

Research Ethics Across the 49th Parallel: The Potential Value of Pilot Testing “equivalent protections” in Canadian Research Institutions

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Abstract

Canada and the United States share the world’s largest trade partnership and an increasing concern about divergent regulatory approaches to common industries. Canadian research institutes receive more research funding from the U.S. National Institutes of Health than any other country, much of it to fund multi-centre and collaborative research between the two countries. Because of these close economic and research ties, and the extensive similarities between the two countries in the review and oversight of ethics in human subjects research, we propose that Canada would be an ideal country for a pilot-test of the feasibility of “equivalent protections”, a U.S. regulation that permits comparison of protections for human subjects between institutions in the two countries. The “equivalent protections” has been advocated by various bodies in the United States as a potentially beneficial mechanism for improving oversight of foreign trials. As well, we argue that “equivalent protections” could prove to be valuable for Canada in five specific ways: (1) by potentially reducing administrative burden on Canadian research institutions administering U.S. federal research funding; (2) by creating symbolic value of an explicit recognition by the United States that procedures normally followed for the protection of human subjects in Canadian research institutions are at least equivalent to those provided

by the U.S. regulations; (3) by lowering the opportunity cost of investing in research in Canada; (4) by affording Canada an opportunity to enhance its leadership role in international research by offering an alternative to the U.S. regulatory model for the protection of human subjects; and (5) by providing a model for how the idea of equivalent protections might be addressed for research funded by Canadian agencies but conducted in other countries.

Introduction

Geographically, Canada and the U.S. share the world’s longest undefended border, the majority of which straddles the 49th parallel. Canada and the United States share the world’s largest trade partnership, amounting to approximately \$650 billion dollars per year in goods and services between the two countries.¹ This partnership is often characterized as a one-directional flow of exports from Canada to the United States, since Canada exports approximately 85% of its goods to the U.S., whereas the U.S. exports about 25% of its good to Canada, but in 2003 Canada’s imports from the United States exceeded those of all 25 countries of the European Union.² Canada and the U.S. have a long and respected tradition of bilateral arrangements in scientific exchange, industrial partnership, national security and the



environment, to say nothing of the more recognizable commonalities in culture, sports, and entertainment.

Recently, in light of the increasingly well recognized economic interdependence between Canada and the United States and our status as the world's largest trade partnership, there have been some quiet calls for improved harmonization of the vast and often divergent approaches to regulating common industries between the two countries.³ Currently more than 300 treaties and agreements are in force to provide frameworks for partnerships in a vast range of enterprises.⁴

Although its precise economic value is seldom considered and difficult to quantify, health research conducted with human subjects is clearly an important strategic priority for both governments, and has a considerable economic impact in both countries. Collectively in 2003, Canadian research institutions received almost \$50 million dollars (U.S.) in federal research funding from the National Institutes of Health (NIH), more than institutions in any other country, and approximately 25% of the \$200 million awarded to foreign institutions.⁵ Much of this funding supports research involving human subjects, and so the value of common, or comparable, standards in the protection of human subjects in research is readily apparent. The basic design features of the respective systems for protecting human subjects (e.g., prior review of protocols by an ethics review body and the informed consent of individuals) and the political philosophy informing both systems is very similar,⁶ even if some of the instruments used to implement these protections differ.

The general need for regulatory reform between the two countries provides a context for examining some other specific needs that have been identified recently in the field of human research protection and oversight. Four needs, in particular, are relevant to the proposal that we elaborate below. The first need arises within the Canadian human research protection enterprise. A prior report by one of the authors⁷ on the state of the Canadian system has described an array of deficiencies and challenges. Improvements to the system are likely to require sustained attention and innovation. The papers in this volume help to delineate these challenges and form part of the first response for reform. The need for reform has also been dramatically reinforced by recent violations of human research protections by Canadian research institutions,⁸ and by the fact that corrective oversight action and demands for improved accountability for these violations came, not from the Canadian govern-

ment, but from the Office for Human Research Protections in the United States.

The second need arises within the U.S. regulatory system for protecting human research subjects. Several recent reports, including one directed by one of the authors⁹ (EMM)(8), have clearly established the need for significant reform of the system.¹⁰ The third need is a common theme in proposals for system reform in both Canada and the United States, namely the need to generate data that can guide the development and evaluation of any system improvements and innovation. This need provides critical framing for our proposal, below, since it serves as an admission that our current ability to measure and demonstrate the effectiveness of our systems is rudimentary, at best. The fact that this need is expressed consistently across the 49th parallel provides additional weight to our proposal.

