Human Rights and Ethical Considerations in Oral Health Research

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ABSTRACT

Although international agreements set the framework for research ethics, countries vary in their interpretation and execution. The Government of Canada guidelines are based on the *Tri-council policy statement: ethical conduct for research involving humans* (2005) and the new *CIHR guidelines for health research involving Aboriginal people* (2007). In this critical review, we address 3 areas of educational value to practitioners who care for the oral health needs of the public, research trainees and research investigators who advance knowledge pertaining to oral health: protection of human study participants, conflicts of interest and investigator integrity. Its main message is that ethical health care should be supported by a strong foundation of ethical research.

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Ethical evidence-based health care should be supported by a strong foundation of ethical health research. During the past 50 years, the international community has endorsed key agreements that establish guiding principles and specify standards that define universal human rights.[1] Human rights accords constitute the foundation on which both international and national laws and guidelines for conducting human research are based. Yet, great disparities exist among nations in the interpretation, compliance and execution of these fundamental agreements, as well as the research ethics guidelines that derive from them.

No region, country, jurisdiction, race, ethnic group, religion or gender has a monopoly on human rights. Although virtually every person can define what it is to be "human," there is enormous public angst and disagreement over when "human-ness" begins and to what extent authorities can dictate how to be humane.

The public has a great investment in and growing influence over questions of ethics in research. For example, the news media and the greatly expanded use of digital communications technology as a societal norm have kept questions of reproductive biology, organ transplants and stem cell research in the headlines. Flashpoint conundrums that tend to polarize society, such as defining the origins of life, evolution, research on embryonic cells or fetal tissue, gene therapy, cloning and applications of stem cell research, are debated in the public forum, and the limits of future research that depends on these topics will be determined by political decisions shaped by public debate.

These issues are vital to the future of dental research, as there is considerable promise for improving human health through leading-edge biotechnology that is positioned at hotly debated ethical boundaries in our society. A good deal of pioneering research is already being carried out in gene therapy, stem cell

research and regenerative medicine applied to oral health problems. Indeed, a recent editorial in the *Journal of Dental Research* focused on the contentious issue of the potential research applications of human embryonic stem cells in tissue engineering and regenerative medicine.[2] Those who conduct oral health research are compelled by regulations and convention to follow established ethical standards to protect human rights, regardless of where their research is conducted. As for most areas of research that come under ethical scrutiny (e.g., involving human participants, animals and tissues or cells derived from specified sources), special circumstances may raise ethical questions pertaining to oral health research. Such questions do not release investigators from meeting international obligations. They merely present opportunities for the oral health community to clarify how international, national and local standards can be met under particular circumstances.

Our objective is to focus on challenging and, perhaps, underappreciated problems that may confound attempts to conduct oral health research that is consistent with the expectations that apply to all ethical research. We address 3 linked topics: protection of human subjects; conduct and management of research, including conflict of interest; and investigator integrity.

Protection of Human Study Participants

Most countries that have signed international agreements on human rights, such as the World Medical Association's Helsinki accords,[1] have established compatible guidelines governing the protection of human research participants. In Canada, all research involving human subjects must comply with the tri-council policy statement of the Government of Canada, which was developed through the collaboration of the Canadian Institutes of Health Research (CIHR), the National Science and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada.[3] The tri-council policy is grounded in international guiding principles (**Box 1**).

The policy requires that universities, hospitals, research institutes, nongovernmental organizations and corporate entities maintain or use research ethics boards (REBs) that scrutinize proposals for compliance with the policy. A prospective review is required for proposals that involve research with human participants; research with human remains, cadavers, biological fluids, embryos and fetuses; interviews, surveys and questionnaires; and secondary analysis of data from human subjects whose identity can be traced. REBs may vary in composition but must include, at minimum, 2 members with experience in research methods, 1 member knowledgeable in ethics, 1 member knowledgeable in the law ("knowledgeable in ethics and law" was not defined further), 1 member not affiliated with the institute (often a lay person) and ad hoc members who have special expertise required by the proposal under review.[3] Research proposals must be detailed, yet written in accessible language that helps the board fully comprehend the objectives and how the health, safety and dignity of human participants will be protected in full compliance with the substance and spirit of international standards. Approved proposals must be updated and reviewed annually.

