Minimal Risk and Large-scale Biobank and Cohort Research

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Introduction

Minimal risk is a core concept in research ethics, but its proper role in the regulation of large-scale biobank and cohort research is unsettled. By framing a project as posing only minimal risk to research participants, researchers may be afforded a degree of latitude in the design and implementation of consent procedures. In the context of large-scale population biobank and cohort studies, whether and to what degree of specificity one is required to seek informed consent from study participants is a critical issue.[1]

Large-scale population biobank and cohort studies are best understood as research platforms rather than discrete research projects. They may involve very large numbers of research participants. The UK Biobank, for example, is aiming to recruit 500,000 participants and, as of December 2008, the project already has more than 200,000 individuals enrolled.[2] They may be designed to run for decades and encompass a great number of separate research projects over their lifespan.

While it is generally recognized that researchers have an obligation to seek the informed consent of research participants, the complexity of large-scale biobank and cohort studies poses a significant challenge to obtaining informed consent for each research project. As noted by the UN's ethics committee [UNESCO], "[a] system which required fresh consent would be extremely cumbersome and could seriously inhibit research."[3] In response, a variety of less onerous approaches to informed consent have been proposed and implemented.[4] The most common approach is a broad or blanket consent, which is a one-time consent covering all future research projects, including those not currently planned.[5]

While the legal, ethical and policy issues associated with these initiatives are complex,[6] it seems clear that blanket consent relies on a "less strict standard" of consent.[7] In other words, it is an alteration from what would normally be required.[8] As a result, from a regulatory standpoint, the use of a blanket consent approach would need to fulfill the requirements of a waiver of consent. In part, this would require that the research pose only "minimal risk" to participants.[9] It is commonly thought that large-scale biobank and cohort research often poses only minimal risk. For example, it has been suggested that studies involving low penetrance genes that have little clinical relevance should be regarded as posing only minimal risk.[10] Likewise, though most biobanks link genetic data to identifiable information, there are often strict privacy policies and procedures limiting the risk of inadvertent disclosure of private information.[11]

The Roles of Minimal Risk in the *Tri-Council Policy Statement*

The *Tri-Council Policy Statement* [TCPS] defines minimal risk as follows:

> [I]f potential subjects can reasonably be expected to regard the probability and magnitude of possible harms implied by participation in the research to be no greater than those encountered by the subject in those aspects of his or her everyday life that relate to the research, then the research can be regarded as within the range of minimal risk.[12]

To put it more simply, minimal risk refers to the risks of daily life. Minimal risk is used in three different ways

in the TCPS. First, it is used to limit risk to vulnerable groups in research. Article 2.5 says that "…individuals who are not legally competent shall only be asked to become research subjects when…(c) the research does not expose them to more than minimal risks without the potential for direct benefits for them."[13] Clinical research often contains a mixture of therapeutic (e.g., drugs) and nontherapeutic procedures (additional tests for scientific purposes only). This standard limits the risks of nontherapeutic procedures to which children and incapable adults may be exposed to no more than minimal risk.[14]

Second, minimal risk is used to direct the scrutiny of research ethics boards [REBs] in initial and continuing review to riskier research.[15] Article 1.6 states that: "The REB should adopt a proportionate approach based on the general principle that the more invasive the research, the greater should be the care in assessing the research."[16] When research participation poses only minimal risk to subjects, full REB review may not be required. Institutional procedures may allow for expedited review by a subgroup of the REB when research poses no more than minimal risk. Also, for research in the humanities and social sciences, requirements for peer review of scholarly aspects of the research may be waived.[17] This, in turn, may speed approval of minimal risk studies.

Third, minimal risk is used to allow a waiver of consent in certain circumstances. Generally, researchers are required to obtain the free and informed consent of study participants.[18] Under certain circumstances, the REB may approve a consent procedure that modifies some elements of informed consent, or it may waive the requirement for informed consent. In either case, five conditions must be fulfilled:

1. The research involves no more than minimal risk to the subjects;
2. The waiver or alteration is unlikely to adversely affect the rights and welfare of the subjects;
3. The research could not practicably be carried out without the waiver or alteration;
4. Whenever possible and appropriate, the subjects will be provided with additional pertinent information after participation; and
5. The waivered or altered consent does not involve a therapeutic intervention.[19]

Requirements (1) and (3) are generally regarded as key in the REB's deliberation of modified or waived consent.

