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Law and Risk

Legal Dimensions Series

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Human participants in biomedical research are vulnerable if only because the promotion of their well-being is not the main goal of the research and because their participation may expose them to significant risks. In addition, those who participate as patients are dependent on physician/investigators not only for information about the research and its risks but also for the clinical attention they receive in the process. In our view, sufficient formal legal mechanisms to counterbalance the vulnerability of research participants and to protect their rights and well-being are currently not available. Since extra-legal guidelines provide the main focus of their protection, one could even argue that the law currently contributes to the vulnerability of participants by neglect. There is currently no comprehensive legislation to regulate all research with humans, even though various governmental agencies seem to realize that there is a need to improve protection. The federal government, for example, stated in the 2002 Throne Speech that it intended to “work with the provinces to implement a national system for the governance of research involving humans.”

This chapter focuses on the role of law in dealing with one particular aspect of the protection of research participants: the evaluation and appreciation of risk in biomedical research. This question is obviously relevant to governments and governmental agencies responsible for research-related issues, but it is also vital to members of research ethics boards (REBs), whose mandate is to protect the rights and well-being of research participants. It is their responsibility to ensure that risk to participants is minimized and proportionate to the potential benefit of the research. REB review currently constitutes the major institutional mechanism evaluating research protocols, which contain the physician/investigators’ perceptions of risk. After reviewing, among other things, the risks and the potential benefits of the proposed research, REBs recommend whether physician/investigators can go ahead with the study and start recruiting participants. One way that the approach to the review structure that purports to assess it. Our suggested approach involves a review process that can balance the interests of those proposing the risk in formal research protocols (and subsequently producing the risk in ongoing research) by empowering the critical and protective interests of those who might assume it. We contend that this process requires fundamental changes at the regulatory and REB levels. We will argue for a different kind of engagement between REB members. Our new approach could also involve a legal mandate for the involvement and decisional authority of risk-cautious participant advocates in research review.

Conrad Brunk, Lawrence Haworth, and Brenda Lee have analyzed risk assessment as an inherently value-laden, political exercise in regulatory science. Following this approach, we argue that this exercise may afford questionable estimates when applied to some types of biomedical research. Given current developments in genomics and molecular biology, regulatory science might be especially fallible in assessing the risks of gene transfer and stem cell research. In this chapter, we classify two general types of risk that have been highlighted by this research as it is, or will likely be, carried out in the existing research environment: risks to persons and risks to social values. We then consider three different forms of risk that we believe the law should address. These are risks of physical or psychological harm to participants; risks to the objectivity and scientific integrity of research that are posed by conflicts of interest; and, briefly, risks to other social values, for example, public trust in the ethical conduct of research. These are very different areas of risk, but we think there is merit in addressing them jointly. Conflicts of interests, for example, may have a conscious or unconscious impact on the way researchers represent risks or on other behaviour of research staff during the recruitment process or during the research itself. In areas where there are problems with the understanding and transmission of risk information to participants, there is greater concern about the impact of conflicts of interest and more reason to develop a fully independent review of risks.

We sketch some principles and guidelines for institutional reforms that could inspire the further development of a regulatory or legislative model for the oversight of research involving humans. Our suggestions should help at a later stage to develop a more detailed model that would better manage the three risks noted earlier. It should also allow for the scrutiny of the methodology and the presentation of risk assessments. This scrutiny might occur locally in an REB system in which physician investigators and participant advocates negotiate the politics of risk assessment. It might occur at the provincial or federal level under the aegis of independent provincial or national agencies. Or it may be that a combination of local, provincial, and federal review will be the best solution. While several national committees
in Canada, we believe that there is room for a fully independent national agency that receives paramount authority in this area. However, before sketching the contours of such a review system, we turn first to a critical evaluation of regulatory science.

Value Frameworks, Regulatory Science, and the Politics of Risk Assessment

It is now generally accepted that no medical research involving humans should proceed without proper review by an independent REB. Local REBs are mandated by various ethics guidelines and regulatory documents to review research protocols proposed by researchers and to decide whether these protocols receive their imprimitur. During the review process, REBs examine a variety of issues. For example, although REBs often give most of their attention to informed consent, they are also expected to look at the value and validity of research protocols, the fairness of the selection criteria, potential privacy concerns, and, last but not least, the balance between the risks and potential benefits.

Risk assessments are fundamental to the ethical review of biomedical research. According to existing research ethics guidelines, such as the Canadian federal funding agencies’ Tri-Council Policy Statement,11 REB members must ensure that the risks involved in proposed research do not outweigh the potential benefits. The Medical Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council (Tri-Council) embrace a proportionate approach to ethics review, by which greater levels of risk require increasing levels of scrutiny. What levels of risk are considered acceptable depends on the nature of the research. A different evaluation is required depending on whether research is designed to test new interventions aimed at treating an illness or whether it is focused on gaining knowledge without expectation of therapeutic benefit for trial participants.24 In the first case, the trial should proceed only on the REB’s conclusion that harms have been minimized and are “proportionate to the benefits that might be expected from the knowledge gained by the study.”14 In both cases, research protocols must specify the potential harms to the participants. They sometimes provide quantitative estimates of the chances that participants might sustain these harms in the trial.

Risk analysis has been presented in different ways. Three phases are often noted: risk identification, risk assessment, and risk management.23 Risk identification involves determining whether a defined hazard is present and whether it is of sufficient magnitude to merit concern. A problem will be defined, the purposes of a risk analysis formulated, and the available information gathered and scrutinized. These screening assessments can be “quite crude” depending on the quality and quantity of available information and the state of the science that informs the analysis.16 Qualitative analysis can play an important role in “characterizing the fundamental assumptions of the analysis and the state of the science supporting them.”17 The risk assessment phase determines qualitative or quantitative estimates of the incidence and magnitude of a hazardous, adverse event on a given population. The risk management phase draws upon these estimates to develop policy options that aim to prevent, minimize, or mitigate the risks and evaluate their “health, economic, social, and political implications.”18 Various subspecialties of risk studies have been developed that provide specific assistance to risk analysis. Risk perception studies, for example, examine how people perceive the risks and benefits as well as their preferences for various risk/benefit trade-offs.19 Risk communication studies examine the effectiveness of different formats for interpreting risk analysis results to the public.20

Brunk and colleagues, who have written on environmental risk debates, present the classical model of risk analysis as a two-stage process that moves from risk assessment, or estimation, to risk evaluation. The risk assessment stage is said to involve a purely factual estimation of the level of an identified hazard that measures the magnitude of the potential harm multiplied by the probability of its occurrence. This stage is often alleged to be a value-free assessment of the objective risk. The magnitude of the harm sustained in the event that a hazard occurs, as well as the probability of its occurrence, are usually presented as issues of fact and mathematics.21 The second stage involves risk evaluation – that is, a normative determination of the risk’s acceptability. Also known as risk management, this phase is not value-free. It involves the setting of safety and compensation standards and the allocation of management costs. These decisions reflect value judgments about norms of acceptability. While risk management proceeds from the estimate made at the first stage, it is influenced by public notions of subjective risk or risk perception. In the classical model, the rationality of these
public judgments is assumed to depend on how closely they reflect the assessors' objective estimates of both the magnitude of harm and the probability of its occurrence. Lower estimates should inform higher levels of risk acceptability and vice versa. Differences between the assessors and the public on risk acceptability have been presented as conflicts between those rational experts who understand the objective risks and those irrational lay people who do not. If values exert an unavoidable and significant influence on risk estimations, then the two-stage distinction is suspect.

Some argue that the line between risk assessment and risk management should be drawn less strictly. Even assuming the best of intentions, the assessors' assumptions and beliefs may have normative implications that will make it difficult, if not impossible, to uncouple the quantitative task of risk assessment from the value judgments involved in determinations of safety. Risk assessments may thus have as much or more to do with the values that influence our definitions of harms and benefits as they do with the quantitative methods by which the occurrence of harms is estimated.

There are at least four reasons why risk assessments, including those presented to REBs, should be scrutinized more closely. First, risk assessment is a regulatory or mandated science that seldom produces conclusions with the confidence levels employed by laboratory science. Brunk and his colleagues describe a significant gap between theoretical, or laboratory, research and the need to make defensible regulatory or management decisions. The laboratory scientist is trained to wait until all the necessary data are in and all the variables are sufficiently controlled. Only then can reliable conclusions be drawn. Risk assessors may not have this luxury. Their estimates often undergird a decision to proceed with, or curtail, some potentially risky plan of action “before the data concerning that risk are complete.” Their conclusions will not attain the high confidence levels employed by laboratory science. This process attempts to protect the general public from products and activities that pose unacceptably high levels of risk. Agencies that administer this process must decide among the conflicting interests of the parties to a risk debate. These parties can be more or less risk cautious. Regulatory decision making can protect the interests and values of some parties and curtail those of others.