Box 1 International guiding principles underpinning agreements on human rights[3]

- Respect for human dignity of all persons
- Respect for voluntary, informed consent
- Respect for vulnerable persons
- Respect for privacy and confidentiality
- Respect for justice and inclusiveness, which is defined as the fair distribution of benefits and burdens
- Minimizing harms and maximizing benefits, including the duty to notify participants of unanticipated, potentially harmful outcomes or side effects that may arise during a study
- Scientific soundness
- Recognition of the currently accepted standard of care as the minimum care provided to all participants in the proposed research

Ethical review is the responsibility of every institute that participates in a project. The increase in multicentred diagnostic and therapeutic trials in medicine and dentistry over the past 2 decades has put unanticipated pressure on the REB system. A single project can require ethical review by dozens of independent institutes, and their various REBs may come to different conclusions. The effect on time-sensitive research programs of unanticipated delays in obtaining multiple ethical approvals has led some clinical research investigators to question whether imposing unnecessary delays on ethical research is in itself unethical.[4]

The problem is compounded by research findings in the United Kingdom, France and Mexico that decisions of REBs are too often remarkably inconsistent or too highly focused on the mechanics of the review process rather than on protecting human rights and benefits of research subjects.[5–7] Some jurisdictions have established special REBs that deal specifically with multicentre reviews; yet these REBs may also face delays when recruiting members who have the appropriate scientific expertise. New legislation in Newfoundland and Labrador requires ethics reviews to be conducted by a centralized REB that includes an appointed research ethics officer, which would tend to abrogate institutional responsibility for the review itself.

Even within the existing system of independent institutional REBs, there are ways for investigators to facilitate the review of their multicentred research proposals (personal communication and course content [Research ethics in health sciences]: J. Parsons, University of Toronto, 2007). The proposal can identify core elements that cannot be altered and that must be passed by all the independent REBs. Other elements that can be altered without invalidating the project can be written to comply with the local requirements of independent REBs. In some jurisdictions, REBs may choose to coordinate their reviews.

Our free-market society has also given rise to an entrepreneurial approach in the form of independent, commercial non-institutional review boards (NIRBs).[8] One type of NIRB functions under the direction of a corporate entity that assures high-quality ethical review on a fee-for-service basis. The advantage is that standing panels of people who are knowledgeable in ethics and paid to work together frequently can be scheduled to deliver timely decisions on complex proposals. A potential disadvantage is that some NIRBs that operate as commercial enterprises may be tempted to sacrifice ethical standards to achieve customer satisfaction.

A second type of NIRB is embedded within a corporation; it handles the company's own ethical reviews, hopefully in a manner analogous to that of a public-sector REB. The advantage of maintaining strict control over the corporation's proprietary information is obvious. Yet, the way in which some of these NIRBs are constituted and their lack of transparency in operations and reporting procedures have been questioned.[8]

Collaborative and multicentred research projects reach a greater level of complexity when investigators cross international borders to engage research populations who may have a unique condition or a particularly high prevalence of a pathological condition. A newsworthy example is the concentrated effort to develop intervention strategies targeting African populations in which HIV/AIDS prevalence is alarmingly high.[9] In oral health research, an analogous international situation where both transborder and vulnerable population elements must be considered are the programs funded by the World Health Organization (WHO) and the National Institute of Dental and Craniofacial Research to identify causative factors of orofacial gangrene (noma) in African children.[10] According to Canada's tri-council policy statement, prospective ethics reviews must be done by both the REB of the home institution and the REB with legal responsibility and equivalent ethical and procedural safeguards in the country or jurisdiction where the research is to be done.[3] That is, an institution is responsible for the ethical conduct of research no matter where it is conducted. Unfortunately, in member states of the WHO Africa Region, there are great disparities between what REBs are mandated to accomplish and what they actually do; in some nations, there is some doubt that REBs meet or even exist.[11]

Moreover, ethics guidelines based on human rights accords dictate respect for justice and fair distribution of risks and benefits. To what extent the population under study faces minimal risk and reaps the benefits of the research is an important issue in the ethics review of international research projects that involve vulnerable populations.[9,12] Principal investigators and their institutions must consider both national and international laws and accords when determining the ethics of conducting human research that crosses international boundaries. Recently, Skene[13] produced a graphic illustration of how both international law and the laws of the sponsoring country interact as a "barometer" of conditions under which international research with human subjects may proceed or should be avoided.

Some countries where European empires gained dominance over Aboriginal peoples have strived to develop community-sensitive guidelines for ethical review of research.

