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Dedication

1 This double issue of the Health Law Review is dedicated to the memory of our friend and colleague T. Douglas Kinsella, CM, MD, FRCP.

2 Doug Kinsella was a leader in the effort to bring about the reform of Canadian governance for research involving humans. He founded and headed the Office of Medical Bioethics at the University of Calgary and served for years as Chair of the University's Biomedical Research Ethics Board. As a founder of the National Council on the Bioethics of Research Involving Humans he led the first (and only) systematic survey of the treatment of human subjects by those working in Canadian medical schools.¹ In 1994 he became a member of the Tri-Council Working Group on Ethics, which was charged by the Presidents of the Councils with the responsibility of developing "new policies and guidelines to replace the Councils' existing guidelines for research involving humans."² It was here that I came to know Doug very well especially as we served as co-members, along with Dr. Jean Joly, of the Working Group's Editorial Committee. I do not believe that the Working Group would ever have completed its task without Dr. Kinsella's insight, determination, and hard work. His deep commitment to the highest principles of accountability and integrity along with the depth of experience he brought as a physician, researcher and bioethicist were essential to the production of the Code of Ethical Conduct for Research Involving Humans.³

3 After we submitted the Code to the Council Presidents, Doug continued his involvement in governance issues. He was a member of my team when we prepared a state of the art assessment of Canadian governance for research involving humans for the Law Commission of Canada.⁴ In that report, he wrote about one of his abiding concerns -- the role of the physician-researcher and the need for effective governance of physician-researchers whether they were in research institutions or operating within their private offices.⁵ In the latter regard, he played a leading part in establishing a Research Ethics Board at the Alberta College of Physicians and Surgeons. To this day, Alberta remains the only province where the provincial regulatory body for physicians has taken effective responsibility for ensuring that all physicians receive the ethical review of research called for in the

CMA Code of Ethics.⁶

4 In 2002, I invited Doug to join the small team that I organized for a research proposal on governance being prepared for CIHR. We were successful in that proposal. With the support from the CIHR one of the major projects we undertook was to bring together scholars interested in the governance of ethical health research involving humans, in order to prepare this special volume of the Health Law Review. We scheduled a meeting for August 2004 at Whistler BC. It is with great sadness that I recall Doug contacting me in May to say that due to serious illness he would be unable to attend. He died on June 15, 2004.

5 So it is to the memory of Dr. T. Douglas Kinsella that we dedicate this publication. We are confident that the theme of this special issue reflects a central concern of his professional career as a physician, medical researcher, and bioethicist.

Introduction

6 In August 2004 with the help of research funding from CIHR, I brought together the individuals who have contributed to this issue as well as others who were part of the discussion. Because we met in Whistler, British Columbia, we playfully described ourselves as "the Whistler Summit on Governance." We were a multi-disciplinary group with a wide range of perspectives on research ethics. Some of us have been intimately involved in the formation of policy at the international and national levels. Many of us have written on this subject matter before. Others were new to the area.

7 We came together with the following objectives:

- To consider the positive and negative features of current governance in Canada for research involving humans
- To propose new directions for such governance in areas identified at the workshop
- To produce articles on this topic for publication in a special issue of the Health Law Review
- To offer useful insights for those making or influencing policy in this area.

8 For several days we engaged in a remarkably open dialogue around governance issues. We asked ourselves about what was necessary for the effective and accountable governance of ethical health research involving humans. We asked why governance (in Canada and elsewhere) had taken the shape it had -- relying almost solely on the front-end application of guidelines for health research by

ethics committees -- but seriously lacking with respect to key criteria of independence, effectiveness, and accountability.⁷ We questioned these developments and sought to articulate practical alternatives. These ranged from complete overhaul of the current system to more localised (but still significant) partial reforms. The discussion was intense but highly amicable. We learned greatly from each other.