Second, numerous studies have shown that the parties to a risk debate can assess the same data with widely divergent results. William Freudenberg notes that calibration errors, or mistakes in estimating probabilities, present “serious problems” for scientifically trained assessors. He claims that “the most serious problems occur in the absence of reasonably definitive data, but [that] the general tendency in risk assessment is for even reasonably definitive data to be in unreasonably short supply.” These problems have been especially relevant to environmental issues, such as the ocean dumping of nuclear waste and the potential release of toxic substances into the environment. These problems can be less relevant if extensive toxicological and epidemiological data on environmental health risks are available. There may, however, be gaps or inconsistencies in the data.

Freudenberg's observations can be applied to assessing the general risks of harm from participating in biomedical research. This task raises issues relevant to both stages of the classical model of risk analysis. These issues concern, first, the methodology by which these risks are estimated and, second, the normative determination of risk acceptability. For instance, the clinical trial staff communicate drug-specific information to potential volunteers, they provide little or no data on the general risks of research participation. Statistical information on the general risks of drug trials might address the following questions: How many participants experience a serious reaction to a study drug? How many participants die annually during a clinical trial? Yet, according to CenterWatch, a monthly industry-sponsored publication that monitors US clinical trials, “this information is simply not available.”

CenterWatch made a provisional attempt to gather some of this information. It collected data from 130 randomly selected new drug applications that received Food and Drug Administration (FDA) approval between 1987 and 2001. These trials represented just under one-third of all new drugs approved by the FDA during this period. Although the data consist of averages that do not “convey the high level of variability between clinical studies," the CenterWatch findings "suggest that death is a rare occurrence during clinical trials while adverse events occur routinely." On average, CenterWatch concluded, one out of every thirty participants per new drug application will have a serious adverse event (for example, one that is “life threatening, permanently disabling or that result[s] in hospitalization”). In reviewing reports from the pharmaceutical industry to the FDA, CenterWatch concluded that one out of ten thousand participants “has died as a result of study drug effects while participating in clinical research studies.” While we are in no position to verify these figures, we agree that the provision of accurate information on general research risks should play a crucial role in the recruitment of clinical trial participants. The estimated one-in-thirty odds of experiencing a serious adverse event from taking a study drug might give some potential trial participants pause. It seems crucial for the protection of research participants, therefore, to create the greatest possible transparency with respect to adverse events and research findings resulting from previous studies. Too often, negative trials and trials deemed uninteresting by research sponsors remain unpublished and unreported.

However, even if negative trials were published and reported, the task of estimating these general risks would be challenging given the high level of
to account for the numerous variables that impact on general research risk — for example, the type of intervention, the trial duration, the severity of the target illness, and the differences in the researchers’ subjective definitions of adverse events. We can also question the extent to which such general averages relate to any one participant’s relative risk — that is, the risk to an individual from a specific intervention of a particular dose and at a particular time. The risks that members of a group may run as individuals are not the same for each. For instance, one subject may be in better physical condition; another may suffer from heart disease that would make the experience even more dangerous for him. In terms of infrastructure, providing estimates of general risk would require a central repository to receive data from all relevant trials as well as a comprehensive reporting scheme that researchers, REBs, research participants, and regulators could utilize.

Brunk and colleagues talk about risk assessment in the context of environmental harms. Their point is that the absence of a sufficient body of accumulated data makes risk assessment an attenuated science. Stem cell and gene transfer research on humans also proceeds in the face of much uncertainty about long-term risks or benefits to humans. We argue that some of the insights of Brunk et al. and others also apply to this area. Who among us can say reliably that stem cell interventions pose minimal risk to research participants? Notwithstanding encouraging reports about the potential clinical applications of stem cell research in cardiology, a recent article in Nature warned in its introduction that “we should be wary of prematurely pushing laboratory research into clinical practice.” The risks posed to gene transfer research participants vary with the techniques used to transfer genetic material into the body. While a risk assessment could plausibly aim to quantify the risk of malignancy, we may currently lack the established database to estimate this hazard with anything approaching the confidence level used by laboratory science. This uncertainty is the gap that risk assessment confronts in the context of this research. And it is this gap that has sustained the characterization of gene transfer research as “high risk.”

The third reason for scrutinizing risk assessments is that safety standard issues such as the protection of human research participants are “trans-scientific,” that is, they oscillate between facts and values. Roger Kaspertson avers an “oft-forgotten truism of risk analysis — that damage to people and what they value is the product of environmental or technological threat, human vulnerability to such threats, and values.” All three terms, and, in particular, the latter two, “are socially and economically dependent.” This fact might limit the extent to which risk analysis is a science for specialists as opposed to a normative exercise to which properly trained laypersons could contribute. The assessment process can reveal implicit normative science and the reality of risk estimation in the regulatory situation.” The challenge to the classical model of risk analysis is that values also exert an unavoidable influence on first-stage estimations. Kristen Shrader-Frechette argues that the quantitative risk assessment of hazardous substances is laden with value judgments in the face of uncertainty: “Assessors must make value judgments about which data to collect; how to simplify myriad facts into a workable model; how to extrapolate because of unknowns” and how to choose the statistical tests, sample sizes, and any other criteria that will be used.

Several other inherently normative questions are relevant to the first-stage estimation of the risks of gene transfer research. For example, is it fair to expect that researchers will always take every effective precaution to minimize the risks of contamination during vector preparation? In order to measure these risks, we need to determine an applicable safety standard. How much significance should we give to the risk of human error? What institutional or individual factors should be seen as increasing this risk and by how much? How much care should we expect researchers to take when preparing the viral vectors to ensure that they are incapable of virus reproduction? How do we define magnitudes of harm? What constitutes a serious adverse event? These are not factual questions. The process of answering them is prescriptive, not descriptive. Values are influential in this case because we have to define what we are trying to estimate. Available facts can help us to identify issues, but these issues can be resolved only by invoking values related, for example, to the acceptable levels of risk. The risk assessor’s value framework thus contributes to the framing of the risk assessment. Since scientific data do not interpret themselves in the estimation of risk, the assessors have no choice “but to employ an interpretive point of view.”

Most risk analyses use numbers. A harm’s probability of occurrence might be rendered statistically. The magnitude of harm might be measured by estimating the expected number of deaths in the relevant population and by assigning some value to these statistical lives. It could also be measured by estimating the incremental risk of death to an average person in this population and attaching some value to this risk. Either way, the “magnitude” of a harm is still a value-laden notion — it produces an expected value, which can be compared against other costs and benefits. For example, once we assess the magnitude of a harm, we might use that information to decide that it is worth $X to society to save a statistical life. The social value of a human life is a controversial issue in assessing the magnitude of risk. Magnitude also relates to the seriousness or severity of harms, which may refer to notions of pain, discomfort, suffering, disability, perceived injustice, or the debasement of values. Unlike death, these aspects “come in different qualities and degrees” and are thus even more difficult to measure.
numbers are generated is insufficient. To understand a risk assessment, we need to understand the values in terms of which the risk is framed—that is, defined and presented. This focus on the qualitative dimensions of risk assessment is also relevant to somatic gene transfer and stem cell protocols since we currently have little in the way of quantitative data on the general risks of participating in this research. Without such data, the promise of benefits to be gained can be seen as a decisive reason for taking risks.31

In practice, risk assessment is often dominated by human judgment in the face of uncertainty.32 The uncertainty inherent in many forms of research adds to the complexity of the risk assessment process. This is clearly the case in the context of genetic research. Indeed, the presentations of risk in some somatic gene transfer protocols admit to pervasive uncertainty about the potential harms.33 There is, we suggest, still much uncertainty about molecular behaviour that complicates risk assessments of gene transfer and stem cell research. As Akshay Anand and Sunil K. Arora point out, “[c]linical genetics is still in its infancy.”34 According to Evelyn Fox Keller, we have not found that gene location explains gene function. The structural gene is the indispensable raw material in the dynamic process of stable genetic development. Yet this process now involves many other variables, including regulatory sequences found elsewhere on the genome, the products of other structural and functional genes, and the signaling network of the living cell. Keller would argue that we are just beginning to understand the complexity of this process.35

In even the clearest examples of single gene disorders, much remains to be learned about the processes by which a defective gene is linked to the onset of disease. The limits of current understanding are “far more conspicuous” in conditions that involve the participation of many genes (for example, heart disease or stroke). Keller posits a “therapeutic gap” between proficient genetic screening and medical benefits from gene transfer interventions. In terms of laboratory science, the data are far from collected.36 As of 2001, attempts to treat single-gene diseases comprised an eighth of the world roster of about 500 approved clinical protocols for gene therapy research. Transient gene expression research, which targets coronary-artery disease and various types of cancer, accounted for most of the remainder.37 This research involves growth-factor genes or genes that might stimulate the immune system. They are transferred into the body through viral vectors for short periods of activity. This might cause new blood vessels to grow around blocked coronary arteries or help to shrink tumours. In short, transient gene expression is a developing hypothesis. Theoretically, the infusion of growth-factor genes should be sufficient to start the process. According to specialists, while these approaches to vascular diseases and tumour immunotherapy are promising, “they are still in their infancy.”38

