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Research with Decisionally Incapacitated Older Adults: *Practices of Canadian Research Ethics Boards*

by Gina Bravo, Marie-France Dubois, Sheila M. Wildeman, Janice E. Graham, Carole A. Cohen, Karen Painter, and Suzanne Bellemare

Although research has provided great insight into neurodegenerative disorders such as Alzheimer disease and other dementias, additional studies are needed to prevent these disorders, delay disease onset, reduce the caregiver burden, and develop more effective therapeutic strategies. Many countries have made dementia a national health priority and have launched action plans on dementia that include a research component.[1] Some of that research must involve affected individuals who are, or are likely to become, decisionally impaired.

The law presumes that adults are capable of making decisions on matters affecting their interests, and the presence of a cognitive disorder does not necessarily imply that a person is incapable of deciding whether to participate in research. However, individuals with Alzheimer disease and other dementias will gradually be unable to understand the nature of a research study or to appreciate the consequences of their involvement. Hence, many potential research participants will not be able to provide valid informed consent to participate in dementia research. Yet excluding all decisionally incapacitated adults from research would be discriminatory[2] and would preclude acquiring the evidence-based medical knowledge underpinning sound clinical practice.[3] Thus, many jurisdictions permit authorized third parties to enroll persons who are decisionally impaired in clinical trials.[4]

Because they cannot advocate for themselves and defend their own interests, adults who are decisionally incapacitated should have human subjects protections that are higher than those for prospective research subjects who are able to provide their own consent and retain decisional capacity throughout a study.[5] Yet regulations and guidelines provide little direction to ethics review committees (research ethics boards [REBs] in Canada) about how best to protect those who are incapable of making informed judgments about participating in research.[6] Moreover, in most jurisdictions, there is no clear guidance about whose consent to participate in research can substitute for that of the incapacitated person.[7] For instance, the U.S. Code of Federal Regulations at 45 CFR 46,[8] the Canadian *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS),[9] and the European Union Directive

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2001/20/EC[10] all require consent from a legally authorized representative but defer to the laws of specific local jurisdictions to define what constitutes a legally authorized representative.

To our knowledge, little empirical research has examined how ethics review committees review protocols for studies that may recruit adults who are decisionally incapacitated or who may become decisionally incapacitated during the trial.[11] In this article we report the results of a study exploring the practices and perceptions of Canadian REBs regarding such protocols. The study is timely as the TCPS is currently being revised. Moreover, clinical trials on diseases that erode decisional capacity are expanding in volume and increasingly involve invasive interventions, compared to surveys or observational studies.[12] In light of uncertainties surrounding the nature and extent of the protections that should be provided to decisionally incapacitated adults who are recruited for and participate in research, our findings could inform public policies aimed at ensuring adequate protection for this population while ensuring that promising research is not unduly impeded.

Surrogate Consent and the Canadian Framework

Regulations, guidelines, and position papers are not consistent about when a substitute decision-maker can enroll a decisionally impaired individual in research.[13] Some limit valid third-party consent to research that offers participants the prospect of direct benefit. Others invoke the "minimal-risk" standard or add the requirement that anticipated benefits outweigh the potential risks. Still others require the study to focus on the condition responsible for the participants' decisional incapacity or only permit third-party consent for studies that cannot be conducted solely with persons who have decisional capacity. Moreover, few official documents address the possibility that decisional capacity may deteriorate over the course of research participation. Under such circumstances, some guidelines favor ongoing monitoring of approved protocols by institutional review boards (IRBs). Others encourage individuals at risk of losing their decision-making ability during a study to express their wishes about remaining in the study if they lose decisional capacity, and to designate a substitute decision-maker before that happens.[14]

In Canada, the governance of research is significantly shaped by the TCPS, which applies to publicly funded studies. The current version imposes the following condition for involving decisionally incompetent adults in research:

> Subject to applicable legal requirements, individuals who are not legally competent shall only be asked to become research subjects when: (a) the research question can only be addressed using individuals within the identified group(s); (b) free and informed consent will be sought from their authorized representative(s); and (c) the research does not expose them to more than minimal risk without the potential for direct benefits for them.[15]

