

Ethical Challenges and Evolving Practices in Research on Ethics in Health Research

**Susan Cox, Anne Townsend, Nina Preto,
Roberta L. Woodgate & Pam Kolopack**

Introduction

'Research ethics' are "the moral principles guiding research, from its inception through to completion and publication of results and beyond."¹ Ethical review offers guidelines concerning the rights, dignity and safety of human subjects, and plays a critical role in governance, the formalized system set in place to maintain and monitor the integrity of the research enterprise.² Although ethical issues in health research are well documented, empirical evidence based on the experiences of those involved in research, is limited. Such knowledge could enhance understanding of the research process and research ethics and underpin an evidence-based system of human subject protection.³ The current oversight system "does not systemically assess performance and outcomes" in health research.⁴ As noted by the Institute of Medicine a "systems-based approach to protecting research participants" is needed, but "the absence of sufficient data regarding human research activities significantly impedes the examination of system performance."⁵

In this paper we identify some of the ethical challenges that both researchers and reviewers face when conducting or reviewing human subject health research. We also describe evolving practices for conducting research on ethical aspects of health research and show how empirical evidence which explores the perspectives of those involved in research can improve research governance.

An evidence-based foundation for research ethics is particularly timely in the context of structural, organizational and political changes which continue to reverberate through the research community. The traditional model of researcher – subject relationship scrutinized by a local REB has been replaced by an increasingly complex model in a dynamic landscape of large-scale multidisciplinary, multi-investigator, multi-site and often global projects. Such developments introduce complications to health research. For example, multidisciplinary projects require negotiation between investigators and institutions about issues on which there may be disagreement (e.g. the securing of informed consent and defining minimal risk). Further complications may arise in multi-site or international studies where traditional notions of autonomy in the consent process may be a source of disagreement between individualistic and community based models. There have also been significant funding changes. For instance, there has been a huge increase in the number of drug and device trials being undertaken in the private sector that are often conducted or coordinated by contract research organizations.⁶ Moreover, the increasing adoption of participatory action research has, in some cases, transformed the once passive human subject to an active research participant, with significant implications for the prioritization of core values informing ethical review as well as research practice.⁷



Approaches to Research on Ethical Aspects of Health Research

Given the emerging complexities of research and the paucity of systematic evidence on the utility of ethics review and governance, a fresh, evidence – based approach is timely. Exploring the research process from multiple perspectives within the health research community (i.e. clinical and social science researchers, REB members, sponsors and policy makers) alongside subject perspectives would add valuable insight to the health research and ethics process. Systematic scrutiny of diverse standpoints allows comparisons to be made, and similarities and differences to be identified, revealing key challenges for ethical oversight of health research involving humans. This could yield new awareness of significant differences in risk predictions by REBs (private and public), researchers, and research subjects,⁸ or varied views on the provision of information dissemination in clinical trials.⁹

Canada could play a leading role in developing a research agenda that would contribute to a systematic body of evidence on research ethics. In McDonald’s words:

we are much more likely to make better decisions about policy and practice if decisions are made on the basis of evidence grounded on a body of well-conducted research...[A]n evidence-based approach to the ethics of research should enable rather than preclude informed debate for policy and governance issues with respect to human subjects research.¹⁰

Particular research designs (e.g. qualitative approaches that attempt to understand the meanings which subjects apply to the research process) would yield valuable insight into the experience of subject participation. Central concepts such as ‘risk’, ‘benefit’, and ‘informed consent’ can be investigated, and novel areas of concern, yet to be identified, revealed. Though there is vigorous debate on many aspects of research ethics within the social and behavioural¹¹ as well as clinical and biomedical arenas, there are few empirical studies that explicitly focus on the perspectives and/or experiences of human subjects or researchers and research workers in health research. Moreover, little is known about the taken-for-granted assumptions of health researchers and REB members and how these may inform the design or oversight of informed consent processes, evaluation of what

constitutes minimal risk, and assessment of how human subjects evaluate the potential benefits and harms of research participation.¹² Further, some argue that specific areas of research and/or particular research methods or traditions are inherently minimal risk and therefore ought to be eligible for expedited review or exemption from the requirement for REB review.¹³ Such assumptions would benefit from systematic investigation.