By January 2004, there were 918 approved clinical trial protocols for gene transfer research. Only 15 (1.6 percent) were Phase III trials, which focus on efficacy and therapeutic value in a larger sample of patients. Most (589 or 64.2 percent) were Phase I trials designed to assess safety. There were 120 (13.1 percent) Phase II trials designed to assess efficacy and 185 (20.2 percent) combined Phase I/II trials. There were 9 (1 percent) combined Phase II/III trials.39 Thus, most of this research cannot be claimed to have potential therapeutic benefit to participants. We suggest that risk assessment of gene transfer research still takes place in an environment where reasonably definitive data are, in Freudenberg’s words, in unreasonably short supply.40 Simply put, assessing the risks of gene transfer and stem cell research is not on par with estimating the risks of lung cancer from smoking, of asbestosis from asbestos, or of HIV/AIDS from unprotected sex. Indeed, epidemiologic studies can identify factors that increase a person’s risk for many chronic diseases.41 Yet, while access to genomic sequences will increasingly shape risk assessment in the coming decades, “genomic researchers are not necessarily focused on risk assessment problems.”42

There is a fourth reason for the law to be concerned with the scrutiny of risk assessments. Those individuals who propose research in which the harm could be sustained may be less cautious about risk than those who might be harmed. Some of those who assume the research risks may be more inclined to err on the side of protection than those who propose them. Brunk and his colleagues remind us that “risk” is a Janus-faced term. A serious risk of harm with a low probability of occurrence can be seen as a good gamble in a scientific attempt to realize great potential benefit. One might even characterize the greater risk as the loss of opportunity to realize potential benefit if the study does not proceed. Yet this risk can also be seen as something to avoid despite potential benefit. These risk perceptions depend on whether one is inclined to risk taking or to risk caution. They can also reflect different values about the importance of certain biomedical technologies or the range of benefits that should be realized in the health-care system. This can politicize risk debates in terms of the agendas the different parties bring to the table. We are sceptical of the notion that risk debates arise between those whose judgments are determined by objective analysis of the risks and those whose judgments are determined by irrationally subjective risk perceptions.43 We argue that they are, in fact, debates “among different value frameworks, different ways of thinking about moral values, different conceptions of society, and different attitudes toward technology and towards risk-taking itself.”44

Concerns about risk assessment in somatic gene transfer research were raised in the mid-1990s. European critics noted in 1994 that inflated publicity about “gene therapy trials” risked misleading the public. They called
for a full public review of ongoing trials in 1994 to provide a “realistic assessment of the risks and state of the technology currently available.” In a report to the US National Institutes of Health (NIH) in 1995, an expert review panel concluded that many physician/investigators and their sponsors were “overselling” the technology and promoting the idea that “gene therapies” were further developed than they were. Despite anecdotal claims of successful therapy and NIH approval of more than 100 human studies, the review panel found that clinical efficacy had not been reliably demonstrated. Contrary to public perception, genetic gene transfer research was still in a very early stage. The panel found that little was really known about the vectors used to transfer genes into target cells. Many of the studies reviewed were found to have a weak design that yielded scant data. The panel also expressed concern that misleading publicity could give research participants erroneous ideas about what was feasible. It warned that turning a “blind eye to the hype could lead to serious consequences.”

Even so, there was very little public or academic discourse about the risks of somatic gene transfer research before the first known death in a US gene transfer study in 1999. Jesse Gelsinger, an eighteen-year-old man with a mild disorder of nitrogen metabolism known as ornithine transcarbamylase deficiency, participated in a gene transfer study at the University of Pennsylvania in which an adenovirus was being tested as a means of transmitting a gene to correct the disorder. He died from an immune reaction four days after the adenovirus was injected into his liver. His was the first death attributed directly to gene transfer research. It resulted in worldwide publicity, a suspension of all “gene therapy” trials at the University of Pennsylvania, and a senate subcommittee investigation.

Three Particular Risks in Biomedical Research

We classify two very different types of risk from gene transfer and stem cell research: risks to persons and risks to social values. We consider three risks in particular that we feel the law should address. These are risks of physical and psychological harm to participants, risks to the objectivity and integrity of science that are posed by conflicts of interest, and risks to other social values, for example, the sanctity of life and public trust in science. Although the risks are not exclusive to gene transfer and stem cell research, the combination of these risks in these forms of new biomedical research merits our attention. Gene transfer and stem cell research are used for our purposes as paradigm cases of new forms of research.

The risks discussed in this essay can also overlap. Risks to participants are often unrelated to conflicts of interest, and conflicts of interest will not necessarily create a situation in which participants are more likely to be exposed to the risk of physical harm. Yet such conflicts seem to have consequences that also compromise professional conduct regardless of participant harm. They also can affect the social value of public trust in the conduct of research. Strong correlations have been observed between trust and the public acceptance of estimated risks and benefits, especially those pertaining to new technologies about which the public lacks “scientific” knowledge. Uninformed trust can make research participants vulnerable to biased risk assessments of gene transfer and stem cell research. We can cite other examples in which such values could be threatened regardless of conflict of interest. For instance, the creation of embryos for stem cell research can affect widely shared assumptions about the sanctity, or the special value, of human life. While we include all of these forms of risk in our discussion, we realize that some risks to social values may not be suitable for REB scrutiny but should be the subject of wider public debates.

Risks of Physical Harm to Research Participants

Recent events have led to growing concerns about the physical risks of, and risk reporting systems for, gene transfer research. Following the death of Jesse Gelsinger, the NIH was quickly informed of 652 previously unreported serious adverse events that occurred during gene transfer trials, of which six were deaths. This new information led to congressional hearings on the oversight of patient safety. The first Canadian “gene therapy” trial was conducted in 1993, and at least thirty other trials have been approved since that time. The first known death of a Canadian gene therapy research participant occurred in 1997. James Dent was diagnosed with a malignant brain tumour and enrolled in a gene transfer study. He was injected with a virus that carried genes to his tumour. He died a few days later. According to the Canadian Broadcasting Corporation (CBC), a Health Canada report found that the second stage of the trial in which James Dent was enrolled contributed to his death. The consent form that he signed contained no information about the “serious adverse brain events” that afflicted seventeen out of thirty patients in a similar trial. Allegedly, James Dent was unaware of this information, despite the fact that it was known both to US regulators and to Novartis, the company that sponsored his trial. There were other omissions. It was never reported to Health Canada that a US patient died in Indiana only days before in the same multi-centre trial. Nor was this first death reported, as required, to the US NIH, which posts such information on its website. According to the CBC, Novartis later acknowledged that it was its responsibility to report the Indiana death to Health Canada within seven days. The company has since terminated all research on the “gene therapy product” that was tested on James Dent. In December 2002, twenty-seven of the more than 200 ongoing US gene transfer trials were suspended after French researchers reported that the vectors used in some of their trials...
US trials were allowed to resume on March 2003, although the FDA refused to approve two suspended US trials similar to the French research that led to the cancer cases.77

We still face significant challenges in determining the physical risks of somatic gene transfer research. We can characterize four of the most important risks: (1) contamination during vector preparation; (2) immune responses that interfere with treatment efficacy; (3) malignancy, that is, if vectors disrupt host tumour-suppressor genes or activate oncogenes; and (4) viral recombination.78 However, vector toxicity levels for animals may diverge from those of humans and immunological predispositions to vectors may vary between individuals. There are also concerns about the reliability of transferring preclinical data from the animal model to therapeutic application in humans.79 In short, while we can characterize these physical harms, we may not yet be able to reliably assess their probability of occurrence. “A reliable assessment of the risk of cancer,” for instance, “will require long-term follow up of large numbers of patients.”80

A long-term monitoring system would have to retrieve, on an annual basis, information covering the causes of any deaths, the appearance of new cancers, any unusual abnormalities or illnesses, and the birth of any children to participants after the trial. Surprisingly, the United Kingdom’s Gene Therapy Advisory Committee found in 2000 that there was no formal long-term monitoring system for gene transfer research participants anywhere in the world. Although the need for such follow-up was recognized early on, the comprehensive retrieval of required data has not proceeded apace with the growth of gene transfer research.81 Indeed, the national databases by which the general risks of this research might be estimated are still being developed.82