The final need that is relevant to our proposal takes us beyond the confines of Canada and U.S. relations to the broader field of international health research. Since the United States remains the dominant figure in the funding of global health research, it is not surprising that its regulations for the protection of human subjects, which are also requirements for the receipt of U.S. federal government research funding, enjoy a privileged position in influencing the development of research ethics and the protection of human research subjects in less developed countries.¹¹ With this dominant influence, however, have come increasing concerns that the aggressive application of U.S. regulations abroad (including Canada) is unethical¹² and potentially also illegal.¹³ As such, there is a pressing need—though perhaps felt less acutely within the United States—to avoid the hegemonical application of the U.S. regulatory scheme internationally, particularly in light of the fact that its effectiveness for the protection of human subjects in research conducted in the United States is in doubt. If Canada's approach—which is rightly the subject of similar scrutiny and criticism—could be demonstrated to provide protections that are at least equivalent to those of the U.S. regulations, it would immediately provide new opportunities and options for developing countries that are currently working to build effective systems. The information obtained would constitute an important step forward in addressing fundamental evaluative issues that have evaded both the U.S. and Canadian systems since their inception.

In the sections that follow, we explore whether a pilot test of the U.S. regulation on equivalent protections offers a potentially valuable way to address each of these needs.



The Opportunity of Equivalent Protections

In a recent paper comparing the experiences of the U.S. and Canada with respect to research ethics policy, two of the authors of this paper recommended that:

It would be useful to develop more fully the potential to make use of the “equivalent protections” provision found in U.S. regulations for research that crosses the U.S. Canada border. This would be helpful for multi-site clinical trials and for NIH funded research conducted in Canada. It would require developing some shared standards and methods for quality assessment for human research protection.¹⁴

This proposal followed from previous recommendations by the U.S. National Bioethics Advisory Commission (NBAC)¹⁵ and the Office of the Inspector General (OIG) of the U.S. Department of Health and Human Services.¹⁶ Both reports arose in the context of controversy related to the rapid expansion of clinical trials in developing countries, where protections for human research subjects are often poorly developed, relative to the extensive regulatory scheme in the United States. The reports independently raised the idea of implementing the “equivalent protections” provision of the U.S. Federal Policy for the Protection of Human Subjects (the “Common Rule”)¹⁷ as a policy mechanism for ensuring that human subjects are adequately protected in research funded by the United States, but conducted in other countries. The “equivalent protections” provision of the Common Rule recognizes that the procedures employed for the protection of human subjects in institutions in other countries may provide protections that are *at least equivalent* to those offered by the Common Rule procedures (see Table 1), and so represents a promising mechanism by which to explore the potential for greater harmonization of rules and guidance in international collaborative research.

Despite the impetus provided by concerns about research in developing countries, it is important to recognize at the outset that the equivalent protections mechanism is not restricted to developing countries. In fact, the regulation is meant to enhance accountability for the protection of human research subjects for research that is conducted in any research institutions outside the United States. And since Canadian research institutions receive a significant amount

of NIH funding—more than any other country¹⁸—there is some rationale for ensuring commensurate levels of accountability for research conducting in Canadian institutions,¹⁹ there is a clear rationale for ensuring commensurate levels of accountability for research conducting in Canadian institutions. This point was driven home vividly recently when the U.S. Office for Human Research Protections intervened to correct oversight deficiencies at the University of British Columbia.²⁰

In this paper we will discuss the equivalent protections provision in some detail and suggest ways in which a pilot test of the provision in Canadian research institutions might serve Canadian, U.S. and international needs.

Equivalent Protections in the U.S. Oversight System

The Value of EP for the U.S.