Empirical studies addressing ethical issues arising in health research have typically centered on specific ethical issues that arise in the context of research conducted for another purpose.

Empirical studies addressing ethical issues arising in health research have typically centered on specific ethical issues that arise in the context of research conducted for another purpose. Such studies focus on topics such as appropriate methods for providing information to participants, adequacy of the informed consent or assent process, vulnerability, or protection of confidentiality.¹⁴ Research designed specifically to investigate ethical aspects of human subject research is sparse.¹⁵ Woodgate’s grounded theory study focused on investigating the notion of risk in health research when children are the participants.¹⁶ REB members, child health researchers, parents, and children all participated in in-depth individual interviews. In addition to providing new insights about how REB members, child health researchers, parents, and children understand and assess risk, this study revealed information about how trust is experienced and negotiated between the various players involved in child health research. Cox et al’s multi-phased study on the meaning and experience of being a human subject in health research¹⁷ involved qualitative interviews with subjects, researchers, REB members and others, and revealed differences between the groups regarding perceptions of risks and benefits, reasons for participating, trust in research relationships, and informed consent. This systematic evidence is crucial in revealing what is important to research subjects in the research enterprise and has both methodological and ethical implications for everything from recruitment to dissemination of results.



In order to implement more effective review and governance of human subjects research, we suggest the need for independent studies on the experiences and perspectives of researchers, similar to those which have been conducted with members of REBs (IRBs).¹⁸ Studies such as these could highlight significant differences in how central concepts are defined and applied in health research ethics as well as contribute new understanding of the key factors shaping such divergences.¹⁹

Empirical studies could equally well focus on individual researchers' experiences and perspectives on ethical aspects of health research. There are, however, different advantages as well as difficulties that emerge when researchers allow their projects to be studied as a whole. As several recent studies utilizing qualitative methods demonstrate, a project – focused design investigating research ethics may expose problems in the research design and process but, with sufficient good will and collaboration, researchers may also pose solutions that will ultimately benefit the goals of investigators. For instance, Donovan *et al.* audiotaped investigators explaining to potential participants the various arms in a controversial study of prostate screening and, as the study progressed, sought to improve the explanation process.²⁰ In a second study, researchers audiotaped the informed consent process during recruitment, identified emergent problems and developed a “better” informed consent process informed by ethical, psychological and linguistic theory.²¹ In their in-depth interview study, Ziebland and colleagues demonstrated that surgeons did not understand the randomized control study for which they were recruiting subjects.²² This had adverse consequences for patient understandings of the trial and hence held some important lessons for the design of future multi-centre trials.

Challenges Arising in Design and Review of Research

The identification of the researcher(s) and/or a specific research project as the relevant unit(s) of analysis has significant implications for the design of the research as well as for the ethical challenges arising. Are individual researchers (such as PI's, co-investigators or research assistants) the focus of analysis or is the project to be studied as an integrated whole where the perspectives of all participants (including REB members) are relevant? Will the study focus on a completed project or will it be conducted prospectively? How should researchers go

about sampling PI's and/or research projects? (i.e., can this be random or is it inevitably a matter of convenience sampling?) If the project is to be studied as whole, can the PI provide consent for another researcher to study members of the research team and/or human subjects participating in the research? What if the PI wants to withdraw once the case study is underway? How might this impact other members of the research team? And, can the REB members who review the proposed case study approve a project that proposes in part to study their own review of the research that is to be studied? These and many other challenges confront researchers who seek to conduct case studies of research in progress and/or recently completed. Here we provide an overview of some of these challenges and some suggestions for evolving research practices, drawn from our current work.²³

What is the relevant unit of analysis?

