”¹⁰² The argument was that, given that poor children in Baltimore were living at the time in housing with lead hazards, to expose these children to lead in the non-abated properties was not to expose them

100 *Ibid.* at 89-90 [our emphasis].

101 *Ibid.* at 76.

102 “Lead-Based Paint Study Fact Sheet” (www.kennedykrieger.org) quoted in Nelson, *supra* note 90 at 8.

to more than minimal risk in the relative sense of risk beyond that which they would have otherwise encountered in their ordinary daily lives.

The court did not endorse this interpretation of the KKI study. On the contrary, it ruled that the regulations, insofar as they reference the concept of minimal risk, were clearly violated in this instance:

The research did not comply with the regulations. There clearly was more than a minimal risk involved. Under the regulations, children should not have been used for the purpose of measuring how much lead they would accumulate in their blood while living in partially abated houses to which they were recruited initially or encouraged to remain, because of the study.¹⁰³

According to the absolute interpretation of minimal risk, the upper limit of harm would be the risks encountered by most or all children, including wealthy and healthy children whose routine daily lives did not include exposure to lead poisoning.¹⁰⁴ It was this standard, and not the relative standard, that the court adopted, although existing regulatory documents contain assertions that could well be interpreted as asserting a relative standard, as we have seen.

There is concern that not only have the courts adopted an absolute standard, they have adopted an absolute standard that is more stringent than a simple absolute interpretation of the federal guidelines. Indeed, comments made in the judgement seem to rule out the minor increment over minimal risk allowed in non-therapeutic research by U.S. (but not Canadian) research guidance documents. Furthermore, some argue that this case creates a new standard in ruling out exposure of participants in non-therapeutic research to any risk whatsoever, a tighter restriction than minimal risk. KKI, in consort with Johns Hopkins University and the University of Maryland and other research bodies, asked the court to reconsider its ruling, warning that the "any risk" standard of the Maryland Court of Appeals could "cripple the pursuit of critical" pediatric research, arguing that:¹⁰⁵

103 *Supra* note 89 at 72.

104 *Supra* note 67 at 42.

105 *Supra* note 94 at 189; R.S. Tyler & J.H. Young, "Brief of the *Amici Curiae* association of American Medical Colleges, Association of American Universities, Johns Hopkins University, and University of Maryland Medical System Corporation in Support of Appellee's Motion for Reconsideration" (17 September 2001),

Unless narrowed, the Court's "any risk" holding would prohibit critically important and potentially promising cutting edge research. For example, a great deal of research is being done in early detection of adult diseases. Completely normal children whose parents have Type I diabetes are being screened for antibodies to pancreatic islet cells. There is some risk associated with these tests and the findings from these blood tests will not benefit these normal children since, at present, the significance of having the antibody (or not) is unknown. Opportunities to do many types of genetic research would also be prohibited by the Court's "any risk" standard. The ability to do skin biopsies, for example, of disease-affected children and their non-affected siblings is necessary to determine the association of abnormal genes with disease. Again, these biopsies are not risk free, and they are nontherapeutic for the non-affected siblings.¹⁰⁶

The Appeals court denied the motion for a reconsideration, and in its *Per Curiam Opinion* it issued a clarification:

...by "any risk," we meant any articulable risk beyond the minimal kind of risk that is inherent in any endeavor. The context of the statement was a non-therapeutic study that promises no medical benefit to the child whatever, so that any balance between risk and benefit is necessarily negative.¹⁰⁷

The court in this clarification perhaps failed to appreciate that the regulatory approach, in addition to labeling two kinds of research "therapeutic" and "non-therapeutic," also considers a portion of the procedures that research participants undergo in so-called "therapeutic" research to constitute a "non-therapeutic" component; or perhaps the court considered the request for clarification to present issues that could only be considered in a ruling on cases of "therapeutic" research. The *Per Curiam Opinion* does not clarify whether the courts may reason in similar absolute terms for the non-therapeutic portion of a "therapeutic" trial or whether the courts would accept the regulatory stipulation that (for instance) a lumbar puncture for some patient groups is minimal risk.

online:AttorneysforAmiciCuriae<<http://www.hopkinsmedicine.org/press/2001/SEPTEMBER/briefs.htm>> at 13.

106 *Ibid.* at 12.

107 *Supra* note 89 at 3.

b. *T.D. v. New York State Office of Mental Health*

The court in *Grimes* also endorsed the National Commission's conclusions with respect to the moral authority of parents: "Parents do not have the moral or legal authority to enroll healthy children in research that does not offer the prospect of direct benefit unless the risks of that research are no greater than the ordinary risks of daily life."¹⁰⁸ In *T.D. v. New York State Office of Mental Health*, the courts addressed the question of what guardians of incompetent adults could authorize on their behalf.