NBAC and OIG explained the potential value of the equivalent protections regulation as a way to address shortcomings in U.S. oversight of clinical trials funded by the U.S. government but conducted in foreign countries. NBAC, in particular, recognized the potential for EP, as an existing U.S. domestic policy mechanism, to address a number of contentious and unresolved ethical and policy issues in international research, such as resolving disagreements between local and “remote” Research Ethics Committees,²¹ and the international relations consequences of requiring compliance with U.S. rules in foreign countries,²² especially since the appropriate Congressional authority for such extraterritorial application is unclear.²³

More recently, proposed legislation—*The Research Revitalization Act of 2002*—was introduced to the United States Senate that, if passed, would have required the Office for Human Research Protections (OHRP) to develop and maintain a list of countries in which institutions²⁴ had been granted equivalent status.²⁵ Although this bill was not passed by the U.S. Congress, it signaled that the equivalent protections approach endorsed by NBAC and OIG had achieved some credibility and currency at the most influential level in U.S. policy-making. At the time of writing, it is not clear whether a revised version of the *Research Revitalization Act* will be re-introduced in the Senate.



The Specifics of the Equivalent Protections Regulation

U.S. regulations for the protection of human subjects have included the concept of equivalent protections since their inception. Three particular provisions are directly relevant. The first makes it clear that the policy applies to “research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States.”²⁶ The second emphasizes that the policy “does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research.”²⁷ And finally,

“When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries may differ from those set forth in this policy. [An example is a foreign institution which complies with guidelines consistent with the World Medical Assembly (sic) Declaration (Declaration of Helsinki amended 1989) issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized.] In these circumstances, if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy ...”²⁸

The regulation is concerned with: (a) procedures normally followed in foreign institutions; (b) that may differ from the procedures described in 45 CFR 46 (but that may be consistent with guidelines issued either by sovereign states or by an organization whose function for the protection of human subjects is internationally recognized); (c) if these procedures can also be demonstrated to afford protections that are at least equivalent to those provided by 45 CFR 46; then (d) the relevant Department or agency head may substitute the

foreign procedures in lieu of the procedural requirements of 45 CFR 46.

The DHHS Working Group Report

In 2002, the Office for Human Research Protections (OHRP) convened a Working Group of the U.S. Department of Health and Human Services (DHHS), chaired by one of us (JVL), to prepare a report on equivalent protections.²⁹ The report reviewed the limited literature on equivalent protections to date, sought to clarify several points of contention among previous commentators and ambiguity in the regulation itself, and proposed a preliminary framework for implementing equivalent protections.

The Working Group (WG) Report framework involves two parts: first, the steps involved in determining equivalence, and second, a mechanism for establishing an appropriate assurance between the foreign institution and OHRP. The WG identified four steps for determining equivalence between a foreign institution’s protections and those provided by the Common Rule.

First, the articulation of the specific protections embodied in the Common Rule, a preliminary account of which the WG provided in its report (see Table 1).

Second, the assessment of the protections provided by the institution’s own procedures. This would require a process similar to that conducted by the WG, namely, a careful analysis of the established procedures, and some fair assessment of what protections can reasonably be inferred from them.

The third step in the proposed process would involve the comparison of the protections provided by the institution’s procedures with those provided by the Common Rule and a determination of their equivalence, or not.

The fourth and final step in the determination of equivalence would involve the approval by the relevant department or agency head for the substitution of the institutional procedures in lieu of the Common Rule procedures. Each of these steps was described in detail in the WG Report³⁰

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One of the cornerstones of the domestic system in the U.S. is the Federal Wide Assurance (FWA), a legal instrument that formalizes the relationship of accountability between the research institutions that receive federal funding and OHRP, whose mandate involves ensuring that recipient institutions comply with the regulations. FWAs are also negotiated by OHRP with foreign institutions receiving U.S. federal research funding. The Assurance mechanism is meant to hold foreign research institutions to the same standards of accountability as U.S. institutions. In its report on U.S.-funded foreign clinical trials, the OIG specifically identified assurance mechanisms as a way to make improvements in human subject protections, presumably by formalizing relationships of accountability.³¹ In particular, after a determination of equivalent protections, the foreign institution would complete an assurance and file it with OHRP.³²

The assessments by NBAC, the OIG, and the DHHS WG strike us as sensible first steps for the U.S. to take with regard to the more general criticism that some make about the imposition of U.S. research regulations on institutions in other countries.³³ We draw no conclusions about how likely the U.S. will be to implement the EP provision, particularly in the absence of a legislative mandate to do so. At the time of writing, OHRP is reviewing comments on the WG Report

from DHHS agencies. These comments are expected to be published in the U.S. Federal Register with a response from OHRP, though the time-frame for this publication remains unclear.³⁴

A published position from OHRP would help to clarify the likelihood of implementing an EP approach, or at least the critical obstacles that would need to be cleared in order to do so. Whatever the formal U.S. government process, we are inclined to believe that efforts by institutions in other countries to seek equivalent status may themselves encourage further action on the EP provision. We turn now to the question of whether Canada should consider taking up this opportunity.