The relevant unit of analysis needs to be clearly laid out in the early stages of the proposed research. The research design must facilitate ongoing dialogue and precise understanding between the PI of the proposed case study and the PI of the parent study, and clear strategies for recruitment. This will be the case whether the case study adopts a retrospective or prospective design. We caution, however, that there are more potential challenges in studying ongoing research, as participation in the case study itself may influence the process (and so the outcome) in unforeseen ways (e.g., the human subjects' willingness to continue or withdraw their participation in the parent study).

How is access to a case study negotiated?

The PIs of potential case studies can be approached and recruited in a number of ways. In our view, this is a process of reciprocal cooperation, based on incremental steps. The PI must have a sustained interest in, and be committed to the study and, for example, be prepared to offer time for the duration of the project. The steps taken to engage a PI will likely be incremental, based on negotiation and flexibility due to the sensitivity, complexity, and high level of trust that is needed. Practical problems may require extensive time to resolve and delays should be expected at the study inception. Ultimately, the case study PI will determine the limits of their involvement. They may or may not, for example, wish to actively encourage members



of their research team to participate. Thus issues of accessing the experiences and perspectives of research workers and other team members must be negotiated at an early stage. Similarly, methods of recruiting human subject participants in the parent study must conform to existing ethical standards for protecting confidentiality and ensure that the researchers conducting the parent study facilitate but do not bias such selection.

What are the conditions of withdrawal of the case study and subjects?

Depending upon the investment of time, energy and other resources, the case study PI may wish to establish with the PI of the parent study that once the case study is underway, withdrawal of participation as a case study is not possible. The PI, members of the research team, or other participants (such as the human subjects) would, of course, still retain the ability to withdraw their individual participation. A basic tenet of research ethics is the ability of subjects to withdraw, and under these conditions this would be respected. The parent study PI would, however, remain unaware of individual human subject's participation and would have no role in decisions regarding the withdrawal of specific individuals.

Members of the research team and the REB need assurance that declining to participate will not affect their employment or position on the REB though this may, in practice, be problematic as the PI and/or the REB chair will have agreed to take part. Studying other (especially more junior) members of the research team may pose additional concerns if, for instance, aspects of their conduct are unknown to the parent study PI or they have strong opinions on the ethical or scientific validity of the parent study. For this and other reasons, it needs to be absolutely clear that the research design for the case study does not involve 'ethics policing' but nor can it offer an ethics consultation service.²⁴

Under what conditions do the Principle Investigators agree to cooperate?

Given these complexities, a special PI's agreement on the terms and conditions of the case study is needed over and above the usual individual consent provided in the context of more traditional research participation. The PI's agreement is pivotal to establishing an appropriate level of understanding, commitment and cooperation between PIs. The formulation of the document should result from active negotiation and be based on a balance

of structure (too much detail may seem daunting while too little is vague and unhelpful) and flexibility (concrete statements about conditions and expectations of the process is vital, but there may also be a need for an element of open endedness). At an early stage, both PI's need to discuss and agree upon the conditions under which the case study research will be conducted, from access to project documents and the timing and

Members of the research team and the REB need assurance that declining to participate will not affect their employment or position on the REB though this may, in practice, be problematic as the PI and/or the REB chair will have agreed to take part.

methods of recruitment (e.g., of human subjects involved in the parent study) to post field-work activities including publications and dissemination of findings. Depending on the sponsors of the parent study, the parent study PI may also need to seek additional approval to participate in the case study since some commercial sponsors, in particular, are reluctant to allow ancillary use of existing data sets that have only been ascertained at considerable cost.²⁵

How can issues of anonymity and confidentiality be addressed?

The anonymity of the PI and the parent study is another vital area of agreement. The conditions under which research is conducted may not be conducive to maintaining confidentiality despite everyone's best efforts. Given that the health research community in Canada (and elsewhere) is highly networked, parent studies may be recognizable even with only minimal details about the research design and/or sample made public. Although it may in some cases be impossible to disguise the identity of the parent study, in others little may be sacrificed by referring to the parent study in highly generic terms. As such, it seems prudent to attempt to maintain anonymity as the default position. Clearly this decision requires early attention since it



will inform many aspects of the study design. Indeed, the issue even predates active enrollment of a PI and potential parent study since some forms of sampling for potential PIs and case studies might rely upon colleagues to actively recruit other potential participants.