In *T.D. v. New York State Office of Mental Health*, the court was presented with a lawsuit filed in February 1991 on behalf of six involuntarily hospitalized mental health patients contesting the regulations over research in psychiatric facilities licensed or operated by the New York State Office of Mental Health (OMH).¹⁰⁹ The regulations (14 NYCRR 527.10 effective November 7, 1990) had been promulgated by the Commissioner of the OMH with the express purpose to "ensure the protection of patients who participate in research while, at the same time, facilitating research into the very disorders from which they suffer and that underlie their impairment."¹¹⁰ The primary purpose of the plaintiffs' challenge was to contest the validity of the OMH regulations – not federal regulations – that set forth the procedures to be followed for the nonconsensual participation by mental patients or minors in potentially high-risk experiments.¹¹¹ The New York mental health regulation at the time allowed a wide variety of third parties to make decisions about research participation on behalf of children or involuntarily committed patients.¹¹² In a case that involved extensive discovery of overreaching medical research, the New York Supreme Court, Appellate Division, affirmed a

108 Nelson, *supra* note 90 at 11.

109 *T.D. v. New York State Office of Mental Health*, 165 Misc.2d 62, 626 N.Y.S.2d 1015 (Sup. 1995), [*T.D. v. New York State OMH* 1995].

110 *Ibid.* at 1018.

111 *Ibid.* at 1017: "It is important to note at the outset that this action is not a broad-based challenge by the plaintiffs to any and all research performed on human subjects. It is limited to those procedures which may cause stroke, heart attack, convulsions, hallucinations, or other diseases and disabilities including death, and which, while possibly shedding light on possible future treatments to others, offer no direct therapeutic benefit to the participating subject."

112 *T.D. v. New York State Office of Mental Health: Decision on Experimentation on People with Disabilities*, 650 N.Y.S. 2d 173 (A.D. 1 Dept. 1996) at 190 [*T.D. v. New York State OMH* 1996].

lower court's decision that invalidated state regulation concerning informed consent with respect to children or adults incapable of consent to experimentation with more than minimal risk.¹¹³ The research in question was condemned for using unapproved and more than minimal – in specific, high risk – psychotropic drugs that could cause permanent or fatal side effects, although the research was classifiable as “therapeutic” research in the sense in which that distinction intends.¹¹⁴ Whereas the trial court based its decision on grounds that the statutory construction of the OMH regulations was invalid and without proper authority (on grounds of administrative law), the appellate court grounded its conclusions on matters of constitutional and common law.¹¹⁵ The appellate court ruled that the OMH state regulations violated the research subjects' constitutional and common law rights¹¹⁶ – the right to personal autonomy,¹¹⁷ including the right to refuse treatment.¹¹⁸ The court concluded that:

It may very well be that for some categories of greater than minimal risk non-therapeutic experiments, devised to achieve a future benefit, there is at present no constitutionally acceptable protocol for obtaining the participation of incapable individuals who have not, when previously competent, either given specific consent or designated a suitable surrogate from whom such consent may be obtained. The alternative of allowing such experiments to continue, without proper consent and in violation of the rights of the incapable individuals who participate, is clearly unacceptable.¹¹⁹

This case offers evidence of the court's willingness to apply criteria to the identification of “therapeutic” research that go beyond the definition that researchers formulate for themselves, and hence to challenge researchers' description of a study as offering a prospect of direct personal benefit:

113 *Ibid.* at 178.

114 *Ibid.* at 185.

115 *Ibid.* at 185-94.

116 D.M. Maloney, “State Law on Human Research did not Protect Subjects' Rights: T.D. v. New York State Office of Mental Health (Part I)” (2000) 15:1 Human Research Report 7 at 8.

117 *Supra* note 112 at 176.

118 *Ibid.* at 186.

119 *Ibid.* at 177.

The record demonstrates that defendants' experiments involving more than minimal risk expose the subjects to, *inter alia*, invasive and painful procedures and/or the administration of psychotropic drugs, antipsychotic drugs and other medications, which have harmful side effects as severe or even worse than similar medications and procedures currently used for treatment. ... It must be kept in mind throughout this discussion, that we are dealing herein with research that offers no benefit or only minimal benefit to the subject, as opposed to treatment where the sole motivation is a beneficial therapeutic effect on the patient with minimal adverse side effects.¹²⁰

Courts in Canada and the U.S. have ruled in *Grimes*, *Halushka*, and *Weiss* that where an intervention is non-therapeutic, the standard for protection of research participants from risk is if anything higher than in the clinical context, where such risks may be undertaken for the therapeutic benefit of the patient. In this instance, the court seems to be reasoning in a similar direction: in the context of "therapeutic" research, where the experimental "treatment" in question offers a very low chance of benefit to the individual research participant and a significant burden and/or risk of harm, there is if anything a heightened responsibility to protect vulnerable participants from the risks that may be involved.