Equivalent Protections in Canadian Institutions

The Tri-Council Policy Statement

The 1998 *Tri-Council Policy Statement* (TCPS) for the Ethical Conduct of Research Involving Humans is Canada's major document for research involving human beings.³⁵ As indicated by its title, the TCPS belongs to three research councils: the Canadian Institutes for Health Research, the

Table 1. Protections Embodied in the Common Rule

Institution

Establish expectations of ethical conduct and due diligence in review and performance of research within the institution

Ensure adequate authority and independence of the IRB/Research Ethics Committee

IRB

Protection from biased and arbitrary decisions in research ethics review

Ensure sufficient quality and comprehensiveness of research ethics review

Ensure review and oversight are commensurate with risk and vulnerability of study population

Protection from unnecessary or unjustified risk throughout the course of the study (includes responsibilities of investigator(s))

Protection from inadequate disclosure and non-voluntary participation (includes responsibilities of investigator(s))



Natural Sciences and Engineering Research Council, and the Social Sciences and Humanities Research Council. The three councils are the main public sector sponsors of research for Canadian universities and affiliated institutions (including academic health sciences centres). Funding from the three federal agencies is conditional on the recipient institutions following the TCPS for *all* research involving humans, and not just for research funded by the councils. Although it does not have the same regulatory status as the Common Rule, the TCPS functions in the same way in Canada. It is the principal guidance document for human subjects research for Canadian institutions, and therefore provides a close approximation of what the EP provision refers to by “procedures normally followed” in a typical Canadian research institution. It is also a key requirement of the equivalent protections provision.³⁶

Both the Common Rule and the TCPS refer to similar mechanisms for institutions to provide the relevant regulatory authorities (in the U.S.) and funding bodies (in Canada) with a legally-binding assurance that research will be conducted according to the respective standards. In Canada the assurance is formalized through a memorandum of understanding between the relevant federal funding agency and the institution receiving the research funding.³⁷ Although the specific assurance mechanisms differ, institutions in both countries risk the withholding, suspension or termination of research funding by the respective funding agencies if they breach the terms of their assurances.

Similar procedural mechanisms for local, institutionally-based review and approval of protocols are common to both countries and the review committees—Research Ethics Boards (REBs) in Canada and Institutional Review Boards (IRBs) in the U.S.—use similar review criteria for assessment of research protocols, such as informed consent, assessment of risk and potential benefits and fair selection of research subjects. Like the Common Rule, the TCPS provides clear language regarding the responsibility and accountability of research institutions for ensuring competent and independent ethical review of research protocols involving human subjects: “Institutions must ensure that REBs have the appropriate financial and administrative independence to fulfill their primary duties. Institutions must respect the authority delegated to the REB.”³⁸

Whereas the Common Rule has very limited content aimed at resolving substantive ethical issues encountered by investigators and research sponsors in their research, the TCPS also functions as a guidance document for investigators and

research sponsors, spelling out detailed expectations of research conduct. Indeed, one of the strengths of the newer TCPS document is its expanded scope, incorporating topics and issues that are not addressed in the 14 year-old Common Rule. This is most apparent in the TCPS’s integrated approach to ethical issues in behavioural, social science and engineering research involving humans.

Strictly speaking, the equivalent protections regulation requires only that the protections provided by foreign institutions be at least equivalent to those provided by the Common Rule procedures. Any additional provisions in the TCPS would not be directly relevant to the implementation of the equivalent protections regulation, though they are clearly relevant to the broader aims of evaluating how the two systems protect human subjects, an issue we address briefly below.