9 We readily recognize that the topic of this issue is large and complex with diverse aspects -- legal, social, cultural, political, economic and ethical. Thus, in their article "A Cultural Understanding of Research Ethics Governance," Burgess and Brunger state:

All uses of power in relation to research constitute the field of governance of research ethics. All parties who influence research through their various forms of power (legal, bureaucratic, financial, rhetorical, etc.) will have inevitable influence on the standards and practices of research and research ethics. Explicitly powerful forces such as industry can be negative or positive in terms of how they promote, or are antithetical to, the goals of research ethics. Research ethics itself -- its definition, its purpose, its process -- is also shaped by cultural, political and economic forces.

10 In the papers that follow we take up various aspects of governance and examine a series of important topics including the conduct of clinical trials, information data-bases, and many other issues. As Guest Editor, I have grouped the papers under four headings:

1. The legal context of governance
2. Clinical trials
3. The social and cultural context of governance
4. Reforming governance

Common Themes

11 While each of the authors is responsible for his or her views, I think that it is fair to say that our discussion at Whistler reflected a number of common concerns which I would formulate as follows.

12 First, research involving humans is not a right but a privilege. The privilege of conducting research on human subjects requires meeting basic norms. These are reflected in major statements of ethical conduct of research involving humans. They include respect for human dignity, honouring informed consent, ensuring that subjects do not face excessive risk, sound research with overall

potential benefit, and the like.⁸ The onus or burden of proof for meeting these norms lies on those who would conduct, house, or sponsor such research. This ethical onus is, to a certain extent, reflected in the legal duty of care which is a topic discussed by Zimmerman in her paper, "Translating Ethics into Law: Duties of Care in Health Research Involving Humans."

13 Second, the major tool used in Canada for human research protection is review by an expert committee of researchers and community members. But ethics review is a means to an end and not the end itself; the end is ethically conducted research. In multiple reports, grave questions have been raised about whether ethics review achieves its ends⁹

14 One of these reports, the year 2000 report to the Law Commission of Canada, makes five major points:

1. The complexity and fragmentation of Canadian governance arrangements poses major ethical challenges and is inadequate to withstand the major pressures on health research today (globalization, privatization, competition and rapid scientific and technological development).
2. Current policies (such as, Tri-Council Policy Statement¹⁰ and the International Convention on Harmonization Good Clinical Practice¹¹) and processes (viz., the REB system and current oversight mechanisms) suffer from "ethical tunnel vision." The net result is that REBs and researchers become too focussed on paperwork -- the bureaucratic processing of research proposals and the administration of consent forms -- and not enough on substantive protection.¹²
3. While major oversight responsibilities are placed on REBs, they lack knowledge of what happens after research proposals are approved. This is in large part due to the lack of monitoring and auditing processes for on-going and completed research. In short, Canadian human research protection lacks "the virtuous learning loops" which provide quality assurance and quality improvement.
4. Research subjects are treated as passive rather than active participants in the research process and its governance.
5. Little attention has been paid to the culture of research and the ethics education for researchers and REB members. At local and national levels there are systemic conflicts of interest due to absence of arm's length

oversight for human research protection. Evidence-based research and experimentation on effective modes of human research protection are missing.¹³

15 In their 2002 report to the Institutes of Medicine (IOM) in the US, Federman and his colleagues reach many of the same conclusions when they recommend "a systems approach to protecting research subjects."¹⁴ Such a systems approach treats ethics review as but one component (albeit an important one) of human research protection. A systems approach adds continuous quality improvement, research on systems effectiveness, management of conflict of interest, and other measures. The authors of the IOM report see these measures integrated into "a responsible Human Research Participation Protection Plan" established under federal oversight.

16 Emmanuel and his fellow members of the Consortium to Examine Clinical Research Ethics Issues reach similar conclusions to the preceding in their recent assessment of the situation in the US.¹⁵ They divide problems into three major categories:

1. Structural problems including regulations that do not apply to all research, inconsistencies in regulations, lack of effective mechanisms for IRBs to address problems, inherent institutional conflicts of interest, no systematic management of conflict of interest, repetitive IRB reviews, absence of resources devoted to IRBs, and inadequate education.
2. Procedural problems including time-consuming review processes, poor quality of IRB review, inadequate guidance on IRB operations, excessive focus on consent forms, and ineffective adverse event reporting.
3. Performance assessment problems including no validated measures of IRB performance and no systematic collection and dissemination of research performance data.