In the context of stem cell research, two recent Canadian developments are worth mentioning. The first initiative came from the Canadian Institutes for Health Research, which has convened a Stem Cell Oversight Committee to review government-funded stem cell research. This committee will, however, have no authority to monitor private-sector stem cell research.83 A more rigorous regulatory structure was introduced with the new legislation on assisted human reproduction. Bill C-6, An Act Respecting Assisted Human Reproduction and Related Research,84 requires the establishment of a Canadian Assisted Human Reproduction Agency. It will oversee and control research activities related to assisted human reproduction and enforce various statutory prohibitions (for example, a prohibition on reproductive and therapeutic human cloning).85

Members of the risk analysis community have argued that new genomic data may require an assessment framework that has yet to be appropriately developed.86 We see no reliable basis for stating that, as of 2004, the hypo-

about which we are just beginning to learn.87 Indeed, we may be running risks of physical harm that we have yet to discern.88 Consider the current state of stem cell research. It is very difficult to remove implanted stem cells from the body should something go wrong. There is still speculation about how implanted stem cells, especially embryonic ones, might proliferate in the human body. Embryonic stem cells are undifferentiated and pluripotent - that is, they have an unlimited capacity to divide. Hence, there is the concern that they might form teratomas or cancerous growths.89 For instance, a recent study by Lars M. Bjorklund and colleagues involved the transplantation of mouse embryonic stem cells into the brains of twenty-five adult mice. Five of these mice died and were found in a post-mortem analysis to have teratoma-like tumours at the implantation site.90

Writing for the NIH in 2000, Ron McKay noted that “we may gain a deeper understanding of the process of cell replacement” by studying stem cells.91 Furthermore, this research hypothesizes huge potential benefits to human health, ranging from generating new neurons for treating patients with Parkinson’s disease to learning about the molecular processes that cause tumours. However, McKay also noted that we have much to learn about the processes by which stem cells replicate and differentiate. We know “little about how stem cells can differentiate across boundaries [for example, how blood cells might differentiate into brain cells] and how we could divert them into the pathway of choice.”92 He also reminded us that we do not know “where unexpected benefits may suddenly emerge.”93

Fair enough, but we suggest that McKay’s last statement is also applicable to unexpected risks. If so, the risk assessment of stem cell research may face problems similar to those encountered in the risk assessment of novel environmental health hazards. Scientific knowledge usually refers to “known processes and their influence on known state-variables. Within this domain of reproducibility and control, uncertainty can be explicitly stated and reduced by reproducible experiments under controlled conditions.”94 Thus, our lack of knowledge about stem cells might be characterized by the “interaction between unknown processes and/or unknown state-variables.”95 This might pose a “fundamental obstacle to credible risk assessment” at this early stage of stem cell research.96 Government regulators, scientists, and REB members should approach risk assessments of this research with caution. We see a need for the ongoing collation and independent appraisal of risk assessment data that is beyond the capacity of local REBs.

Risks Posed by Conflicts of Interest: Impact on the Conduct and Outcome of Research

Conflicts of interest (COIs) are traditionally not discussed in the same context as the issue of risk assessment. We believe that the potential impact of

in medical research. The impact of COI on behaviour is hard to quantify and can be estimated only on the basis of comparisons with retrospective studies. Like the determination of risk to human health or the natural environment posed by the introduction of new biomedical technology or chemicals, agents, the influence of COI is seldom established clearly in individual cases. It is measured in terms of the likelihood of occurrence. "Guesstimates" of influence of COI are determined through studies indicating patterns of behaviour. Like risk to the environment or to health, the impact of COI is determined through statistical measurements.

The Committee on Assessing the System for Protecting Human Research Subjects of the US Institute of Medicine points to the link between COI and risk assessment. Although it suggests that REBs should not bear the primary responsibility for assessing COI, they should, according to the committee, be concerned about how "bias or overly optimistic promises of potential benefits are clouding risk assessments." The committee therefore believes that REBs should assess how "financial conflicts of interest have the potential to affect participant safety, and, if necessary, how participants should be informed of any resulting risk."99

The subject of COI in medical research has received an extraordinary amount of attention in the professional literature of the last decade.99 New articles appear weekly in leading medical journals discussing the increasing commercial interests in medical research. Their authors note the potential impact of these interests on the conduct of investigators, on research participants, and on the objectivity and integrity of the scientific enterprise. Commercial interests are not the only interests that create conflicts for investigators. Inherent in any form of medical research involving patients is a tension between the clinical duties of health-care professionals and their research interests.99 Many - if not most of the historical instances of research misconduct have taken place in the context of government-funded research and were unrelated to significant financial interests. They have resulted mainly from an inherent drive by researchers to succeed with research without proper regard to the rights and well-being of research subjects.100 Indeed, the desire for fame, the need for academic publications, or, perhaps, simply a strong enthusiasm for what researchers believe will be a scientific breakthrough have often been the main causes of inappropriate research behaviour. The review of research protocols by a committee without a direct interest in the research was introduced as a counterbalance to this potential for an overzealous commitment to science. The system of REBs is thus in itself a recognition of the inherent conflict involved in medical research.

The sheer number of recent publications on the growth of financial conflicts of interest suggests that they merit special attention. Official reports including the US Office of Human Research Protection100 and the Association of the American Medical Colleges,102 explicitly recognize that financial conflicts of interest are an increasing cause for concern in medical research. As Denis P. Thompson points out in a frequently cited article in the New England Journal of Medicine, many of the other conflicts of interests are unavoidable and are an inherent part of conducting research.103 They require a balanced review, but they cannot completely be avoided. Financial conflicts, in his view, deserve special attention for two reasons: first, because many of them can be avoided; and, second, because money is a strong motivator and a driving force behind many human actions.

We agree with Thompson that financial conflicts merit special attention, given the growing private-sector investment in medical research. Medical research, more than ever before, is part of a highly profitable pharmaceutical and biotechnology industry. Research undertaken outside of academic health centres and universities has systematically increased and is now more prevalent than academic research.104 Private-sector funding is currently driving much of the clinical research taking place in industrialized countries. Moreover, academic institutions have significantly augmented their collaboration with industry. Academic research is increasingly aimed at the development of commercial drugs or medical devices, often in partnership with industry sponsors. A growing part of the income generated by universities comes from patents on research inventions. Governmental funding agencies are increasingly making funding for research conditional on matching funding from the private commercial sector.105

Genome Canada is an example of an agency that is a major funder of health research, yet one that has as its main mandate the economic development of genomics and biotechnology. Genome Canada and several other agencies involved in the funding of health research require that every dollar allocated for research purposes be matched by private contributions. These agencies emphasize the importance of creating patents and intellectual property through the research they fund. Research accomplishments, which are crucial determinants for future funding opportunities, are measured with those outcomes in mind - the idea being that economic development of the health-technology sector goes hand in hand with medical progress and that both economic development and health care will benefit from such stimulation. The Canadian Stem Cell Network, a research network funded through the Canadian Centres for Excellence, follows the same approach. It is planning the establishment of a commercial stem cell company, in collaboration with the various universities and hospitals involved in the network, and is promoting interaction with industry.124 The creation of patents and the promotion of Canadian-based biotechnology companies...
What are the concerns? They can be divided into two main categories. First, the concern for the impact of financial interests on the recruitment of participants and on the conduct of researchers during the trial is directly relevant to the protection of research participants. A second major concern, which deals more with the long-term impact of COIs, has to do with the integrity of the scientific process and the independence of medical science. A detailed discussion of how financial interests may impact on patient recruitment and on the conduct of researchers exceeds the scope of this essay. It suffices to refer to some of the issues discussed in the literature. The significant financial interests in clinical drug trials, for example, have had an influence on recruitment practices. An increasing number of drug trials are being undertaken, with the result that there is growing competition for research subjects between contract research organizations (CROs), pharmaceutical companies, academic institutions, and private physicians. Payments to research subjects\textsuperscript{[67]}
 and financial rewards to clinicians, health-care workers, and research coordinators to promote fast recruitment\textsuperscript{[108]} may undermine crucial aspects of what should be voluntary informed consent. Patients increasingly participate in research because of the financial rewards or to obtain access to new therapies, often ignoring the potential risks involved in the study. The sometimes staggering amounts of money offered to reward fast recruiters in industry trials\textsuperscript{[109]} are sufficient to make us worried about violations of informed-consent procedures and even about the potential bending of inclusion criteria to enter people into a clinical trial.\textsuperscript{[110]}

Financial conflicts in the recruitment process are obviously related to other structural and even more significant COIs. Patients, clinical investigators, and others involved in the research are offered money because of the financial interests in the development of drugs, medical devices, or therapies. Lawsuits launched by the Securities and Exchange Commission in the United States, as well as recent empirical studies, indicate, for example, that insider trading exists in clinical research.\textsuperscript{[111]} While this fact does not necessarily mean that research subjects are directly threatened by such behaviour, it does indicate that people who are involved in research may act according to their financial interests and that some of them are even tempted to engage in illegal behaviour.