This issue of the anonymity of the parent study is also integral to the process of undergoing ethics review and thus it requires additional clarity. When the decision has been made to keep the study identity confidential, there is no need for the parent study to be named for the purpose of review. During review, however, the REB may essentially be deciding whether or not to allow itself to be studied as part of the case study as many research designs will require access to ethical review documents, decisions of specific REBs and/or individual interviews with REB members or chairs. There will likely also be multiple REBs involved in review of the case study since the parent study may or may not have approval from the same institution(s) as the case study. This further complicates the intention to maintain anonymity.

How can issues of publication be dealt with?

Although negotiable, we suggest that the PI of the parent research study should not have the power to veto publications arising from the case study, but it should be agreed that any findings are, as a matter of courtesy, presented to the PI of the parent study and their team before being more widely disseminated. There is, however, no absolute guarantee that this will not become contentious if the case study unearths irresolvable ethical or other problems or if the identity of the parent study is impossible to conceal. Alternatively, it may also be the case that the PI of the parent study seeks co-authorship on resulting publications. This may or may not be workable but it does raise the issue of ownership of the data arising from the case study.

Case study documents: clarity and collaboration

Finally, the wording of all case study documents (including the letters of introduction, consent forms, and the PI agreement) needs to be clear and informative. It is not intended that these documents be formal legal contracts, but instead that they create a shared understanding that will ultimately allow the many complexities and sources of inevitable tension to be resolved through a spirit of trust and collaboration.

Implications for the Governance of Human Subjects Research

What impact will this growing field of research have for the governance of human subjects research? Through thorough exploration of the experiences of human subjects, researchers, research workers and the REB approval process, case studies of specific health research projects seem well suited to identify and pose potential solutions to the most serious gaps and fragmentation in what we know about the effectiveness of our system of research oversight. Moreover, through such concerted efforts to highlight the diverse perspectives of multiple participants in the research enterprise, greater understanding and appreciation for the needs, concerns and challenges faced by each may ultimately also help support and nurture a culture of ethical research. This will, in turn, further the interests and ends of all involved in the research enterprise.

In order to advance the governance of research ethics in this way, researchers must see the value of such work and endorse it. Such research must also become a priority for funding agencies as well as those who mandate and/or oversee research. It is early days in terms of assessing the potential for this but it is our view that this kind of multifaceted research into every aspect of an approved research study stands to yield insightful, evidence based suggestions for improved research oversight and more effective human subject protection.

Susan Cox is an Assistant Professor and Michael Smith Foundation for Health Research Scholar at The W. Maurice Young Centre for Applied Ethics at the University of British Columbia, Vancouver, B.C.

Anne Townsend is a Post-doctoral fellow at the Maurice Young Centre for Applied Ethics, University of British Columbia, Vancouver, B.C.

Nina Preto is a PhD student at the W. Maurice Young Centre for Applied Ethics at the University of British Columbia, Vancouver, B.C.

Roberta L. Woodgate is an Associate Professor, Faculty of Nursing, University of Manitoba, Winnipeg, Manitoba.

Pam Kolopack is a PhD Student at the Dalla Lana School of Public Health, Joint Centre for Bioethics, University of Toronto, Toronto, Ontario.

Correspondence to Dr. Susan Cox, W. Maurice Young Centre for Applied Ethics, 227-6356 Agricultural Road, Vancouver, B.C. Canada V6T 1Z2. Email: suecox@interchange.ubc.ca