17 Like the authors of the Law Commission of Canada and the IOM reports, Emmanuel and colleagues call for "fundamental reforms to the oversight system."

18 I would sum up the general conclusions reached in these and similar reports quite bluntly. The current régime for governance of health research involving humans fails to discharge the burden of proof described above. In Canada (or elsewhere) the research community (including sponsors and regulators) is not in a position to provide transparent evidence-based demonstrations of effective human research protection. This raises acute questions about the ethical legitimacy of a core segment of the health research enterprise.

19 Third, in the especially complex and fragmented situation that we have in Canada -- with

federal-provincial division of powers, a tradition of strong majority government, civil and common law systems, and our political culture -- remedying the problems we face in governance will take a coordinated effort on the part of multiple authorities, agencies, and organizations.¹⁶ In a number of the articles that follow, the authors suggest necessary steps. The group gathered at Whistler would agree with a remark that Pullman makes at the end of his paper "Research Governance, Bio-politics and Political Will: Recent Lessons from Newfoundland and Labrador." Pullman says, "Although all agree that ethics oversight of health research is important, the reality is that this issue is generally not a vote getter, and hence it is not a hot button issue for government."

20 We asked then how do we get politicians and bureaucrats to align political with ethical priorities. Part of the problem is a lack of political will, but there are important antecedents for this. Canada's system for human research protection is opaque. Even basic information about it is lacking. Thus, as Schuppli and McDonald point out in "Contrasting Modes of Governance for the Protection of Humans and Animals in Canada: Lessons for Reform," we know how many animals are used in Canadian research but not how many humans. In contrast to the U.S., there are no publicly known situations in which Canadian authorities have disciplined (e.g., through the withdrawal of research funding) Canadian research institutions or researchers for unethical behaviour. It is far easier to find out about research mishaps in Canada from U.S. authorities than from Canadian authorities. (Of course such information is limited to Canadian research which is U.S. funded.) In these circumstances it is very difficult (short of a major public scandal) to bring about needed changes.

21 Fourth, we recognised that while the case for systemic reform is ethically persuasive, there are worthwhile initiatives that can be tried on more limited bases. For example, Pullman describes the initiative in Newfoundland to provide a legislated regime for health research involving humans. In "Research Ethics Across the 49th Parallel," Lavery, McDonald and Meslin suggest an experimental initiative that would involve a number of leading Canadian research centres. These would be research centres that have a significant amount of NIH or other U.S. funding for health research. For such research these centres have to follow both U.S. and Canadian rules. The suggestion is to pilot test a system of ethics review that would make use of the heretofore dormant "equivalent protections" clause in U.S. regulations. The net result would be that compliance with Canadian rules would satisfy American requirements. Administrative efficiency would be improved and elements of effective protection would be demonstrated.

22 One reason for discussing such partial measures is political realism. Systemic reform may be a long time coming. One may recall that promises for human research protection reform were made in the 2002 Speech from the Throne, but they never materialised. Moreover, we believe that collective inaction should not be an excuse for individual inaction on the part of the research community, research institutions and sponsors. It is also worth noting that the move to accreditation in the U.S. under the Association for the Accreditation of Human Research Protection Programs, Inc. (AAHRPP) came about due to the initiative of a broad band of non-governmental organizations including the Association of American Medical Colleges, the Association of American Universities,

the Consortium of Social Science Associations, and the Federation of American Societies for Experimental Biology.¹⁷

23 Fifth, we collectively recognised that research involving humans is a dynamic area that generates significant new ethical challenges as it progresses. Willison identifies one such area in his paper, "Trends in Collection, Use and Disclosure of Personal Information in Contemporary Health Research: Challenges for Research Governance." In "Consent Revisited: Points to Consider," Knoppers raises similar issues around the new complexities posed by the use of human tissue and data in health research. Similarly, in their paper, "The Long Arm of Administrative Law: Applying Administrative Law Principles to Research Ethics Boards," Carver and Hadskis argue that the law may apply in ways that have not heretofore been anticipated.