Looking beyond the EP regulation

The nature of the equivalent protections regulation, which does not have a specific counterpart in Canadian guidelines, dictates that Canadian institutions must demonstrate compliance with U.S. minimal standards. This presumption is offensive to many Canadians, particularly in light of the reasonable expectation that Canadian institutions can already satisfy these requirements, and even go beyond many of them. Taken in isolation, there appears to be little incentive for Canadian institutions to submit to this type of scrutiny. But the recent case involving the University of British Columbia, in which the University’s Clinical Research Ethics Board was found to have approved more than 500 research protocols on the basis of review of summaries only, and had failed to adequately inform some patients of research-related risks,³⁹ provides a potent illustration of how viewing these protections as national attributes, rather than institutional ones, could mislead in individual cases. The exercise of pilot testing the equivalent protections mechanism in Canadian institutions is not likely to uncover vast differences from the regulatory protections required of U.S. institutions. But the process of examining institutional procedures and grappling with ways in which these protections might be successfully defined and measured, could prove to be extremely valuable in light of the general needs outlined above. In this way, the equivalent protections mechanism provides the impetus and some structure for tackling broader issues in system reform, including the generation of the necessary measures and data.



Why should Canada care about equivalent protections?

If Canadian institutions chose to make use of the equivalent protections provision in the Common Rule (assuming it were available), the U.S. federal government would, in effect, gain more precise information from Canadian institutions hosting U.S. government-funded research than they currently receive in the Federal Wide Assurance, and so improve the oversight effectiveness for research conducted in these institutions. Since the FWA functions as a promissory instrument, rather than a detailed contract, it does not require extensive reporting or documentation, whereas the requirements for equivalent protections are likely to be more extensive. One specific concern, then, is that the equivalent protections mechanism would effectively expand the current reporting requirements contained in the Federal Wide Assurance, and fuel further resentment about the imposition of U.S. standards on Canadian institutions. How then would Canadian institutions, and Canada as a whole, gain from such an initiative?

A recent Canadian federal government advisory panel on regulatory reform released a report indicating that there are countless minor differences in the way Canada and the U.S. regulate the same industries, and that these divergences in regulatory standards are damaging to both countries.⁴⁰ One solution to these problems, according to the panel, is increased cooperation. Therefore, in very general terms, the main answer to the question why Canada should care about EP is that research—in particular the type funded by the NIH and CIHR—constitutes a cross-border “industry” in which shared standards might prove beneficial to both countries. Given the recent experience with Severe Acute Respiratory Syndrome (SARS) in both countries, the need to remove unnecessary regulatory obstacles to cooperative research and public health practice becomes even more apparent.

Foreign relations considerations aside, there are five additional reasons why we believe pursuing an equivalent protections approach with the U.S. might be useful for Canada and Canadian institutions. First, it is possible that implementing the equivalent protections policy could reduce the administrative burden on Canadian REBs in their review, oversight and monitoring of U.S.-funded research, by reducing certain registration and documentation requirements for OHRP and FDA. As we have acknowledged above, it is also conceivable that the higher resolution information required

by the equivalent protections mechanism, compared with the current compliance requirements of the Federal Wide Assurance, could result in an increased administrative burden on Canadian institutions.⁴¹ But any increased reporting and documentation burden for Canadian institutions would also entail additional review and oversight activity for OHRP, which might limit the appeal of burdensome administrative requirements for OHRP and eligible institutions alike. One likely scenario would involve considerable up-front investment of time and resources, both by OHRP and the Canadian institutions, to establish equivalence—similar to the process of accreditation—followed by a reasonable window during which onerous administrative requirements could be either waived or significantly reduced. Although such minor changes alone may not represent significant alleviation of burden for Canadian REBs, we suspect that further study may reveal other opportunities to reduce administrative burdens, and so improve both the efficiency and quality of the review process.

Second, in addition to a potential for reduction in administrative burden in cross-border research in the long-run, there is an important symbolic value to equivalent protections for Canada. Under the current Federal Wide Assurance program in the United States, Canadian institutions promise the U.S. government that they will abide by the U.S. regulations in conducting the funded research. Although this requirement does not result in dramatic departures from the procedures normally followed within Canadian institutions, the assurance amounts to a voluntary decision to submit to U.S. procedures.

The OHRP Working Group identified that foreign institutions were likely to view determinations of equivalent protections as valuable since they would entail explicit recognition that procedures other than those described in the U.S. regulations could be at least as likely to protect human subjects in research. This does not completely erase the appearance that the U.S. standards are considered superior to any other, and therefore the “gold standard” to be matched, the significance of formal recognition by the United States that equivalent ends in the protection of human research subjects may be achieved by different means should not be underestimated. Although it is arguable that this benefit would have the most significance for developing countries, and not for a G8 country such as Canada, given Canadian concerns about U.S. dominance in trade and cultural arenas, the symbolic value of equivalent protections might be very high.