Article 2.6 further requires REBs to ensure that the following four conditions are met: 1) the researcher shall show how the free and informed consent will be sought from the authorized third party, and how the subjects' best interests will be protected; 2) the authorized third party may not be the researcher or any other member of the research team; 3) the continued free and informed consent of an appropriate, authorized third party will be required to continue the participation of a legally incompetent subject in research, so long as the subject remains incompetent; and 4) if the subject becomes competent during the project, his or her informed consent shall be sought as a condition of continuing participation. Two additional articles of the TCPS refer specifically to those who are not competent to consent for themselves. Article 2.7 requires researchers to ascertain the wishes concerning participation of legally incompetent individuals who understand the nature and consequences of the research, and to respect their dissent. And Article 5.3 states that legally incompetent persons "shall not be automatically excluded from research that is potentially beneficial to them as individuals, or to the group that they represent."

Study Methods

The present study was part of a larger research program investigating knowledge, opinions, and practices regarding Substitute Consent for Research in Elderly Subjects (SCORES). The SCORES study targeted five groups of people, including REB members. It was conducted in four Canadian provinces: Nova Scotia, Ontario, Alberta, and British Columbia. Provinces were chosen to represent the four main English-speaking regions of Canada and to capture diversity in laws governing substitute decision-making for research with decisionally impaired individuals. At the time of our study, there was no legislation in Nova Scotia that explicitly addressed the issue. In Ontario, substitute decision-making about research was addressed only in its express exclusion from the ambit of that province's health care consent and guardianship/advance directive legislation. The medical advance directive laws in Alberta and British Columbia allowed for proxy consent to research under prescribed conditions. Alberta's law prohibited an appointed proxy from giving substitute consent to "research or experimental activities" without prior authorization, if the proposed research or experiment offered "little or no benefit" to the subject.

Table 1.
Respondent Characteristics (n = 46)

Age (in years)	mean = 56.5, sd = 9.6, from 35 to 79	
Sex (male)		27 (58.7%)
Province	Nova Scotia	6 (13.0%)
	Ontario	30 (65.2%)
	Alberta	6 (13.0%)
	British Columbia	4 (8.7%)
Training background[1]	Medicine	10 (21.7%)
	Other health sciences	15 (32.6%)
	Law	3 (6.5%)
	Ethics/Philosophy	9 (19.6%)
	Social sciences/Humanities	16 (34.8%)
	Other	3 (6.5%)
Highest degree	PhD degree or equivalent	32 (69.5%)
	Master's degree or equivalent	5 (10.9%)
	Bachelor's degree	1 (2.2%)
	Professional degree (e.g., MD)	7 (15.2%)
	Other	1 (2.2%)
Current occupation	University professor	25 (54.3%)
	Clinician with no academic appointment	9 (19.6%)
	Health services administrator	7 (15.2%)
	Other	5 (10.9%)
Years as the chair of the REB	median = 3.0, from 2 weeks to 16 years[2]	
Years as a member of the REB	median = 5.8, from 13 months to 23 years[2]	

[1] More than one answer was possible.
[2] n = 44

Implicitly, where more than "little or no benefit" was held out, no express authorization was required. British Columbia's law prohibited an appointed proxy from giving substitute consent to medical research not approved by a statutorily recognized REB, or "experimental health care" involving a foreseeable risk not outweighed by the expected therapeutic benefit, again unless prior authorization was in place.[16] That said, British Columbia alone expressly authorized substitute decision-making about REB-approved research whether the decision-maker was a guardian, a proxy appointed under an advance directive, or the default decision-maker recognized under the province's health care consent legislation.

For the current study, REBs from the four targeted provinces were eligible to participate if they were affiliated with a university or health care institution and if they reviewed research protocols involving older adults. Eligible REBs were not limited to those reviewing only medical research protocols. We identified eligible REBs from lists posted on various Web sites, including that of the Canadian Association of Research Ethics Boards. We then contacted REB chairs by phone to solicit their participation in a brief interview on their practices and perceptions with regard to protocols seeking to enroll older adults whose capacity for research consent may be compromised by their health conditions.