Specific Initiatives

24 The following suggestions were prompted by ideas put forward by participants at the Whistler Summit on Governance. However, to say they were "prompted" is also to say that the directions offered here are the guest editor's sole responsibility. We believe that these would contribute to desirable systemic change. However, even in the absence of such change, they seem promising in their own right. There are important common themes running through the recommendations.

- The need for evidence-based human research protection
 - The systemic use of meaningful performance indicators for quality assessment and improvement
 - Public accountability and transparency
 - Effective management of individual and institutional conflicts of interest.
1. In his paper "Federal Regulation of REB Review of Clinical Trials," Lemmens argues that "REBs fulfill an important public function and that Health Canada has recognized that REB review is a fundamental part of the protective régime surrounding clinical trials." Federal regulation to ensure that REBs are free of conflict of interest seems an obvious step forward. A further step along the road to the ethical management of conflict of interest in clinical trials is recommended by Caulfield in his paper, "Legal and Ethical Issues Associated with Patient Recruitment in Clinical Trials: The Case of Competitive Enrolment."

2. A complementary step is recommended by Dinsdale in "Professional Responsibility and the Protection of Human Subjects of Research." In line with the recommendations made in the 2001 IOM report, *Preserving Public Trust: Accreditation and Human Research Protection Programs*, Dinsdale recommends the establishment of a human subjects accreditation process for Canadian research institutions.¹⁸ Such a process would build on the traditions of self-regulation represented in professional bodies (such as physicians and nurses) and in universities. In this regard, it is ironic to note, as Schuppli and McDonald do, that an independent Canadian system of certification and oversight is in place for research involving animals but not for research involving humans.
3. As a number of authors (e.g., Hadsakis and Carver) in this collection note, the regulation of health research is, to a considerable extent, a provincial responsibility. There is, then, room for provinces to follow the example of Québec by establishing regulations for ethical health research involving human subjects. Pullman describes moves in this direction on the part of Newfoundland. Ideally one would like to see this done in a coordinated way so that there would be a common Pan-Canadian approach.
4. Research institutions, either individually or collectively, should create a data base of key information about human subject protection. The objective would be to provide at least as much information about research involving humans as we have about research involving animals (see the article below by Schuppli and McDonald). Ideally such a data base would have expert input so that it would track ethically meaningful criteria (see, for example, the paper by Lavery, McDonald, and Meslin). One would hope, as well, that there could be a consensus on key measures. Such a data base would facilitate planning locally and nationally. It would facilitate inter-institutional comparisons concerning costs, administrative burdens, types of research and the like. It would provide regulators and the public with important information. When stories appear in the media about research misadventures, there would be an accurate idea of the total amount of research conducted in Canada. That is, there would be a denominator as well as a numerator. The costs for this step would likely be minimal since research institutions already collect information for REB review of research proposals and for annual reports from researchers.
5. In a similar vein, Health Canada, CIHR and the pharmaceutical industry

could establish a standard centralized data-base on adverse events. It should be one that is annotated with respect to levels of risk and is made easily accessible to REBs reviewing clinical trials, researchers and research subjects. The Canadian HIV/Aids Network provides a useful model.¹⁹

6. Like evidence-based medicine, evidence-based human research protection would have two key components: (a) a research component and (b) a dissemination component. For (a), the research component, to work a commitment would be needed from sponsors (such as the Tri-Council, Health Canada, and industry) to support research that builds a strong evidence base. This would include research on the experiences of human subjects, research on the effectiveness of various types of review procedures, or research on various forms of monitoring. The article by Lavery, McDonald and Meslin provides an example of such research. CIHR recently took a step in this direction with its call for proposals for a study of conflict of interest in clinical trials (Evaluation of the Integrity of Clinical Research in Canada www.cihr-irsc.gc.ca/e/22307.html). The NIH has a model program in this area "Research on Ethical Issues in Human Studies" (grants2.nih.gov/grants/guide/pa-files/PA-99-079.html). However, as Caulfield notes in his short commentary "Conflicts of Interest and Research on Ethical, Legal and Social Issues," it is important that funding for research in ethics be robustly independent and not tied to matching dollar requirements that create potential conflicts of interest. For (b), dissemination of research to practitioners there has to be an effective knowledge translation strategy. Here research sponsors and regulators could provide incentives. Accreditation could also play a useful role.