Endnotes

- 1 Economic and Social Research Council (U.K.), *ESRC Research Ethics Framework* online: ESRC <http://www.esrc.ac.uk/ESRCInfoCentre/Images/ESRC_Re_Ethics_Frame_tcm6-11291.pdf> at 7.
- 2 For an excellent discussion on the relationship between Health Canada's regulatory role and the institutional REB ethics oversight role, see Paul B. Miller, "Institutional Oversight of Clinical Trials and the Drug Approval Process" (2006) 44 *Osgoode Hall L.J.* 679.
- 3 Michael McDonald, *The Governance of Health Research Involving Human Subjects* (Ottawa: Law Commission of Canada, 2000) [McDonald, *Governance*]; Michael McDonald, "Canadian Governance of Health Research Involving Human Subjects: Is Anybody Minding the Store?" (2001) 9 *Health L.J.* 1 [McDonald, "Minding the Store"].
- 4 Ezekiel J. Emanuel *et al.*, "Oversight of Human Participants Research: Identifying Problems to Evaluate Reform Proposals" (2004) 141:4 *Annals of Internal Medicine* 282 at 286.
- 5 Daniel D. Federman, Kathi E. Hanna, & Laura Lyman Rodriguez, eds., *Responsible Research: A Systems Approach to Protecting Research Participants* (Washington, D.C.: The National Academy of Sciences, 2002) at 16.
- 6 Philip Mirowski & Robert Van Horn, "The Contract Research Organization and the Commercialization of Scientific Research" (2005) 35 *Social Studies of Science* 503; Sheldon Krimsky, *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* (Lanham, MD: Rowman & Littlefield Publishers Inc., 2003); Kathleen Cranley Glass, "Questions and Challenges in the Governance of Research Involving Humans: A Canadian Perspective" in Trudo Lemmens & Duff Warring, eds., *Law and Ethics in Biomedical Research: Regulation, Conflict of Interest, and Liability* (Toronto: University of Toronto Press, 2006) 35; Lorraine E. Ferris & C. David Naylor, "Promoting Integrity in Industry-Sponsored Clinical Drug Trials: Conflict of Interest for Canadian Academic Health Sciences Centres" in Trudo Lemmens & Duff Warring, eds., *Law and Ethics in Biomedical Research: Regulation, Conflict of Interest, and Liability* (Toronto: University of Toronto Press, 2006) 95.
- 7 Sara Goering, Suzanne Holland, & Kelly Fryer-Edwards, "Transforming Genetic Research Practices with Marginalized Communities: A Case for Responsive Justice" (2008) 38 *Hastings Center Report* 43.
- 8 McDonald, "Minding the Store", *supra* note 3.
- 9 P.R. Ferguson, "Patients' Perceptions of Information Provided in Clinical Trials" (2002) 28 *Journal of Medical Ethics* 45; P.R. Ferguson, "Information Giving in Clinical Trials: The Views of Medical Researchers" (2003) 17 *Bioethics* 101.
- 10 McDonald, "Minding the Store", *supra* note 3 at 18.
- 11 Interagency Advisory Panel on Research Ethics (PRE), *Process and Principles for Developing a Canadian Governance System for the Ethical Conduct of Research Involving Human* (Ottawa: Interagency Advisory Panel & Secretariat on Research Ethics, 2002).
- 12 Brenda Beagan & Michael McDonald, "Evidence-Based Practice of Ethics Review" (2005) 13:2-3 *Health L. Rev.* 62.
- 13 See for example discussion on biobanks by Timothy Caulfield & Charles Weijer, "What Lens? Defining Minimal Risk in an Era of Large Scale Biobank and Cohort Research," (2009) 17:2 *Health L. Rev.* (PAGE NO.); Will C. van den Hoonaard, ed., *Walking the Tightrope: Ethical Issues for Qualitative Researchers* (Toronto: University of Toronto Press, 2002); Juliet Corbin & Janice M. Morse, "The Unstructured Interactive Interview: Issues of Reciprocity and Risks When Dealing with Sensitive Topics" (2003) 9 *Qualitative Inquiry* 335; Janice M. Morse, "Are There Risks in Qualitative Research?" (2001) 11 *Qualitative Health Research* 3.
- 14 Fabienne Jay *et al.*, "Children's participation in vaccine research: parents' views" (2007) 19:8 *Paediatric Nursing* 14; Silvia Salinas Mulder *et al.*, "Unethical Ethics? Reflections on Intercultural Research Practices" (2000) 8:15 *Reproductive Health Matters* 104; Steven E. Seltzer *et al.*, "Factors Affecting Patient Enrollment in Radiology Clinical Trials: A Case Study of the American College of Radiology Imaging Network" (2002) 9 *Academic Radiology* 862.
- 15 Jack Katz, "On the Rhetoric and Politics of Ethnographic Methodology" (2004) 595 *The Annals of the American Academy of Political and Social Science* 280; Ulrike Felt *et al.*, "Refusing the information paradigm: informed consent, medical research, and patient participation" (2009) 13 *Health* 87; Roberta L. Woodgate & R. Yafnosky, "Parents' decisions and experiences in