We designed and pretested a semistructured telephone interview guide containing both closed- and open-ended questions falling into three main sections. Section one assessed REBs' attitudes toward the enrollment in research of decisionally incapacitated older adults and investigated what safeguards they would then require, if any. It also elicited REBs' views about research advance directives and longitudinal studies. Sections two and three collected descriptive information on the REBs and on the interviewees, respectively. A copy of the survey is available on request from the first author. Following oral consent, all interviews were audiotaped, transcribed, and coded for statistical and thematic content analyses. Interviews lasted from nine to 28 minutes. They were conducted by two of the authors (KP and SB) between August 2008 and April 2009.

Study Findings

We identified 87 eligible REBs, of which 46 (52.9%) agreed to participate. The proportion of REBs responding varies from 33% in British Columbia to 86% in Nova Scotia. Lack of time was the main reason for refusing the interview. Characteristics of the interviewees are shown in Table 1. As expected, most of the respondents were from REBs in Ontario, the largest of the four provinces in our sample. Respondents were trained in diverse disciplines and most hold a doctorate degree. A slight majority of chairs were currently employed as university professors. Of note, due to time constraints, two respondents were the coordinator of the REB rather than the chair. Because coordinators attend REB

Table 2.
REB Characteristics (n = 46)

REB member(s) with legal expertise	34 (73.9%)
REB member(s) with expertise in ethics	43 (93.5%)
REB has community representative(s)	43 (93.5%) (from 1 to 5)
Takes part in educational activities on a regular basis	29/45 (64.4%)
Some educational activities deal specifically with decisionally incapacitated older adults	15/29 (51.7%)
Number of protocols reviewed in the last 12 months (counting full-board and expedited reviews)	median = 130, from 4 to 900
Percent of protocols involving decisionally incapacitated older adults	median = 0, from 0 to 25

meetings, we felt they were reliable sources of information for our survey.

Selected characteristics of the REBs are presented in Table 2. Most included someone with legal and ethics expertise as well as community representatives not affiliated with the institution. Two out of three chairs said their members attend educational activities relating to the REB on a regular basis. Of those, half responded that some of these activities dealt specifically with research subjects who may be incapable of giving direct consent to participate in research. REB annual workload varied considerably, with some reviewing as many as 900 protocols per year. On average, few protocols involved decisionally incapacitated older adults.

■ ***Attitudes Toward Protocols Involving Decisionally Incapacitated Older Adults.*** Figure 1 gives an overview of chairs' responses to our questions investigating their REB's approach to protocols that may involve decisionally incapacitated older adults. Twenty REBs had reviewed such protocols in the year preceding the interview, and all of them allowed this population to be enrolled under certain conditions related to the substitute decision-maker and the risk/benefit balance. Four REBs—all from Ontario—had allowed decisionally incapacitated older adults to be enrolled even when there was no one with the legal authority to give third-party authorization, provided the study carried minimal risks for participants and could benefit them personally. Three of the four REBs permitted this population to participate in minimal-risk studies that would not directly benefit them without requiring consent from a legally authorized representative; additionally, two of the REBs permitted them to participate in studies involving serious risks, provided their anticipated benefits were greater.

■ ***Special Requirements.*** In Table 3, we report the proportion of chairs among the 20 who had reviewed protocols involving decisionally incapacitated older adults in the past 12 months who stated that they imposed specific requirements for research with this population. Sixteen required researchers to seek the decisionally incapacitated individual's assent where possible, in addition to consent from the substitute decision-maker. Twelve imposed particular requirements on those responsible for assessing individuals' decisional capacity, pertaining mostly to the training and experience of the assessors. Twelve chairs said their REB asked for the criteria researchers would use to determine decisional capacity. One of the 20 REBs imposed none of these requirements, and eight (40%) imposed all three simultaneously.