7. Currently the three federal research agencies provide funding to research institutions conditional upon their compliance with several Memoranda of Understanding (MOUs).²⁰ Several of these are relevant to human research protection, in particular the MOU, "Ethics Review of Research Involving Humans." As well, the Councils are in the process of developing an MOU around conflict of interest. What we propose is that the Councils and the research institutions develop and implement a plan for open accountability around these MOUs. Such a plan would require annual public reporting of such matters as:
 - Steps taken to implement the institution's policy on ethical research

involving humans

- Put in place educational programs such as required classes, certification, seminars, and open houses to help researchers understand their responsibilities
- Provisions, if any, for monitoring on-going research and for regular auditing
- Information about REBs reporting relationships, appointment procedures, training, and support (including annual budget)
- Measures taken, including audit procedures, to deal with both individual and institutional conflict of interest in research.

The objective would be to provide all stakeholders (especially research subjects and the public) with accurate information about what research institutions are doing to implement the MOUs that they have with the three federal research Councils. As well the councils should provide annual public reporting of how they have met their responsibilities under the current MOUs. All parties would agree to have their compliance with these standards subject to audit.

8. In all human research protection processes, transparency should be the prevailing norm. That is, there should be the rebuttable presumption of transparency. Thus, we envision web-posted reports of REB decisions with systemic institutional effects. This would include the interpretation of clauses or key concepts (e.g., minimal risk, expedited review requirements) in TCPS or other relevant documents. Both private and public sector research institutions should provide annual public reports of the number of protocols reviewed by REBs, results of review (acceptance with or without modification, deferral, or rejection), policy decisions, monitoring, complaints from subjects, and other pertinent information of interest to stakeholders (especially actual and potential human subjects). Similarly, regulators and overseers (including professional licensing bodies, Health Canada, the Tri-Council/Agency, Québec authorities and industry) should provide detailed annual reporting of the measures taken to provide human subjects protection. These would include the number and general nature of complaints, methods of monitoring, and the like. Where possible there should be independent verification of the accuracy and thoroughness of such reports. We recognize that there will be some confidential

information that should not be publicly reported but this needs to be compensated for by measures of accountability that have clear public credibility. While we value transparency primarily for its contribution to greater public accountability, there is an added advantage to the presumption of transparency. It may well reduce the discontent that researchers express with inconsistencies in REB review. If REBs publicly state their decisions and the reasons for them, greater consistency is a likely result.

9. As suggested by Enzle and Schmaltz in their paper, "Ethics Review of Multi-Centre Clinical Trials in Canada," other steps should be taken to improve inter-institutional coordination and cooperation in ethics review and other aspects of human subject protection. They consider various ways in which ethics review can be coordinated and facilitated at diverse sites and note particularly the steps being taken in Alberta to this end. It is worth noting that steps have also been taken towards shared ethics review processes in cancer research -- (e.g., for paediatric oncology research through the U.S. based Children's Oncology Group and the European based Société Internationale d'Oncologie Pédiatrique). We also think that research institutions could establish reciprocity agreements for REBs to exchange information, use common forms, and develop shared educational activities. They could also create REBs for highly specialized areas. Of course, as Beagan and McDonald have argued in "Evidence-Based Practice of Research Ethics Review?" inter-institutional cooperation is much more likely if evidence rather than anecdote is used to drive the process of ethics review.
10. Finally, members of our group suggested some simple steps to improve human subjects protection.
 - In advance of asking for consent, provide potential subjects with a short statement of their rights.
 - Ask subjects about their experiences through exit interviews and surveys, and then use the information generated to improve REB, researcher and institutional performance.

- Research intensive institutions could appoint research subject advocates to act as resource persons for researchers designing projects, a consent monitor during subject recruitment and an advisor and advocate for subjects during and following research.

- Through education and funding, research institutions and sponsors could encourage researchers to incorporate effective modes of protection into their research proposals.

- Research institutions should hold an annual research ethics open-house for the public, investigators, and trial coordinators, to explain what research is, what rules are required, how REBs work and in general how human subjects protection is provided at the institution.