Respect for vulnerable people and voluntary, informed consent require special consideration in oral health research. In Canada, dental diseases are prevalent among Aboriginal populations, the elderly, the poor and those without dental insurance. Serious ethical concerns revolve around informed consent for children and for medically compromised adults who are unable to provide their own consent.[12,14] Language considerations arise for immigrant populations. Research has also shown that destitute people who rely on public health institutions may have difficulty understanding the nature of consent procedures.[15]

Aboriginal groups and certain ethnic groups may also display community sensibilities and sensitivities that diverge from the more individualistic Eurocentric conventional wisdom on which informed consent procedures are usually based. Indeed, increasingly, reports highlight communitarian, collectivist, familial and individualistic perspectives that tend to differentiate populations.[14,16] Some countries where European empires gained dominance over Aboriginal peoples, such as Canada, Australia and New Zealand, have strived to develop community-sensitive guidelines for ethical review of research. CIHR[17] recently approved a new set of research ethics guidelines specifically adapted to comply with communitarian practices among Aboriginal peoples. The guidelines require prospective, frequent and thorough consultation with the target community of participants for approval of the objectives and design of the study and a prospective

ethics review by an appropriate council in the community, before seeking institutional REB approval and funding. We urge readers to study these new guidelines.

Dentistry is in a unique position; most contact with patients is through private clinics in which the practitioner is both health care provider and proprietor. In North America, government granting agencies and foundations attached to professional associations have promoted the idea that more clinical research should target participants at the point of care, within private practice settings. Indeed, experimentation during provision of care may arise when a dentist recommends a treatment option that involves elevated risk and an outcome that is not predictable.[18]

When experimentation in practice is a part of a formal community research network, who has responsibility for conducting the ethical review? We assume that the practitioner would be appointed to a sponsoring hospital, university or research institute team, but we have been unable to locate a document that recommends a specific formal process. In many cases, practitioners report the analyzed results of treatment outcomes from their own practice in peer-reviewed journals. For example, some analyses of long-term maintenance care in private settings are considered "classics" in the periodontology literature. This type of research should certainly comply with the ethical review procedures outlined in government policies. Yet, it is unclear how arm's-length ethical review of private practice-based research is currently conducted. Perhaps this is an issue that should be debated by professional associations and licensing bodies.

Conflicts of Interest

Research investigators are in a position of trust; they must conduct, and be seen to conduct, research that is unbiased and not confounded by personal gain. Their choice of human research subjects should pose no conflicts of interest; therefore, they should try to avoid study groups that include people who, by the nature of their relationship with the investigator, may be considered to be in a vulnerable position. For example, professors should avoid involving their own students. Dentistry has a long history of using dental students as a convenient sample of "volunteers," such as in the numerous gingivitis trials used to screen the efficacy of mouth rinses and in anesthetic and analgesic trials to test methods of pain control. Research colleagues and laboratory personnel, who may depend on the principal investigator for their career advancement or livelihood, have volunteered as convenient subjects for the collection of saliva, enamel biopsies and oral epithelial cells or blood. Such conflicts can be minimized through dialogue, transparency and arranging for this part of the research to be managed by a collaborator. Practitioners who directly recruit their own patients for research may also be in a conflict of interest situation, because patients may fear that they cannot deny consent without compromising their health services. Clinicians receiving compensation to "sign up" their patients for participation in clinical trials are also in contravention of conflict of interest guidelines.

Conflict of interest may be defined as "a set of conditions in which professional judgement concerning a primary interest (e.g., validity of research) tends to be unduly influenced by a secondary interest (e.g., financial gain)."[19] In a comprehensive review of the relation between dental investigators and the corporate sector, Barnett[20] identified several situations in which conflicts of interest may compromise research or bias the way in which investigators approach their research. Most obvious is the bias introduced by the lure of personal financial incentives or the prestige of serving as a board member, consultant or sponsored speaker. More subtle, but just as troublesome, would be bias due to selective reporting or lack of balance in presentations or publications. A major conflict would be an investigator's lack of vigilance or frank participation in the development of research protocols designed to produce favourable results for the foundation or corporate partner that sponsors the research.