Financing the research institute, in which it had invested US$20 million. Moreover, the sponsorship contract between the institute and the company was up for renewal, and significant results in research would clearly have provided an incentive for further funding. In this context, it is hard not to make a connection between the financial interests involved and the fact that research risks were either understated or not disclosed. Various commentators have pointed out that researchers with strong financial interests in recruiting participants for a clinical trial may oversell the trial to their patients by downplaying the risks or exaggerating the potential benefits.\textsuperscript{[113]}

Financial interests in drug trials may influence investigators' choice of research design. Placebo-controlled trials, for example, require fewer research subjects than active control trials to obtain statistically significant results. Placebo trials are therefore cheaper and can be conducted faster, which may serve the interests of investigators since the increase in research activities has made it much harder to find sufficient numbers of trial participants. These trials, however, also expose subjects to the risks of being deprived of treatment. This factor is problematic, in particular, when we are dealing with serious medical conditions.

The impact of COIs on the protection of research participants is just one of the concerns expressed in the literature. Concerns about the potential impact of the commercial interests of investigators on the scientific process and on the outcome of research have received even more attention. The various ways in which commercial interests shape research have been identified.\textsuperscript{[114]} Several studies have shown a correlation between the sources of funding and the research outcome, which suggests that either researchers are pre-selected on the basis of their favourable views towards sponsors' products or the source of funding influences more directly the results of research.\textsuperscript{[115]}

Research sponsored by industry is much more likely than independent research to conclude that drugs of the kind produced by sponsors are efficacious. Commercial interests may affect the study outcome in different ways. The selection of the study population and the choice of statistical method will influence the research outcome and may thus be used to manipulate the results. Studies can be designed in such a way that they will more likely result in a positive outcome, benefiting drug approval and post-approval marketing. Increasingly, studies are either undertaken by the commercial sponsors or are under their control. Research coordinated through CROs often involves many community-based physicians, who are less likely to be interested or trained in analyzing the appropriateness of the methodology and the results. In addition, some commentators have noted how sponsoring companies sometimes control the writing process by using a so-called ghostwriter and then subsequently approach academic investigators to
Various controversies — for example, the well-known controversy involving Dr. Olivieri and her dispute with the pharmaceutical company Apotex, the Hospital for Sick Children, and the University of Toronto — have shown that sponsors may try to hinder the publication of negative results and that the financial interests of research institutions may influence, or appear to influence, support for researchers.\textsuperscript{119} Interestingly, one study also indicates that even when no explicit publication restriction exists, many researchers who receive gifts from those who sponsor their research still think that they have to obtain permission from the sponsor before publishing the results of a study.\textsuperscript{120} The impact of these developments should not be underestimated. Given the growing emphasis on evidence-based medicine, the outcome of research will influence clinical practice. Drug agencies, clinicians, and the public depend on research results to determine whether particular drugs are safe and efficacious. If medical research is compromised by COI, then trust in medicine as a social endeavor is at risk.

**Risks to Social Values**

The risks posed by COI to the conduct and outcome of research brings us to another type of risk: the risk to social values. In our estimation, this involves more than the risks to social values from, for example, the sources of stem cell research (for example, embryos) or the uses to which genetics might be put (for example, eugenics). COIs also risk compromising the social value of public trust in the ethical conduct of research. Social values can be characterized as “the importance to members of the group of experiencing their public lives and social interactions in certain ways ... [V]alues about how the society's risks are structured and distributed ... are social values, not individual feelings.”\textsuperscript{119} They pertain to notions of how persons are treated; how society is to be structured in terms of the risks that its members will jointly face; how public policies promote the sense of solidarity citizens feel towards each other; or how these policies reflect the shared values that give society its identity. Distributive issues of risks, costs, and benefits as well as the value of human life are examples of social values.\textsuperscript{120} These values can reflect concerns about justice — for example, if risks are deliberately confined to an uninformed and vulnerable group whose members are abused in the acquisition of scientific knowledge. Jeremy Fralberg and Michael Trebilcock capture the role of this idea of social values in an insightful way, noting “the instinctive aversion most people have to placing certain groups under high risks for the benefit of other groups ... even when one is a member of the group that benefits. This aversion is heightened when those at risk are among society's already disadvantaged.”\textsuperscript{121} In this way, the Tuskegee syphilis study and the Cold War radiation experiments violated social values as well as the unwitting

Ethical research is premised on achieving scientifically and socially important aims. Public trust is thus crucial to the conduct of ethical research. Students must trust supervisors; principal investigators must trust subordinates; and colleagues need to trust each other. Researchers need to trust journals, granting agencies, and research institutions. Research participants and other citizens need to trust researchers.\textsuperscript{122} Given the billions of dollars invested annually in North American research and development, it can be argued that “the erosion of public confidence in science that may occur” if society does not deal effectively with COI could be “damaging and corrosive to democracy.”\textsuperscript{124}

We noted earlier that strong correlations have been observed between social trust and the public acceptance of the estimated risks and benefits of new technologies about which the public may lack “scientific” knowledge. Indeed, research indicates that the lay public relies on social trust in risk/benefit judgments when personal knowledge about hazards is lacking.\textsuperscript{125} “Biotechnology and especially its implications for the 'new' human genetics raise major concerns about risk and trust in regulatory regimes.”\textsuperscript{126} Some critics argue that there has been a loss of trust in biotechnology because of inherent weaknesses in its conventional regulatory agencies.\textsuperscript{127} Brian Salter and Mavis Jones argue that human genetics, especially its controversial domains of stem cell and gene transfer research, cannot be regulated solely through an expert discourse on technical safety. At the political level, the regulation of risk must address dynamics of value and belief and incorporate value assessments into the assessments of technical safety.\textsuperscript{128}

“Our policies for reducing risks,” writes Douglas MacLean, “must remain sensitive to our social values.” Furthermore, these values can determine that different principles can guide policies in different contexts of risk.\textsuperscript{129} We suggest that these analyses highlight the need for law reform in the governance of biomedical research. We want to know that things we value deeply — for example, the welfare of research participants and the integrity and reliability of scientific investigation — are being protected by the institutions that we have created to be the trustees of these values. Consequently, REBs are easily seen as “public institutions, which the public expects in part to give voice to the ideals of a society that cares deeply about the lives and the health of its citizens.”\textsuperscript{130}

**Principles for Law Reform**

What are the general ideas, or principles, that might guide aspects of law reform in biomedical research with human participants? We cannot present an exhaustive list of these guiding principles, but we intend to present ones that we hope will incite a conceptual as well as policy-oriented debate. We will propose our own ideas about the legal infrastructure that might reflect
After noting the limitations and value-laden nature of regulatory science, and the importance of maintaining trust in risk-assessment agencies, Paul Slovik sees the need for a new approach— one that focuses upon more public participation in both risk assessment and risk decision making. This approach would aim at making the decision process more democratic, improving the relevance and quality of technical analysis, and increasing the legitimacy and public acceptance of the resulting decisions. Numerous models for public participation in regulatory science have been proposed. The need for a similar approach to research review has been a recurring theme in bioethics since at least 1975, when the philosopher Robert Veatch alleged a basic disjunction in REB structure. Veatch saw REBs as anomalous committees that fell between two different regulatory models: the model of professional review and the model of the citizens' jury. The membership of REBs consisted predominantly of scientific experts, with some spots reserved for lay people who were supposed to function as community representatives. Veatch felt that this predominance could shift the framing of risk towards the researchers' value framework. It might even lead to a shift towards greater risk taking. He was not convinced that community members could prevent this predominant shift in favour of the researchers' interests. These interests could include the ones noted earlier in this essay, such as the desire for professional renown, the need to acquire funding and publish academic papers, and a strong enthusiasm for scientific development. This enthusiasm implies a particular sensitivity to benefits that are achievable only if the research proceeds, and it creates a mind-set that favours the launching of the research project. In the risk environment of increasingly commercialized science, researchers' interests can also reflect a shift in values towards profit and economic growth.

Paul McNell claimed in 1993 that "the schism described by Veatch is still apparent in REBs all over the world." We argue that McNell's claim is no less relevant today. Since REBs will be evaluating protocols and risk assessments that are formulated by those who endorse the research, we suggest a principled approach to review that could balance the interests of those proposing the risks by empowering the risk-cautious interests of those who might assume them. This balance could "be found in a process that allows the holders of various points of view to have an equal opportunity for expression and control." There should be as many participant representatives on REBs as representatives of science. This approach will require a different kind of engagement between REB members by which risks and values are negotiated. It should involve a legislated mandate for REB structure and membership, including the participation and decisional authority of participant representatives or advocates from relevant consumer health groups. These members should be informed of the research issues from the perspective of the participants that they would represent. Ideally, they would be accountable to an appropriate community group that can represent the interests of the research participants. Like McNell, we argue that community group affiliation is required to give participant representatives "some ground and support for their views." To avoid bias towards the researchers' values, participant representatives should have no past or present affiliation with the research institution. Indeed, we would take this precaution a step further by mandating that the community groups they represent must also not be affiliated with, or funded by, private-sector corporations that conduct or fund research. While the representatives' fundamental concern would be to protect research participants from harm, they would also address concerns about methodology, participant selection, access to research results, privacy, and "the manner of arriving at conclusions and the conclusions themselves." We argue that these representatives should be legally mandated to reflect a risk-cautious value framework in deciding whether the study should be approved.