Further to this ruling, the plaintiffs twice returned to court to obtain temporary restraining orders (TROs) in an effort to force the OMH to stop experiments that were continuing despite the court's order.¹²¹ The first contempt proceeding started on August 21, 1995 when the plaintiffs succeeded in obtaining a TRO,¹²² in which the courts described some research as being "possibly therapeutic greater than minimal risk experiments" and applied to these experiments the same restraining order as the research that could be described as greater than minimal risk non-therapeutic research.¹²³ As Capron notes in his critical commentary on the T.D. case, "The premise that research is 'therapeutic' is often dubious both in theory and in execution."¹²⁴

120 *Ibid.* at 185.

121 *Ibid.* at 177-179; A.M. Capron, "Incapacitated Research" (1997) 27:2 *Hastings Center Report* 25 at 25.

122 *T.D. v. New York State OMH* 1996, *ibid.* at 176.

123 *Ibid.* at 178-79.

124 Capron, *supra* note 121 at 26.

c. *E. (Mrs.) v. Eve*

In the Canadian context, it has been argued that the Supreme Court's ruling in *E. (Mrs.) v. Eve*, while not a case involving research, has implications for how researchers should understand permissible research risk. According to Bernard Dickens, the ruling raises the question of whether any parent may consent to medical intervention that is not in the best interests of their children; would the courts understand *any* medical research as reaching that standard?¹²⁵ If parents may only authorize medical interventions in the best interests of their children, how, then, could parents legally authorize the participation of their children in any research study, given that research, by definition, is constructed first and foremost to produce generalizable knowledge as opposed to providing therapy?¹²⁶

E. (Mrs.) v. Eve is a landmark case pertaining to the issue of the scope of a parent's right to substitute decision-making on the part of his or her individual incompetent child. In this case, "Mrs. E" filed a lawsuit to secure authorization to have her intellectually disabled daughter undergo a tubal ligation, in order to save herself the potential burdens associated with pregnancy and childbirth.¹²⁷ The plaintiffs declared that Eve was incapable of using any other method of contraception, that Eve had an inadequate understanding of pregnancy and childbirth, and that in the end Mrs. E. would be unable to care for the prospective child if Eve were to conceive.¹²⁸ The counsel of the defendant pointed out that sterilization is not therapeutic, and "in the absence of the affected person's consent, it can never be safely determined that it is for the benefit of that person."¹²⁹ The Court then explored whether the government could grant the right of sterilization under *parens patriae* jurisdiction which allows the state to make authorizations in the child's "best

125 *Supra* note 13.

126 R.J. Levine, *Ethics and Regulation of Clinical Research*, 2nd ed. (Baltimore: Urban & Schwarzenberg, 1986) at 8-10. See also Baylis & Downie, "An Ethical and Criminal Law Framework," *supra* note 13 at 41: "For example, with research it is generally hoped that patients will eventually benefit but the primary objective is to contribute to generalizable knowledge (i.e., to generate and validate new knowledge). With therapy, the primary objective is to benefit the patient (i.e., to enhance his/her well being by providing him/her with safe and effective therapy)."

127 *E. (Mrs.) v. Eve*, [1986] 2 S.C.R. 388 at 2-3.

128 *Ibid.* at 9-10.

129 *Ibid.* at 4.

interests" if no other source of consent is attainable, as is the case sometimes with incompetent children or intellectually disabled persons. Eventually the Supreme Court of Canada ruled unanimously against the request, holding that the risks in question were too great and the benefits too indeterminate and obscure to warrant via *parens patriae* a procedure that was not medically required,¹³⁰ and not clearly to Eve's benefit.¹³¹ The Court further underlined that, just as parental authority is properly exercised only in children's best interest, so also "the *parens patriae* jurisdiction is ... founded on necessity, namely the need to act for the protection of those who cannot care for themselves. The courts have frequently stated that it is to be exercised in the 'best interest' of the protected person, or again, for his or her 'benefit' or 'welfare.'"¹³²

Citing *E. (Mrs.) v. Eve*, Dickens argues that a precedent has been set that may make it impossible for parents to give their authorization for the participation of their children in research, or any guardian on behalf of an incapable patient. Dickens furthermore accepts the argument that it is inaccurate ever to describe research as "therapeutic," and so he sees the implications of this decision as extending beyond "non-therapeutic" research. In *Eve*, the Court noted "discretion is to be exercised for the benefit of that [dependent] person, not for that of others."¹³³ Parents are accordingly denied legal power to dedicate their children to participation in medical research of no immediate benefit to their children out of conscientious concern for the progress in general of medical care for newborns, infants, children or adolescents.¹³⁴

Baylis and Downie have pointed out that the courts do not second-guess parental decisions about best interests as closely as Dickens suggests: benefits of participating in research may extend beyond medical benefits to character formation through participation in such altruistic projects as medical experimentation.¹³⁵ *E. (Mrs.) v. Eve* was argued on assertions about what Eve would want if she were decisionally capable, and the court disputed that any justifiable assertion could be made about that supposed fact; the developmental and legal context of a child assenting to and parents

130 *Ibid.* at 48-49, pt.80.