Productive research investigators should expect to be sought out by corporations and potential industrial partners to serve on advisory boards, to participate in symposia and continuing education courses, to lead or collaborate in research projects, to conduct peer review and to sign confidentiality agreements when any of these formal relations are arranged. These acts, in and of themselves, are not considered conflicts of interest unless they bias or interfere with the conduct of other research and teaching interests. The usual ethical practice is to declare potential conflicts of interest prospectively if there would be perceived bias in one's primary duties and in relations with other parties. One proposal to avoid most cases of perceived conflict among the growing number of investigators who establish relations with industry is the establishment of a formal intermediary body through which investigator–corporation relationships are conducted, such as the "collegiate research council" recently proposed by Soleto.[21]

Investigator Integrity

Closely interwoven with conflicts of interest that lead to personal gain is the issue of compromised investigator integrity. Research investigators have an ethical obligation to conduct their research honestly through the judicious use of grant and contract funds for the purposes intended; accuracy in fully disclosing all research strategies, methods, results and analyses; and generous and accurate citation of other investigators' preceding or competing work. For whatever reason or pressure — career advancement, financial gain, personal fame or competitive spirit — some investigators are drawn into the dishonest prac-

tices of falsifying research findings, withholding data, making false claims or plagiarism. Over the past few years, the international media have catapulted some of these academic "crimes" that involved some of the most prestigious international journals into headline news, including a case of 2 fraudulent reports by a leading stem cell researcher in Korea,[22,23] a case of selective data omission by a visiting scientist working in a top-level plant research group in Sweden[24] and falsified data in reports by a well-recognized oral cancer researcher in Norway.[25]

The incidence of dishonest research may be increasing or our awareness of a growing problem of deteriorating investigator integrity may be due to wide distribution of alarming news through the Internet. Indeed, many features of the Internet and electronic submission of scientific manuscripts may embolden some investigators to engage in dishonest practices. The ease of "cutting and pasting" may lead to the growth of plagiarism. The ease of manipulating digital images has already led to heightened concern among editors and to strict instructions for submission to scientific journals.[26]

Today's university students are tomorrow's professors. They have been brought up with the Internet, in a culture in which downloading free information or music is seemingly acceptable. A troublesome exposé of the high prevalence and increasing trend toward cheating among university students recently appeared in one of Canada's major news magazines.[27] Coincidently, news items about serious cheating incidents among students in a few U.S. dental schools have also been widely disseminated.[28,29]

The dishonesty of some may present a serious challenge that could tarnish society's image of scientists as generally unbiased seekers of truth. When reviewing ethical issues that may affect dental research, Marjorie Jeffcoat,[30] the former editor of the *Journal of the American Dental Association*, identified multiple features of the research process that would serve as safeguards to protect against scientific fraud or systematic bias. The scientific method is based on hypothesis-driven research and a system of mentored personal integrity, with publication of advances controlled by a system of peer review in which knowledgeable, arm's-length peers scrutinize submitted manuscripts. Moreover, research investigators target their papers at highly intelligent, informed readers who are trained to determine plausibility and who have an impressive memory of preceding publications. One of the surest safeguards against cheating is the ability of other scientists to replicate one's published work. Notably, it was the inability to reproduce experimental evidence that led to the discovery of fraud in the cases cited above. It is imperative that investigators whose research is funded by the corporate sector retain the right to analyze their own data and to publish all the results of their study. A modified system of peer and expert panel review is also used by the government regulatory authorities who review drugs and devices being developed for the marketplace. Similarly, government funding agencies have policies that promote investigator integrity, and they demand prospective ethics reviews for research that involves human participants.

Whether the issue is protection of human participants, conflict of interest or investigator integrity, practising a high standard of research ethics comes down to preparedness, clarity, transparency and patience in one's approach to respect for human rights and justice; rational, sound research; truly informed consent; confidentiality and protection of privacy; sensitivity toward vulnerable groups or individuals; and optimizing benefits and standard of care. Oral health research may present some special circumstances, but this does not alter the high standard of ethics expected of any field of health research.

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References

1. World Medical Association declaration of Helsinki: ethical principles for medical research involving human subjects. Ferney-Voltaire, France: World Medical Association; 2004. Available: www.wma.net/e/policy/b3.htm (accessed 2008 March 13).

2. Smith AJ. Human embryonic stem cell research and its regulation. *J Dent Res* 2007; 86(3):197.

3. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-Council policy statement: ethical conduct for research involving humans, 1998 (with 2000, 2002, 2005 amendments). Ottawa: Interagency Secretariat on Research Ethics; 2005. Available: pre.ethics.gc.ca/english/pdf/TCPS%20October%202005_E.pdf (accessed 2008 March 13).