■ ***Review Process and Monitoring.*** When asked whether protocols involving decisionally incapacitated older adults tended to raise more discussion among REB members than other protocols, 15 out of 20 answered "Yes, somewhat," or "Definitely." These discussions were often about the vulnerability of this population. The issues most often included how decisional capacity would be assessed (9/20), who would provide third-party consent (10/20), and what research risks participants would be exposed to (9/20).

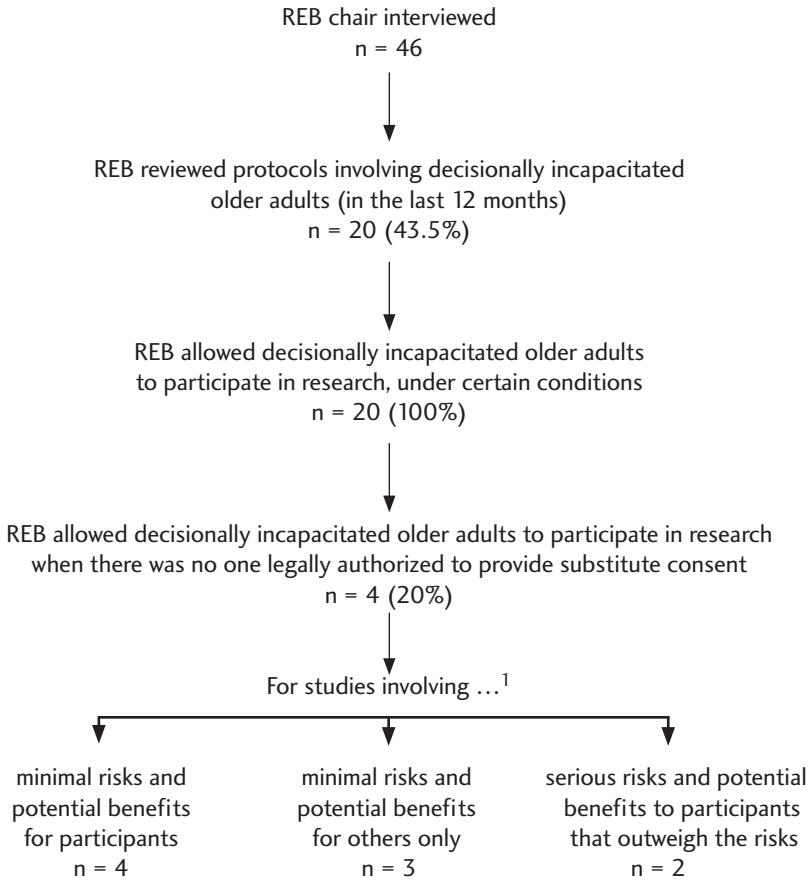
Despite the fact that research involving older adults lacking capacity to provide consent raises unique concerns, REBs did not undertake any particular monitoring of these types of studies. Annual reports, required for all approved protocols, were the sole mechanism REBs used to monitor the conduct of such studies.

■ ***Longitudinal Studies.*** Longitudinal studies that target older adults and include long follow-ups pose particular challenges as some enrolled individuals may lose their capacity for ongoing consent before the study ends. Twenty-five of the 46 chairs interviewed had not yet encountered such studies. Among the 21 who had, 15 reported requiring researchers to revisit the matter of consent at least annually and to obtain consent from an authorized third party for subjects who were decisionally incapacitated. The other six REBs did not impose any special requirements other than requesting an outline of how researchers would deal with decisionally impaired participants in longitudinal studies. Interestingly, one of these REBs expected researchers to ask partici-

pants during the consent process whether they wanted to remain in the study should they lose capacity for ongoing consent. This Alberta-based REB would look for advance directives that appointed substitute decision-makers specifically authorized to make research-related decisions.