A risk-cautious value framework would favour a review of risk assessments by those with no financial or competing interest in the research. It would appreciate the potential importance of biomedical research without assuming that proposed investigations are prima facie benign and worth a decision to run considerable risks in order to realize benefits that might otherwise be lost. It would raise questions that would reflect a predominant concern for risks to participants and the objectivity of science. For instance, REB members should inquire carefully about whether the research participants have been informed of the latest reported adverse events in similar trials. Not only should they review the informed-consent documents presented to them, but they should also monitor how consent is really obtained and what information has been given. Jesse Gelsinger and James Dent were not adequately informed of the risks involved in their studies. REB members should also inquire about whether the investigators have done a thorough review of the relevant literature in formulating their risk assessment of the drug being studied. This was not the case in the 1999 asthma study at Johns Hopkins University in which Ellen Roche died after inhaling hexamethonium. Numerous available studies documenting the pulmonary toxicity of hexamethonium were overlooked before the protocol was submitted to the REB. Neither the researchers nor the REB assessed this literature. A better assessment of the literature by the REB could probably have prevented the death of this healthy woman.

We have acknowledged that different parties to a risk debate can bring different risk perspectives to the table. Differences of opinion also exist in the patient and patient advocacy populations. There are various examples of research participant advocacy that have not reflected a risk-cautious protective approach. The work of HIV/AIDS activists to hasten the development and availability of new anti-retroviral drugs is a seminal case in point.
Indeed, much of this advocacy has expressed an enthusiasm for “the bright side” of research and a willingness to assume risk that many scientific investigators did not share. Rebecca Dresser observes that this attitude is “sharply evident in advocacy efforts to expand patients’ access to clinical trials and unproven interventions.” These advocates have tended to avoid REBs that examine the risks faced by research participants. They have regarded ethics review as a paternalistic distraction from the main goal of promoting benefits to patients. Nor have they complained when researchers or journalists have “put an overly positive spin on the significance of study findings.” Not surprisingly, drug companies and other businesses have sought public alliance with such groups. This outcome has made some advocates susceptible to the same COI that has beset researchers. These precedents might lead one to think that participant advocacy is synonymous with the uncritical promotion of research. We have three reasons for thinking otherwise.

First, we note that it is simply mistaken to conflate participant advocacy with this overly positive approach to research. There are numerous models of advocacy that can be used to promote different mandates: “Advocacy programs, in addition to including many diverse activities, vary according to their objectives, modes of operation, and relationships with the institution or group of institutions within which they function.” Advocacy can thus be concerned with challenging existing practices. The point is to specify a mandate. We suggest that participant representatives on REBs should have a specific mandate to advocate a risk-cautious perspective. Their primary focus would be the protection of research participants. Scrutinizing risk assessments by those who endorse the proposed research would be a crucial responsibility for which they should receive sufficient education and training. This mandate would reflect what has historically been the “main reason” for including “community members” on REBs, namely to represent a concern for the protection of research participants that is free of any bias towards research interests. Like Paul McNeill, we argue that this mandate should be “explicit.” Without such a mandate, participant representatives lack a clear role. Without appropriate training, they may lack “recognized expertise” and be disempowered in their relationships with institutional and professional REB members.

Second, the precedents noted earlier do not tell the whole story. According to Dresser, perspectives on research participant advocacy are currently changing. Some HIV/AIDS activists have qualified their early enthusiasm for expanded access. They have come to question the benefits of the FDA’s accelerated approval program and now argue that “patients would be better off if the agency applied more rigorous standards in deciding when new drugs may be marketed for clinical use.” It has become increasingly clear to such advocates that experimental drugs can be ineffective or dangerous.

Further, there is a growing awareness that an exclusive emphasis on expanded access could hinder attempts to discern which new drugs are safe and effective. Dresser notes other examples. Certain women’s health advocates now protest the widespread availability of high-dose chemotherapy and bone marrow transplantation for breast cancer, for which they once advocated. This change came with the release of trial data showing no benefit from these interventions. These advocates now argue that women “would be better served if constraints were placed on their access” to these “burdensome and questionably effective” procedures.

Third, there are indeed research participant advocacy groups whose mandates reflect a risk-cautious, protective approach. For instance, the Alliance for Human Research Protection is a US network of lay and professional people with a mandate to advance ethical research practices; to ensure that the human rights, dignity, and welfare of research participants is protected; and to “minimize the risks associated with such endeavors.” This group argues that the “explosion” of biomedical research over the past decade has not been accompanied by an “effective system of oversight or enforcement” to protect research participants. COI in commercially funded research and the incomplete disclosure of risks are two systemic problems that this group aims to address. Citizens for Responsible Care and Research is another US group of lay people and professionals that is dedicated to the protection of vulnerable research participants, especially “the mentally incapacitated, children, seniors, the homeless and the poor.” This group has been instrumental in bringing documented evidence of abuse in human subject research to public attention. These groups may become more influential as public awareness of research risks is heightened. We feel that they serve as timely models for a risk-cautious mandate in research review.

Obviously, we do not want to suggest that lay members of REBs necessarily have to take the same often strongly critical stand of some of these advocacy groups or to have the same approach towards research. We simply believe that because of the protective function of REBs, it is important to have an REB membership that has no direct and strong interest in seeing specific forms of research immediately proceed. People who have for several years been involved in advocacy to promote funding for stem cell research on Parkinson’s and who are themselves affected by the disease, or who have close family members affected by it, can be more biased and enthusiastic about experimental clinical trials than the researchers. In our view, a legislative basis for REBs would also symbolically reflect the importance of their administrative function. They are regarded de facto as crucial players by funding agencies and drug regulators. They are also given an increasing role in other statutory regimes, such as those introduced by certain provincial privacy statutes. And yet, REBs do not fulfill basic standards that are imposed by administrative law on regulatory and judicial bodies.
The risks posed by COI to medical research should be dealt with at various levels. As pointed out, REBs have been developed to deal with the general COI embedded in research. Their role in assessing financial COIs, however, is more complex. REBs have the mandate to protect human research participants and to assess the informed-consent procedure. They also have to determine whether there are particular factors that would increase the risk to participants. This should include an assessment of the likelihood that investigators will act inappropriately, for example, by misinforming participants about the risks and potential benefits. In the current climate of pervasive COIs, REBs must not avoid questioning the impact of financial interests. They certainly have to decide whether those interests require additional safeguards, such as independent monitoring of the consent process or increased monitoring of who is included in the trials. However, they generally lack both the expertise and the means to obtain all the relevant information about financial conflicts. It thus seems problematic that Health Canada’s Therapeutic Products Directorate relies currently on REBs as the authority to deal with COIs. This reliance is highlighted by a regulatory impact analysis statement, which accompanies new regulations on clinical trials.

In recognition of how financial interests may impact on the rights and well-being of participants, various agencies and commentators have recommended the establishment of independent COI Committees in research institutions. Clinical investigators and other research personnel should have an obligation to divulge any financial relationships between themselves and potential research sponsors. This should include information on consulting relationships, remunerated lectures, membership on advisory boards, and any stock in a company that could benefit from their research. These committees should also have the mandate to review institutional COI that could impact on research. REBs should be informed by the COI Committee of all relevant financial interests.

While we believe that this oversight would be an important first step in dealing with the immediate impact of COI on participant safety, it seems an insufficient means of dealing with the broader impact of COI on the integrity of science. The review by COI Committees would work only in academic institutional settings. Since much research is undertaken outside these institutions, only a small portion of research activities would be affected. We have noted that Canadian REBs are currently affected by both financial and institutional COI. We see a COI when REBs decide upon the ethical acceptability of research protocols “when the institution in which they are based stands to gain from research it conducts.” It is therefore untenable to rely on REBs within these institutions to deal with such conflicts. Moreover, many research protocols are being reviewed by private REBs located in for-profit CROs or pharmaceutical companies. These REBs are also affected by fundamental COIs. If REBs ought to play any reliable role in the area of COI, then it seems to us that they should be fundamentally reformed to guarantee their administrative independence. We will make some suggestions later in this essay about the establishment of a governmental agency for the protection of research participants. REBs should report to such an agency and be disconnected from their institutional conflicts and the commercial interests of research sponsors.