Third, while Canada represents 2% of the global market for pharmaceutical sales, it has attracted only 1% of the world's research and development investment.⁴² The United States, by comparison, holds 47% of this investment market. There are limits to how much research and development Canada can effectively absorb, but it is clear that the regulatory environment has been a rate-limiting factor for investment.⁴³ Although the equivalent protections mechanism should not be viewed as an instrument for economic development, it could enhance Canadian participation in the global pharmaceutical research enterprise by helping to clarify shared standards between the Canadian and U.S. systems, which could lower the opportunity cost of investing in research in Canada.

Fourth, given the complexities of oversight and regulation within institutions in developing countries, and the urgent appeal by NBAC, the OIG and some U.S. legislators to tackle equivalent protections at the global level, the opportunity for the U.S. government to establish the proof-of-principle for equivalent protections with Canadian institutions would serve as a low-risk testing ground for doing the same in other countries. We expect that similar experiments could occur initially in economically developed countries such as Australia, the UK, and Sweden, but soon thereafter in economically developing countries such as Kenya, Uganda, India, South Africa, Brazil and the Philippines—countries with growing research activity and similar oversight procedures. Thus, an equivalent protections approach might offer Canada a unique opportunity to play a strong leadership role in international research ethics by demonstrating an alternative approach to the U.S. regulatory model, one which is now being rapidly disseminated throughout the developing world and about which there is a growing concern.⁴⁴ Whether the will and leadership exists in Canada to champion such an initiative is a critical, and potentially rate-limiting, factor. But if it does exist, the equivalent protections mechanism would serve as a crucial element in the necessary strategic framework. It is also conceivable, though perhaps unlikely, given the current

political climate in Washington, that a pilot test of equivalent protections in Canada could open the door for the negotiation of a different kind of bilateral agreement between the two countries. This agreement could focus on joint improvements in standards, rather than the presumption of the superiority of the U.S. regulatory scheme.

Fifth and finally, Canadian research institutions also have the responsibility for the ethical review of research conducted by their researchers abroad, as well as inside Canada.⁴⁵ With the CIHR expressing a clear commitment to continue to increase the Canadian contribution to global health research, our proposal could well provide a useful model for determining equivalent protections within the TCPS, and in guiding Canadian funding agencies in their collaborative relationships with other foreign research institutions.

We are mindful of the perception that might arise among Canadians (researchers, REBs, institutions, and government officials) that pursuing EP status is somehow an effort to legitimize Canada's policies against the "gold standard" of the U.S. Common Rule. Such a perception could add fuel to the argument that Canada is already

on a path of cultural and economic convergence, or assimilation, with the U.S.⁴⁶ This argument rightly angers those of us who believe that there can be effective "made in Canada" solutions to the problems confronting research oversight,⁴⁷ and that these Canadian solutions can have global relevance. Our rationale for examining the potential EP status for Canada is not to mimic or mirror U.S. policy, nor to seek to legitimize the TCPS by testing it against the Common Rule. On the contrary, we are inclined to believe that even a cursory comparison between the TCPS and the Common Rule will demonstrate that Canada's protections are more comprehensive, more current, more realistic and more sensitive to new areas of research than their U.S. counterparts. But what is clearly shared between the two countries is an urgent need to develop better strategies for generating the kind of evidence necessary to make meaningful improvements in the protec-

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tion of human research subjects, and to forge agreement on how these standards should best be applied, particularly in the context of international collaborative research.

A Proposal for Pilot-Testing Equivalent Protections in Canada

Given this background, we believe that formal study of the topic should be undertaken to demonstrate the feasibility of an equivalent protections initiative in selected institutions in Canada as a test case for a broader international application of equivalent protections by OHRP. In essence, the idea is to establish “proof of principle” for equivalent protections, using the framework developed by the OHRP WG as a starting point and minimum standard. Although the details for such a proposal have yet to be fully worked out, the main components would involve the following.⁴⁸ We envision this project would involve 3-5 Canadian institutions, each with significant NIH funding and at least one Research Ethics Board (REB) reviewing high volumes of research across various disciplines. Although research volume is not a criterion for equivalent protections, we are assuming that greater volume and diversity of human subjects research is a reasonable measure of the scope of protections that a given institution requires.