■ ***Research Advance Directives.*** REB chairs were asked about their views on research advance directives, which can be used by individuals with decisional capacity to name a substitute decision-maker for research purposes (proxy directives) and/or to instruct others of their desire to participate or not in certain types of research (instructional directives) after they lose decisional capacity. Only two chairs (numbers 5 and 32)—one from Alberta and the other from Ontario—had come across research advance directives. Chair number 5 was skeptical about the value of instructional directives, given their typical lack of specificity and the difficulty of foreseeing all types of research into which an individual might later be enrolled on the sole basis of his or her prior expressed agreement. This chair felt "the range of research that might be considered is simply too broad to make advance directives useful." However, this chair valued proxy-type directives that authorize a person to make research-related decisions on behalf of a research participant who is decisionally incapacitated. Chair number 32 was more supportive of research advance directives, at least where a subject's close relative is available to oversee participation in the study, defend the subject's interests, and request withdrawal if need be. Six of the other 44 persons interviewed felt they were insufficiently familiar with the concept of research advance directives to express an opinion, and four shared chair number 5's skepticism about their utility. Despite their lack of direct experience with research directives, all other chairs supported a role for prior expressed wishes about research participation in recruiting a person who is incapable of consenting or in retaining a participant who has become incapacitated. Several, however, recognized how difficult implementation of an instructional directive would be due to concerns about the vagueness of the content and stressed the need for a third party to look after the subject's interests.

Figure 1.
REBs' Approaches to Protocols That May Involve Decisionally Incapacitated Older Adults



[1] More than one answer was possible.

Discussion

As part of the larger SCORES study, we investigated Canadian REBs' approaches regarding research with decisionally incapacitated older adults. We also explored chairs' opinions about related issues, such as research advance directives. We observed great variability in practices and opinions, as well as some instances of noncompliance with prevailing ethical norms and legal obligations.

Before commenting on the findings, we stress some study limitations. First, because the data are from REBs located in four Canadian provinces, caution must be exercised in generalizing the findings to REBs in other jurisdictions. Second, some eligible REBs were not involved in the study. Although we had wide variation in responses, nonparticipating REBs might have responded differently to

Table 3.
REB Requirements for Protocols Involving Decisionally Incapacitated Older Adults (n = 20)

Requires researchers to obtain subject assent in addition to substitute consent	16 (80%)
Requires those responsible for assessing subjects' decision-making capacity to meet particular requirements	12 (60%)
Requires researchers to provide a detailed description of how decision-making capacity will be assessed	12 (60%)

our survey. Third, the small sample size limits the possibility of linking REB practices to existing provincial legislation. Fourth, while telephone interviews allow geographically dispersed populations to be surveyed, they are susceptible to a social desirability bias. Given the sensitive nature of the issues under investigation, some chairs may have responded to our questions in a manner they thought would be more socially acceptable. Fifth, chairs' experience with protocols involving decisionally incapacitated older adults was somewhat limited (see Figure 1 and Table 2). Finally, chairs' views about research with decisionally incapacitated older adults may be different from the views of other REB members.

Despite these limitations, our study provides informative data about the practices of REBs in reviewing such protocols. Figure 1 shows that none of the REBs were in principle opposed to research with decisionally incapacitated older adults. All but four REBs from Ontario required an authorized third party to provide consent when a potential participant was decisionally incapacitated. This latter finding may be the result of the greater weight of Ontario REBs in our sample. However, it may be the case that in the absence of legislation in that province indicating who may provide third-party consent for research purposes, the four REBs in Ontario felt that it was permissible to allow decisionally incapacitated individuals to participate in research with consent from a third party authorized under the health care consent legislation.

Of the 20 REBs that had reviewed protocols involving decisionally incapacitated older adults, more than half imposed requirements involving additional protections for this population of research participants. These protections included requirements for assessing decisional capacity and obtaining assent from incapacitated individuals when substituted consent was provided (Table 3). Yet the fact that some REBs did not require these additional safeguards is cause for concern. Moreover, no REBs undertake specific monitoring of research with this population once a study is underway. As yet, there is little evidence about the effectiveness of safeguards to protect research participants,[17] though it's possible REBs could impose them without placing an unreasonable burden on researchers.