Conclusion

25 The papers in this collection identify major areas of concern in Canadian governance of ethical health research and offer, what we believe are, useful suggestions for improving this situation. We hope that this collection of papers stimulates a wider public debate and generates momentum for ethically imperative changes in our mode of governance.

26 To sum up, human subjects protection is not an optional goal in health (or other types of) research. The onus lies on those who conduct, sponsor and benefit from such research to ensure ethical protection of human subjects. The challenge then is to adequately demonstrate to research subjects that "we" (researchers, sponsors and regulators) are doing a good job of protecting their interests and rights. We have a long way to go in this country before we can truthfully say that we are doing this. Honest recognition that we have a problem of ethical legitimacy is the first essential step towards effectively remedying the situation.

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1 National Council on Bioethics in Human Research, "Protecting and Promoting the Human Research Subject: A Review of the Function of Research Ethics Boards in Canadian Faculties of Medicine" (1995) 6 NCBHR Communique 3.

2 Tri-Council Working Group on Ethics, Code of Ethical Conduct for Research Involving Humans, (Ottawa: Tri-Council Working-Group on Ethics, 1997).

3 Ibid.

4 Michael McDonald et al. *The Governance of Health Research Involving Human Subjects*, (Ottawa: Law Commission of Canada, 2000).

5 T. Douglas Kinsella, "Research Involving Humans: Current Regulatory Status of the Canadian Medical Profession" in *ibid.* at 165-171.

6 Timothy Caulfield et al. "Research Ethics and the Role of the Professional Bodies: A View from Canada" (2004) 32 *J. L. Med. & Ethics* 365.

7 *Supra* note 4; Michael McDonald & Eric M. Meslin, "Research Ethics as Social Policy: Some Lessons from Experiences in Canada and the United States" (2003) XXIV *The Tocqueville Review/La Revue Tocqueville* [McDonald & Meslin].

8 E. Emmanuel, D. Wendler & C. Grady, "What Makes Clinical Research Ethical?" (2000) 283 *Journal of the American Medical Association* 2701; B.A. Brody, *The Ethics of Biomedical Research: An International Perspective* (New York: Oxford University Press, 1998).

9 *Supra* note 4; U.S., OIG Office of the Inspector General, *Institutional Review Boards: A Time for Reform* (Washington, D.C.: Department of Health and Human Services, 1998); U.S., IOM Institute of Medicine, *Responsible Research: A Systems Approach to Protecting Research Subjects* (Washington D.C.: Institute of Medicine, 2002); E. Emmanuel, et al. "Oversight of Human Participants Research: Identifying Problems To Evaluate Reform Proposals" (2004) 141 *Annals of Internal Medicine* 282 [Emmanuel].

10 Tri-Council, *Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans* (with updates of May 2000 and September 2002) (Ottawa: Tri-Council, 1998).

11 ICH, *International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guidelines* (Ottawa, Ontario: Minister of Health, 1997).

12 The same fixation on paper as opposed to substance occurs at the policy level in particular on the revision of the Tri-Council Policy Statement.

13 *Supra* note 4; McDonald & Meslin, *supra* note 7.

14 D.D. Federman, K.E. Hanna & L.L. Rodriguez, eds., *Responsible Research: A Systems Approach to Protecting Research Participants* (Washington, D.C.: The National Academy of Sciences, 2002).

15 Emmanuel, *supra* note 9.

16 McDonald & Meslin, *supra* note 7.

17 See online <www.aahrpp.org/www.aspx?PageID=174>.

18 IOM Institute of Medicine, *Preserving Public Trust: Accreditation and Human Research Participant Protection Programs* (Washington, D.C.: National Academy Press, 2001).

19 See Canadian HIV Trials Network, online: <www.hivnet.ubc.ca/ctn.html>.

20 See e.g. Tri-Council, *Memorandum of Understanding on the Roles and Responsibilities in the Management of Federal Grants and Awards (MOU)*, online: Natural Sciences and Engineering Research Council of Canada <www.nserc.ca/institution/mou_e.htm>.