- childhood cancer clinical trials" (Paper presented at *Making Connections: A Canadian Cancer Research Conference Celebrating the National Cancer Institute of Canada's 60th Anniversary*, Toronto, Ontario, 16 November 2007) [unpublished]; M.P.M. Richards *et al.*, "Issues of consent and feedback in a genetic epidemiological study of women with breast cancer" (2003) 29 *Journal of Medical Ethics* 93.
- 16 Roberta L. Woodgate, "Risks to involving children in research: Perspectives of research ethics board members, child health researchers and families" (Paper presented to the 19th Annual Canadian Bioethics Society Conference, St. John's, Newfoundland 18 June 2008) [unpublished]; Roberta L. Woodgate & M. Edwards, "Parents' and children's perspectives of the risks to involving children in research: It's a family affair" (Paper presented to the 19th Annual Canadian Bioethics Society Conference, St. John's, Newfoundland, Canada, 19 June 2008) [unpublished].
 - 17 Michael McDonald *et al.*, "Accounts of Human Subjects: Optimizing Trust in Health Research Relationships" *Journal of Empirical Research on Human Research Ethics* [forthcoming]; Susan M. Cox, "Shifting Perspectives: Human Subjects talk about Ethics in Health Research" (2007) 15 *NCEHR Communiqué* 24; Susan M. Cox, & Michael McDonald, "Research on Research Ethics: Must the Ethics Researcher Become an Ethics Cop, Consultant or Conduit?" (2007) 2 *Journal of Empirical Research on Human Research Ethics* 94.
 - 18 See for example, Seema Shah *et al.*, "How do institutional review boards apply the federal risk and benefit standards for pediatric research?" (2004) 291 *JAMA: The Journal of the American Medical Association* 476 investigating how IRB chairpersons assessed the meaning of minimal risk in pediatric research; See also C. Lenk *et al.*, "Non-therapeutic research with minors: how do chairpersons of German research ethics committees decide?" (2004) 30 *Journal of Medical Ethics* 85 and Diane K. Wagener *et al.*, "Human Participants Challenges in Youth-focused Research: Perspectives and Practices of IRB Administrators" (2004) 14 *Ethics and Behavior* 335.
 - 19 McDonald, "Minding the Store", *supra* note 3.
 - 20 Jenny Donovan *et al.*, "Quality Improvement report – Improving design and conduct of clinical trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study" (2002) 325 *BMJ: British Medical Journal* 766.
 - 21 R.F. Brown *et al.*, "Developing ethical strategies to assist oncologists in seeking informed consent to cancer clinical trials" (2004) 58 *Social Science and Medicine* 379.
 - 22 S. Ziebland *et al.*, "Does it matter if clinicians recruiting for a trial don't understand what the trial is really about? Qualitative study of surgeons' experiences of participation in a pragmatic multi-centre RCT" (2007) 8:4 *Trials* 4.
 - 23 "Centering the Human Subject: Understanding the Meaning and Experience of Participation in Health Research" is a five-year project funded by CIHR (Cox and McDonald, Co-PI's, Kaufert & Kaufert, and Townsend, Co-Investigators).
 - 24 Cox & McDonald, *supra* note 17.
 - 25 Krinsky, *supra* note 6; Ferris & Naylor, *supra* note 6; Michelle M. Mello, Brian R. Clarridge & David M. Studdert, "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry" (2005) 352 *New England Journal of Medicine* 2202.