4. Nicholl J. The ethics of research ethics committees. *BMJ* 2000; 320(7243):1217.

5. Angell E, Sutton AJ, Windridge K, Dixon-Woods M. Consistency in decision making by research ethics committees: a controlled comparison. *J Med Ethics* 2006; 32(11):662–4.

6. Valdez-Martinez E, Trumbull B, Garduño-Espinosa J, Porter JD. Understanding the structure and practices of research ethics committees through research and audit: a study from Mexico. *Health Policy* 2005; 74(1):56–68. Epub 2005 Jan 21.

7. Valdez-Martinez E, Turnbull B, Garduño-Espinosa J, Porter JD. Descriptive ethics: a qualitative study of local research ethics committees in Mexico. *Dev World Bioeth* 2006; 6(2):95–105.

8. Lemmens T, Freedman B. Ethics review for sale? Conflict of interest and commercial research review boards. *Milbank Q* 2000; 78(4):547–84.

9. Guenter D, Esparza J, Macklin R. Ethical considerations in international HIV vaccine trials: summary of a consultative process conducted by the joint United Nations Programme on HIV/AIDS (UNAIDS). *J Med Ethics* 2000; 26(1):37–43.

10. Enwonwu CO, Falkler WA, Idigbe EO. Oro-facial gangrene (noma/cancrum oris): pathogenetic mechanisms. *Crit Rev Oral Biol Med* 2000; 11(2):159–71.

11. Kirigia JM, Wambebe C, Baba-Moussa A. Status of national research bioethics committees in the WHO African region. *BMC Med Ethics* 2005; 6:E10.

12. Macklin R. Understanding informed consent. *Acta Oncol* 1999; 38(1):83–7.

13. Skene L. Undertaking research in other countries: national ethico-legal barometers and international ethical consensus statements. *PLoS Med* 2007; 4(2):e10.

14. Kegley JA. Challenges to informed consent. *EMBO Rep* 2004; 5(9):832–6.

15. Verástegui EL. Consenting of the vulnerable: the informed consent procedure in advanced cancer patients in Mexico. *BMC Med Ethics* 2006; 7:E13.

16. Nie JB. The specious idea of an Asian bioethics: beyond dichotomizing east and west. In: Ashcroft RE, Dawson A, Draper H, McMillan J, editors. Principles of health care ethics. 2nd ed. Chichester: John Wiley and Sons; 2007. p. 143–9.

17. CIHR guidelines for health research involving Aboriginal people. Ottawa: Canadian Institutes of Health Research; 2007. Available: www.cihr-irsc.gc.ca/e/29134.html (accessed 2008 March 13).

18. Chambers DW. The ethics of experimenting in dental practice. *Dent Clin North Am* 2002; 46(1):29–44.

19. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med* 1993; 329(8):573–6.

20. Barnett ML. University–industry relationships in dentistry: past, present, future. *J Dent Educ* 2002; 66(10):1163–8.

21. Sotelo J. Regulation of clinical research sponsored by pharmaceutical companies: a proposal. *PloS Med* 2006; 3(7):e306.

22. Cyranoski D. Verdict: Hwang's human stem cells were all fakes. *Nature* 2006; 439(7073):122–3.

23. Cyranoski D. South Korean scandal rocks stem cell community. *Nat Med* 2006; 12(1):4.

24. Zielinska E. Science retracts major *Arabidopsis* paper: scientist acknowledges omitting data, but denies any impropriety. *The Scientist.com* April 20, 2007. Available: www.the-scientist.com/news/print/53081 (accessed 2008 March 13).

25. Vastag B. Cancer fraud case stuns research community, prompts reflection on peer review process. *J Natl Cancer Inst* 2006; 98(6):374–6.

26. Hayden JE. Digital manipulation in scientific images: some ethical considerations. *J Biocommun* 2000; 27(1):11–9.

27. Gulli C, Köhler N, Patriquin M. The great university cheating scandal. *Maclean's* February 12, 2007; p. 32–6.

28. Maitland RI. Disturbing trends in education [My View]. *ADA News* April 2, 2007; 38(7):4–5.

29. Rudavsky S. Half of IU dental class ensnared in cheating scandal. *Advance Indiana* May 8, 2007. Available: http://advanceindiana.blogspot.com/2007/05/half-of-iu-dental-class-ensnared-in.html (accessed 2008 March 13).

30. Jeffcoat MK. A well-founded trust: a seven-tier defense against scientific misconduct. *J Am Dent Assoc* 2002; 133(7):804, 806.