However, we believe that a more fundamental solution is required to deal with the impact of financial interests on the integrity of the scientific enterprise. Other commentators have already noted that the pressures created by the staggering increase in clinical research and the lack of control over drug development can be dealt with only by a national drug review and testing agency. Such an agency would determine on the basis of preliminary data which trial could go ahead and would coordinate the clinical research using a clinical trial design that it would develop internally, in consultation with the producer of the compound. This type of national agency would relieve the pressure that currently leads to inappropriate competition for research participants and lower standards of protection. It would also allow for a more independent assessment of drug development, which is crucial to safeguard public confidence in evidence-based medicine.

Other measures could be integrated in the existing system. Indicating an increased awareness within professional organizations of these issues, the Association of American Medical Colleges made some interesting recommendations in two reports on COIs. One of them is particularly relevant to our discussion. The association recommends that institutions introduce a rebuttable presumption that an individual who holds a significant financial interest in a study may not participate in its conduct. This recommendation is a recognition of the evidence discussed earlier, which indicates that financial interests risk undermining the integrity of research and may affect the behaviour of researchers. The association also recommends that it may be inappropriate to have research conducted in institutions that have a significant financial interest in the research outcome.

There are two problems with recommendations of this sort: First, they are mere guidelines issued by an organization that has no impact outside academic institutions. Second, they open the door for various exceptions by introducing the qualifier “rebuttable.” Considering the extreme variability by which North American institutions embrace the commercialization of their research, it is unlikely that situations such as those surrounding the Jesse Gelsinger case will be avoided by such recommendations. Some institutional cultures will simply have a different interpretation of when the presumption can be put aside. We suggest, nevertheless, that these recommendations provide an important baseline for evaluating the risk created by financial interests in research and that they should be integrated in more
stringent regulatory documents. The recommendations could be refined and strengthened. The premise should be that researchers or institutions with financial interests in the outcome of the research ought not to be involved in the research. Further, review bodies, such as REBs and COI Committees, should issue a formal justification in individual cases where they think it is necessary to make an exception. By qualifying financial interests as a significant risk factor, additional mechanisms seem required when such exceptions are made. They could consist, for example, in requirements that researchers divest themselves of their financial ties; in ordering the research to be conducted and/or monitored outside the institutions; in closer monitoring of the consent process; and in requiring a rigorous external review of the data. Again, it should be emphasized that the introduction of the term “rebuttable” should not create a “business as usual” climate in which the formulation of exceptions becomes a mere bureaucratic hassle.

Governance of Biomedical Research with Human Participants: Proposals for Legal and Structural Reform

Our analysis suggests that risk assessments of gene transfer and stem cell research proceed in the face of considerable uncertainty. We suggest that there is much to be learned about the magnitude and probability of the physical harms this research poses to human participants. Given the national scope of gene transfer and stem cell research, the task of collecting and analyzing risk-related data is beyond the capacity of local REBs. Furthermore, risk assessments are influenced by the value frameworks of the different parties to a risk debate. Assessments that are formulated by those who endorse the research may reflect a value framework that is weighted in favour of taking risks. Patients who seek novel therapy through science can share a strong enthusiasm for research with the industry sponsors and medical investigators who endorse it. Yet if risk estimation can influence perceptions of risk acceptability, then there is at least an apparent COI in allowing those who endorse the research to be the sole arbiters of its estimated risks. We want the law to ensure that the value frameworks of cautious participants who might assume the risks are given equal weight in the process of research review. In short, we envisage a review process that responds to those who might be risk cautious in the face of significant potential benefits.

With these remarks in mind, we want to offer some general recommendations for law reform. These recommendations are not exhaustive. The Canadian funding agencies have embraced a uniform approach that makes the Tri-Council Policy Statement applicable to all forms of research with humans in the biomedical and social sciences. We realize that our more elaborate legislative structure may be neither feasible nor necessary for some forms of research. The forms of research to which it ought to apply should also be subject to further debate. We believe that it ought to apply to biomedical research that raises the three risks discussed earlier in this essay.

1 We recommend federal legislation to govern the oversight of biomedical research in Canada. Bernard Starkman has summarized a number of reasons for regulating research through legislation instead of guidelines. Legislation is debated openly, its provisions are publicized, and the legislative process provides accountability. Notwithstanding the limitations of our parliamentary democracies, legislators are subject to the electoral process, and parliamentary debates on legislative proposals are subject to public scrutiny. Legislation promotes uniformity, enforceability, and could contain clarifications about the conditions under which vulnerable persons can legally be participants in research. In short, “legislation has all the advantages that have been claimed for guidelines, and none of the disadvantages.”

We acknowledge that the protection of human participants in biomedical research may not be seen as a single matter over which either Parliament or the provinces can assert exclusive legislative jurisdiction. Indeed, some might question whether the federal government has any jurisdiction in this area. We do not want to pursue that debate in this essay. The pros and cons of a federal or provincial legislative scheme should also be subject to further debate. Comprehensive legislation to regulate the management of risks to research participants, to the reliability of research, and to the public’s trust in the research enterprise would likely require significant cooperation between both levels of government. While we cannot resolve the jurisdiction debate in this essay, we suggest that federal jurisdiction under the criminal law power can recognize significant scope for provincial action. This is reflected in the model outlined in sections 68 and 69 of An Act Respecting Assisted Human Reproduction and Related Research, which allows provinces to pass laws equivalent to key sections of the federal legislation.

2 We recommend the creation of an independent national agency for research review. This agency could receive a limited regulatory mandate and remain accountable to the federal Parliament. It should be independent from the current government agencies that regulate drugs and fund research. It should have an unequivocal mandate to focus on the protection of human research participants, and it should not be committed to industry development or health-care funding. It could coordinate, accredit, and monitor the activities of local REBs. To these ends, it would formulate research policies, review and publicize significant decisions made by itself and local REBs, and serve as a source to which local REBs could turn for advice and guidance. The oversight of all biomedical
research would be a daunting task for this proposed agency. We suggest
an incremental approach by which the agency limits its initial oper-
ations to the oversight of gene transfer and stem cell research. The agency
could then gradually expand the range of its oversight activities to other
types of biomedical research.

3 We recommend that this national agency have a branch that would gather and
analyze data relevant to risk assessments of new biomedical interventions
and that it could coordinate activity in this area with Health Canada. CenterWatch
has noted the practical difficulties faced by REBs in coping with the task of
monitoring adverse events in hundreds, if not thousands, of clinical
trials at individual institutions each year. While some data monitoring is
"study specific," there is no mandatory, audited monitoring of adverse
events by an outside, independent source. Critics of the current US
regulatory system have argued that there is a need for a combination of
standardized reporting and auditing by an independent body as opposed to
"subjective reporting" by researchers involved in the trials who "decide
when something is worth reporting." The task of monitoring international
multi-centre trials only adds to this challenge.

With respect to gene transfer and stem cell interventions, the agency
we propose would be similar to the Gene Transfer Safety Assessment Board
proposed recently by the NIH in response to the Gelsinger case. It would
ensure that "the safety, toxicity, and efficacy data accumulated from
trials be regularly reviewed ... identify areas of potential promise or con-
cern and ... promote awareness of these findings among the various sec-
tors of the [scientific community and the] public." We envision the
creation of a national database to organize the safety data from gene
transfer and stem cell research. Like the Gene Therapy Advisory Com-
mittee proposed in the United Kingdom, this branch would coordinate
the long-term monitoring of research participants. The agency would
also ensure that all active medical research studies are registered and that
study results are available even if they are not published. This reporting
obligation to, and data gathering by, a central agency would aim to pre-
vent the selective use of clinical trial data in the review process.

4 We recommend that this national agency have a branch that would assist local
REBs in the selection and training of participant representatives from relevant
consumer health groups. This training should contain a module on risk
analysis.

5 We recommend that this national agency have a branch that would investigate
complaints or concerns about local REBs or clinical trials. This branch could be
similar to the US Office for Human Research Protection.

6 We recommend that local REBs become part of, and accountable to, this na-
tional agency. On our account, the current Canadian system of REBs is
affected by significant COIs, given the close affiliation of most REBs with
research institutions and the fundamental COIs embedded in private,
commercial REBs.

7 We recommend that this national agency develop uniform conflict of interest
guidelines and oversight mechanisms for application at the institutional level.

8 We recommend that this national agency also function as a public forum for
dealing the impact of new biomedical research on social values. It could,
for example, take the initiative to debate particular moral concerns raised
by the use of embryos in stem cell research or other moral issues in
research that affect the values of the wider community.

9 We support the development of COI Committees within institutions. These
committees should keep data on financial and other relations between
clinical researchers and other research personnel. They should deter-
mine whether there is a risk that financial or other relations could impact
on research activities. The development of more detailed national
restrictions would facilitate this task.

10 We recommend a reporting obligation by the COI Committees to the REBs.

11 REBs should receive a clearer, but limited, mandate to review the potential
impact of COIs on the conduct of investigators.