Half of the chairs we surveyed said their REB reviewed protocols for longitudinal studies that included an ongoing consent process if older adults lose decisional capacity during the course of the study. When asked to describe what requirements, if any, their REB imposed on such studies, a significant minority of the chairs did not spontaneously mention a requirement to periodically reassess a participant's cognitive abilities during the course of the study. Although this could simply have been an omission, it might indicate that REBs have not given much thought to the matter of participants' future cognitive abilities. Only one REB mentioned the need for researchers undertaking these types of longitudinal studies to discuss the possibility that some participants might lose decisional capacity during the study. Proxy and instructional research advance directives may prove useful when such situations occur.

Some of the variation in REB practices as well as possible confusion about how to deal with the type of studies at issue here might be ameliorated when the current TCPS is officially revised. The revised draft second edition of the TCPS was released for public comment in December 2009.[18] Although the provisions regarding individuals with decision-making capacity are in many respects the same as those in the first edition, the revised draft second edition more emphatically directs REB members to take account of group-based benefits in deciding whether research justifiably seeks to include persons who cannot provide consent because they are decisionally incapacitated. Proposed Article 4.5 stipulates that the research question can be addressed only with participants within the identified group; that the research must involve either minimal risk or a minor increase above minimal risk if justified; and that the research maintains an appropriate balance of risks commensurate with the potential to provide direct benefits to the participants or to the relevant group to which they belong. This draft provision aims to integrate the justice-based concern

for inclusion (reflected in Article 4.5 of the first edition) more explicitly into the risk-benefit analysis that in Article 2.5 of the first edition was directed exclusively at the individual research participant (requiring that the research pose no "more than minimal risk" without the potential for "direct benefits" to the individual). Thus, under the revised draft second edition, REBs are more explicitly required to weigh individual-specific risks against group-specific benefits than they are under the current version of the TCPS.

Additionally, the revised draft second edition recognizes the use of research directives "as information on a potential participant's preferences when the third party is asked to provide substitute consent." Yet the proposed version does not address the legal efficacy of research directives. Rather, proposed Article 3.11 states, "Researchers and authorized third parties should take these directives into account during the consent process." The draft commentary explains that research directives do not preclude the requirement of third-party authorization at law, and moreover, that "Research directives should be as specific as possible and in the event of ambiguity or imprecision, should be interpreted narrowly." These proposed revisions may provide important guidance to REBs on the subject of research directives.

In 1998, Cahill and Wichman asked the directors of the 29 Alzheimer Disease Centers funded by the U.S. National Institute on Aging for their policies regarding research involving cognitively impaired subjects.[19] They were surprised that half of the 24 respondents had no policy providing specific guidance to their researchers and IRBs. The authors recommended that all institutions conducting research with cognitively impaired subjects develop policies articulating appropriate safeguards for these vulnerable subjects. Furthermore, they invited funding agencies "to consider requiring such institutional policies as one condition of receiving research funds."[20]

In Canada, the TCPS—and, to some extent, provincial legislation—already speaks to some of these issues. However, given the variability we identified in Canadian REBs' requirements for studies involving older adults who are or may become decisionally incapacitated, these regulatory mechanisms are not adequate to guide or ensure consistency in REB oversight activities. Thus, we recommend that policy-makers and stakeholders consider developing appropriate protective measures for this population. Although Canada's federal structure gives significant autonomy to each province to develop an appropriate regulatory regime, a national strategy regarding policies for research with older adults who are decisionally incapacitated may be appropriate.

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15. See ref. 2, TCPS Article 2.5.

16. See ref. 7, Bravo et al. 2005, for complete reference to these laws.

17. See ref. 11, Stocking et al. 2003.

18. Interagency Advisory Panel on Research Ethics. Draft 2nd ed. of the TCPS, revised 2009, http://pre.ethics.gc.ca/eng/policy-politique/tcps-eptc/readtcps-lireeptc/.

19. See ref. 5, Cahill and Wichman 2000.

20. See ref. 5, Cahill and Wichman 2000, p. 26.