Focusing the initial examination on these institutions would provide a relevant sample for the EP experiment, since these institutions are most likely to have well-developed programs for the protection of human subjects and are also most likely to house research funded by the NIH and other U.S. funding agencies. In fact, these Canadian institutions would all likely hold current Federal Wide Assurances with OHRP. Clearly, this initiative would require substantial buy-in and technical input from CIHR and Health Canada, the National Council for Ethics in Human Research (NCEHR), as well as the relevant participating institutions.

Our proposal has two components. The first will follow the 3 main parts of the WG scheme described above: (1) describe the procedures normally followed within the institutions and assess the protections they provide, using an analysis similar to the analysis conducted by the WG; (2)

compare these protections with those described for the Common Rule by the WG; and (3) provide a comprehensive analysis of the relationship between the two sets of protections, and establish a position on their equivalence, using a consensus-building method with a panel of experts from both countries.

Once these steps have been performed, we would present our findings to the relevant Canadian and U.S. oversight bodies. In Canada, we would present these findings to Health Canada, the Canadian Institutes of Health Research,

NCEHR, and the Interagency Advisory Panel on Research Ethics,⁴⁹ which reports directly to the Presidents of Canada’s three research agencies. In the U.S. we would present these findings to OHRP, and the Secretary’s Advisory Committee on Human Research Protections (SACHRP),⁵⁰ and, if appropriate, to the DHHS Office of the Inspector General, and the Food and Drug Admin-

istration. Findings would also be widely disseminated through the peer-reviewed literature.

The second component of our proposal aims to examine the idea of equivalent protections beyond the limited requirements of the Common Rule. This would include assessments not only between the U.S. and Canada, but also of other countries that might stand to gain from such analyses. In effect, we propose to use equivalent protections as a platform to develop a rigorous approach for generating empirical evidence that might help to break new ground in developing meaningful measures of how human subjects are actually protected in research, an aim that has been elusive to date.⁵¹ Although a full account of the methods required by this proposal is clearly beyond the scope of this paper, we aim to work closely with the participating institutions and relevant agencies and regulatory authorities in both countries, and to use (and develop, where necessary) the most appropriate methods for addressing these issues.

Conclusions

Recent developments in international research ethics have highlighted the challenges faced by U.S. government departments, most notably the Office for Human Research

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Protections and the Food and Drug Administration in providing adequate oversight for clinical trials funded by the U.S. government, but conducted in foreign countries. An obscure provision of the U.S. regulations governing human subjects research, the “equivalent protections” provision, has been recommended as a mechanism that might extend the oversight capabilities of OHRP and FDA, but at the same time might also offer benefits to the foreign countries involved. We believe that Canada is an ideal country in which to examine the feasibility and potential effectiveness of the equivalent protections provision and may benefit both countries in various ways.

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4. *Supra*, note 1.
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9. National Bioethics Advisory Commission (NBAC), *Ethical and Policy Issues in Research Involving Human Participants* (Washington, D.C.: U.S. Government Printing Office, 2001).
10. The need for reform has been identified by numerous different sources. See, for example, Department of Health and Human Services, *Institutional Review Boards: A Time for Reform* (Washington, D.C.: U.S. Government Printing Office, 1998); E. Emanuel *et al.*, “Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals” (2004) 141 *Annals of Internal Medicine* 282; A. Wood, C. Grady and E. Emanuel, “Regional Ethics Organizations for Protection of Human Research Participants” (2004) 10(12) *Nature Medicine* 1; and E. Slater, “IRB Reform” (2002) 346 *New England Journal of Medicine* 2002 1402.
11. James Lavery, *The challenge of regulating global human subjects research*, The Science and Development Network (June, 2004), online: <<http://www.scidev.net/dossiers/index.cfm?fuseaction=policybrief&dossier=5&policy=52>>. Last accessed February 27, 2005.
12. National Bioethics Advisory Commission (NBAC), *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, vol. 1 (Washington, D.C.: U.S. Government Printing Office, 2001).
13. W. DuBois, “New Drug Research: The Extraterritorial Application of FDA Regulations, and the Need for International Cooperation” (2003) 36 *Vanderbilt Journal of Transnational Law* 161.
14. See Michael McDonald, *supra* note 6.
15. *Supra* note 12.
16. Department of Health and Human Services, *The Globalization of clinical trials: A growing challenge in protecting human subjects* (Washington, D.C.: Department of Health and Human Services, 2001).
17. Title 45 of the United States Code of Federal Regulations, § 46.101(h).
18. *Supra* note 5.
19. *Ibid.*
20. *Supra* note 8.