131 *Ibid.* at 51, pt.86.

132 *Ibid.* at 75, pt.73.

133 *Ibid.* at 47, nt.77.

134 Dickens, *supra* note 13 at 133-34.

135 Baylis & Downie, "An Ethical and Criminal Law Framework," *supra* note 13.

authorizing research participation is significantly different and involves no counterfactual reasoning about what the child would choose if not a child; it is also significantly different from the *T.D.* case of overriding refusal of treatment or research participation. Furthermore, the courts may or may not agree with Dickens's argument that no research offers a relevant chance of direct benefit, but may decide depending on the case whether there is a sufficiently high chance of personal benefit for research participation to be considered consistent with the child's best interests. We have no indication of what the courts would consider a relevantly robust chance at direct benefit: the ruling in *T.D.* suggests that some "therapeutic" research (e.g. equivalence trials of highly toxic psychoactive drugs) does not meet such a standard, and therefore that the courts are prepared to establish standards independent of the definitions that research guidelines assert. What the courts would think of a trial offering a 70 percent chance of benefit and 30 percent chance of harm compared to standard of care has not been asked; likewise, we do not know what they would think of a trial that offers (for the sake of argument) a 70 percent chance of significant permanent harm and a 3 percent chance of cure of a condition that is fatal within weeks or months. It seems unlikely, however, that any claim that such odds constitute "minimal risk" – based on the combined application of the standard of clinical equipoise and the relative interpretation of minimal risk – would be accepted.

Conclusion

The regulatory fiction of the relative standard for "minimal risk" is unlikely to be successful when reviewed, as it eventually may be, by the courts. Not only is non-therapeutic "minimal risk" research that actually poses risks likely to be redescribed accurately by the courts as above minimal risk, but also "therapeutic" research that offers only a remote benefit to individual research participants may come to be distinguished as a particular category to which the same considerations apply as to non-therapeutic research. We should turn our attention to articulating just what the higher standards are for exposure of vulnerable populations to research risk.

We recommend distinguishing the different goals which "minimal risk" is now supposed to serve and articulating permissible levels of risk and reasons for their permissibility that are appropriate to each case. We should not expect the same dividing line and justification to support three purposes: to excuse the highest level of scrutiny in ethics review, to justify authorization for research participation given by guardians on behalf of children or on

behalf of adults without capacity, and to create the possibility of excusing the need for fully free and informed consent. For the first and third purposes, we may well want an absolute standard that equally protects all. In addition, the first purpose would also best be met by standards that can be applied in a “cookie cutter” fashion. For the second purpose, enabling important research with vulnerable populations, we may well need to articulate the standards by which higher than minimal risks are accepted in some circumstances – without misdescribing such risks as minimal. These standards are likely to be ones that cannot be applied in a “cookie cutter” fashion. The standard for judging a study to have an acceptable harm-benefit trade-off should be clearly distinguished from the standard for judging a study to be minimal risk.

If the risks of the research necessary to avoid the result of depriving vulnerable groups of the benefits of research turned out to be only minimal, then it would seem that we could permit sufficiently risky research with vulnerable populations to provide them with the benefits of medical advance and at the same time protect those populations from any risk above those of daily living – a result that would indeed be ethically desirable if it were possible. However, only a relative definition of risks of daily living that redefines invasive or risky experimental procedures, or invasive monitoring and testing procedures, as minimal risk can accomplish such an ethically admirable purpose, and it does so by mislabeling serious risks as minimal. That is, the good is clearly one that can be achieved in word only, and not in deed.

Even though we wish to ensure that high risk procedures are not passed off as minimal risk, we do not advocate shutting down all non-therapeutic research for vulnerable populations which is above minimal risk. Hutt describes the effects of thwarting research for vulnerable populations in the 1970s: when populations considered vulnerable (for instance, the mentally disabled and pregnant women) and hence excluded from research did receive new treatments, there was very little data by which to predict what might result.¹³⁶ Note that in such cases, what the protective move was attempting to avoid (exposing the vulnerable to unknown risks) was in fact intensified by the form that protection took: more of the vulnerable populations received the (experimental) treatments, and with less medical over-

136 P.B. Hutt, “Five Moral Imperatives Five Moral Imperatives of Government Regulation” (1980) 10:1 *Hastings Center Report* 29.

sight, than would have received them if they had been permitted to participate in the research. We should turn to making explicit such reasoning behind research with vulnerable populations, and articulating true standards for its acceptability, rather than relying on the fiction that the risks involved are minimal.