12 We recommend the integration of a presumption in regulatory policies that
individual researchers cannot conduct research in which they have a signifi-
cant financial interest. We also recommend that similar presumptions be is-
issued with respect to institutions in which the research takes place.

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Halifax, Nova Scotia.

Notes

1 Kathleen Cranley Glass and Trudo Lemmens, "Research Involving Humans" in Jocelyn
Downie, Timothy Caulfield, and Colleen Rood, eds., Canadian Health Law and Policy, 2nd
ed. (Markham, ON: Butterworths, 2002) 459 at 459.

2 The Canada We Want: Speech from the Throne to Open the Thirty-Seventh Parliament of Canada,
<www.sft-dlt.gc.ca/hnaw/hnw07_e.htm>.

3 We will use the Canadian terminology. In the United States, the common term for such
review boards is "institutional review boards." Other countries and some international
guidelines prefer the term "research ethics committees."

4 Medical Research Council of Canada, Natural Sciences and Engineering Research Coun-
cil of Canada, and Social Sciences and Humanities Research Council, Tri-Council Policy

S 12 Glass and Lemmens, supra note 1 at 460.  
S 13 Tri-Council Policy Statement, supra note 4 at 1.5.  
S 14 Ibid. at 1.5.  
S 15 Ingar Palmquist, "Social Drama and Risk Evaluation" in Krimsky and Golding, eds., supra note 6, 197 at 207.  
S 17 Ibid. at 164.  
S 18 Mary R. English, "Environmental Risk and Justice" in McDaniels and Small, eds., supra note 16, 119 at 131.  
S 21 Brunk et al., Value Assumptions, supra note 6 at 4.  
S 22 Ibid. at 4. See also Kasper son, supra note 6 at 155: There can be a "most striking disjuncture" between the technical and the socio-perceptual analysis of hazards.  
S 24 Bert et al., supra note 20 at 100.  
S 25 Brunk et al., Value Assumptions, supra note 6 at 3 and 33-37; Brunk, "Risk Assessment," supra note 6 at 757-58.  
S 26 Brunk et al., Value Assumptions, supra note 6 at 2-3.  
S 27 William B. Friedrichsen, "Heuristics, Bases, and the Not-So-General Publics: Expertise and Error in the Assessment of Risks" in Krimsky and Golding, eds., supra note 6, 229 at 236; Harry Orway, "Public Wisdom, Expert Futility: Toward a Contextual Theory of Risk" in Krimsky and Golding, eds., supra note 6, 215 at 220-22. Orway claims that the final estimates of risk from "technical systems" to the public are "notoriously unreliable." After acknowledging the importance of the "qualitative dimensions of risk" in the acceptance of new technologies, he urges the public to be cautious about "any suggestion that we know what the 'true' (or objective) risks are because of the size of the effort made to make and refine the estimates." See also Brunk et al., Value Assumptions, supra note 6 at 5; and Brunk, "Risk Assessment," supra note 6 at 757.  
S 29 Ibid. at 979.  
S 30 Deborah Borzutz, "Quantifying Risk in Clinical Trials" (2001) 8(10) CenterWatch 1 at 1.  
S 31 Ibid. at 1.  
S 32 Ibid. at 2.  
S 33 Ibid. at 1.  
S 34 Ibid. at 1.  
S 35 Ibid. at 5.  
S 36 Ibid. at 4.  
S 37 Ibid. at 5.  
S 38 Ibid. at 4.  
S 39 Ibid. at 5.  
S 41 Ibid. at 5.  
S 43 Brunk et al., Value Assumptions, supra note 6 at 3.  
S 45 Glass et al., supra note 8 at 6.  
S 47 Kasper son, supra note 6 at 163.  
S 48 Ibid. at 163.  
S 49 Brunk et al., Value Assumptions, supra note 6 at 4.  
S 51 Compare Brunk et al., Value Assumptions, supra note 6 at 28-29. Compare Glass et al., supra note 8 at 6.  


MacLean, supra note 50 at 78.

Brunk et al., Value Assumptions, supra note 6 at 144.

Ibid., at 26. For an excellent discussion of the sources of uncertainty in risk assessment, see Freilich and Trevillen, supra note 47 at §§5-57.

The following statement appears in the consent form in the consent form of a Protocol for Treatment of Progressive or Recurrent Pediatric Malignant Supratentorial Brain Tumor with Herpes Simplex Thymidine Kinase Gene Vector Producer Cells Followed by Intravenous Ganciclovir, which was conducted in the Children's Hospital in Washington, DC, in 1995: "We emphasize that we do not know if this therapy will be effective. It is entirely possible that this experimental treatment will have no effect on your/your child's disease. It is possible that the therapy will make you/your child worse ... This investigational procedure is relatively new and it is possible that despite extensive efforts, other unforeseen problems may occur including the possibility of unknown and possible disabling effects or death." From the Baylor College of Medicine and Affiliates consent form for a Phase 1 Trial of Adenoviral Mediated Suicide Gene Therapy with HSV-1k and Intravenous Ganciclovir in Locally Advanced and Refractory Supratentorial Bladder Cancer, circa 2001: "it is not known what the long-term consequences are going to be from injecting this virus into tumors as mine."

From the University of Arizona consent form for a Phase 1 Dose Escalation Study of Intraperitoneal E1A-Lipid Complex with Combination Chemotherapy in Women with Epithelial Ovarian Cancer, circa 1999: "Only a limited number of women with ovarian cancer have received E1A-Lipid Complex and it has never been given in combination with chemotherapy. Unpredicted, serious side effects, including life-threatening ones, could occur."


Keller, supra note 47 at 70-72.


This would be uringwise to rule out that possibility or to stake the (research) farm on it."

Abbott, supra note 59 at 410-12.

These data are available online at http://www.wiley.co.uk/germs/cennet/clinical.

Freudenberg, supra note 27 at 289.


Brunk et al., Value Assumptions, supra note 6 at 141-44.

66. Ibid., at 6-7.


73. We acknowledge that shared assumptions about the "sacred" or "intrinsically" value of human life are open to different interpretations. A mentally competent adult and a fertilized ovum can both be seen as intrinsically valuable human life forms that ought to be respected appropriately. Yet persons differ over the appropriate level of respect that each should receive. Ronald Dworkin argues that what we share in understanding human life to be prime face intangible is more fundamental than our quarrels over the best interpretation of intrinsically value. See Ronald Dworkin, Life's Domain: An Argument about Abortion, Euthanasia, and Individual Freedom (New York: Vintage Books, 1993) at 70-71, 76.


78. Glass et al., supra note 8 at 6.

79. Dettweiler and Perielis, supra note 69 at 492-95, 499.

80. Glass et al., supra note 8 at 6.


84. An Act Respecting Assisted Human Reproduction and Related Research, 3rd Sess., 37th Parl., 2004 (amended to on 29 March 2004). The act will come into force on a day or days to be fixed by order of the Governor in Council (hereinafter Assisted Human Reproduction Act).

Ibid., at clauses 21-39 and clause 5(1a) respectively.

86. Bishoff et al., supra note 64 at 987.


89. These points were made to us by Dr. Jonathan Kimmelman, post-doctoral fellow with the Bioethics Unit of McGill University.


92. Ibid., at 362-63.
159. For a good discussion of their role and implications, see Goldner, supra note 98.
162. See the two reports by the Task Force on Financial Conflicts of Interest, supra note 102; Financial Conflicts of Interest, supra note 101; and Responsible Research, supra note 97 at 82-84.
163. McNell, supra note 5 at 194.
167. See both reports by the Task Force on Financial Conflicts of Interest, supra note 102.
171. Related Human Reproduction Act, supra note 84. Note, however, that the intention in the former Bill C-13 to afford exemptions for provinces that pass equivalent laws has been condemned by Patrick Healy as unconstitutional. He argued that provinces have no power to enact laws equivalent to the severe criminal penalties in Bill C-13, for example, ten years' imprisonment and/or up to half a million dollars in fines. See Patrick Healy, "Statutory Prohibitions and the Regulation of New Reproductive Technologies under Federal Law in Canada" (1995) 40 McGill L.J. 905. His analysis referred to Bill C-13, An Act Respecting Human Reproductive Technologies and Commercial Transactions Relating to Human Reproduction, 2nd Seasl., 35th Parl., 1996.

Borlitz, supra note 30 at 6, quoting Dr. Dan Schuster, associate dean of clinical research at Washington University, St. Louis, Missouri.

Ibid. at 7, quoting Arthur Caplan, bioethicist at the University of Pennsylvania.


Nevin and Spink, supra note 81 at 1253.

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Food and Drug Regulations, C.R.C., c. 870 as amended by Food and Drug Regulations: Amendment (Schedule No. 1024) Clinical Trial Framework, S.O.R. 2001-2003, s. C.O.S.0(10d).