21. J.M. Mfutso-Bengu & T.E. Taylor, "Ethical Jurisdictions in Biomedical Research" (2002) 18(5) Trends in Parasitology 231.
22. *Supra* note 12; see also, B.M. Dickens, National Bioethics Advisory Commission 2001. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries*, vol. 2 (Bethesda, MD: U.S. Government Printing Office, 2001).
23. *Supra* note 15.
24. It is likely that the drafters of the Research Revitalization Act misinterpreted the equivalent protections regulation as applying to countries, and their national systems, rather than specific institutions within those countries. The recent report from the DHHS Working Group on Equivalent Protections argued that the regulation should be read to apply to institutions, which reflects the principal focus of the U.S. regulations on institutional accountability. The report is discussed in greater detail below.
25. *Research Revitalization Act of 2002*, U.S.C. (2002).
26. *Supra* note 17.
27. *Ibid.*
28. *Ibid.*
29. U.S. Department of Health and Human Services, online: <<http://www.hhs.gov/ohrp/international/EPWGReport2003.pdf>>
30. *Ibid.*
31. *Supra* note 16.
32. The OHRP web-site currently lists 2917 institutions in 134 countries that hold Federal Wide Assurances. Of these, 275 (9%) are in Canada, more than any other country. (<<http://ohrp.cit.nih.gov/search/asearch.asp#ASUR>>, last visited January 10, 2005).
33. *Supra* note 12.
34. Personal communication, Dr. Melody Lin, Deputy Director and Director of International Programs, OHRP, October 22, 2004.
35. Tri-Council, *Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (with updates of May 200 and September 2002)* (Ottawa: Tri-Council, 1998), online: <http://www.pre.ethics.gc.ca/english/pdf/TCPS%20June2003_E.pdf>.
36. *Supra* note 17.
37. National Sciences and Research Council of Canada, *Memorandum of Understanding on the Roles and Responsibilities in the Management of Federal Grants and Awards (MOU)*, available online: <http://www.nserc.ca/institution/mou_e.htm>.
38. *Supra* note 35.
39. *Supra* note 8.
40. *Supra* note 3.
41. For example, the DHHS Equivalent Protections Working Group Report proposed a set of procedures that would require the collection and analysis of considerable information within the institutions.
42. R&D (Canada's Research Based Pharmaceutical Companies), *Towards Increasing Research and Development in Canada: A New Innovative Pharmaceutical Strategy* (Ottawa: R&D, 2004), online: <http://www.canadapharma.org/Industry_Publications/RXD-ElectionGuide.pdf>.
43. Conference Board of Canada, *Making Innovation Happen—Prospects for Research Intensive pharmaceutical firms in Canada* (Ottawa: Conference Board of Canada, 2002).
44. A.A. Hyder *et al*, "Ethical Review of Health Research: a Perspective from Developing Country Researchers" (2004) 30 Journal of Medical Ethics 68; see also, N.E. Kass, L Dawson & N.I. Loyo-Berrios, "Ethical Oversight Of Research In Developing Countries" (2003) 25(2) IRB 1.
45. *Supra* note 35.
46. Jeffrey Simpson, *Star Spangled Canadians: Canadians Living the American Dream* (Toronto: Harper Collins, 2000).
47. Michael McDonald, *supra* note 6.
48. The comments received by OHRP from other Department of Health and Human Services agencies on the DHHS Equivalent Protections Working Group report have not yet been made public. We expect that these comments will reveal weaknesses in, and propose improvements to, the Working Group's proposed strategy for implementing equivalent protections. Therefore, we fully expect that the details of our proposed approach will require refinement in light of these new insights before it can be pilot tested.
49. Government of Canada, "Interagency Advisory Panel on Research Ethics" online: <<http://www.pre.ethics.gc.ca/english/index.cfm>>.
50. Office of Human Research Protection, Secretary's Advisory Committee on Human Research Protections (SACHRP), online: <<http://www.hhs.gov/ohrp/sachrp/sachrp.htm>>.
51. See the numerous and differing calls for reform, *supra* note 10.