Despite the several distinct roles of minimal risk in the regulation of research, work on the conceptual foundations of minimal risk has focussed on its role in limiting permissible risk in research on vulnerable populations. This is largely a function of the historical origins of the concept. Minimal risk is first mentioned in the early work of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research on research involving pregnant women and prisoners.[20] The concept received its first substantive treatment in the National Commission's report *Research Involving Children*.[21] Subsequent commentators have focussed on the development of a moral foundation for minimal risk and rooting it in the custodial duties of parents to children.[22]

While this may provide minimal risk with a satisfactory moral foundation in its role in protecting vulnerable populations in research, it leaves open the question of whether all three roles minimal risk plays in regulation share the same moral foundation. If not, then how ought we ground minimal risk in its role directing the scrutiny of an REB? What might serve as a moral foundation for the use of minimal risk to allow a waiver of consent in certain circumstances? Finally, we might ask what practical consequences follow?

Minimal Risk and the Waiver of Consent

While minimal risk poses a variety of conceptual issues,[23] we will focus on its meaning and application in the context of waivers of consent in large-scale biobank and cohort research. The question as to whether the conceptual foundation of minimal risk applies to its use in the waiver of consent has, to our knowledge, not been asked.

Freedman and colleagues developed the most widely accepted understanding of minimal risk in which they anchor it in the social and legal limits placed on parental decision making on behalf of children. The REB, in applying minimal risk "is attempting to track those decisions that would be made by informed and scrupulous parents whose children are being invited to participate in research."[24] The reasoning process

involved is a common sense one, applied by good parents every day. The authors invite us to consider a mother considering whether to allow her son on a first overnight camping trip:

> [A] mother asks herself, "Is the child ready for this? Should the child approach this by stages? *Are the risks sufficiently similar to those in my child's everyday life that I should allow this experience at this time?*" In discussions about whether to permit this involvement – with the mother resisting, and the child pressing – a certain logic may be discerned. Appealing to consistency, the child will say that he has been permitted, and successfully undergone, situations relevantly and roughly similar, though not identical while the parent will focus upon difference. In other words, the parental decision to permit exposure to new risks is not itself governed by, but rather anchored to, the risks of everyday life.[25]

The meaning and use of minimal risk in the waiver of consent seems substantially dissimilar from its meaning and use in the protection of vulnerable populations such as children. First, the waiver of consent is typically used in research involving adults who can provide informed consent but the design or circumstances of the study make obtaining consent impractical. Second, as the research participants are generally capable of providing consent, it makes little sense for the REB to try and "track those decisions that would be made by informed and scrupulous parents" or other surrogate decision makers.[26] Third, the importance of allowing for new experiences seems to rest on the developmental psychology of children, and may be inapplicable to adults.

Given such substantial differences, the current foundation for minimal risk may not be appropriate for the waiver of consent. How, then, ought minimal risk be understood? A natural starting place, we suggest, is the law of informed consent. At root, the waiver of consent relies on putting aside the researcher's obligation to seek and obtain the informed consent of study participants. When may one do this? It seems to us that one straightforward answer is, "When the law doesn't require it." Thus, one might legitimately withhold information from research subjects, when there is no obligation to disclose it. More specifically, minimal risk might be thought of as risks which due to their quotidian nature are not "material" to prospective research subjects. Working out the details of this suggestion, will require considerable work. Here we adopt the more manageable task of suggesting that we ought to use a research participant-centered approach to determine what counts as minimal risk in this context.

Canada is a country with a tremendously strong, patient-centred informed consent ethos. With the 1980 Supreme Court of Canada decision of *Reibl v. Hughes*,[27] the standard of disclosure in clinical medicine has shifted from a reasonable physician standard (i.e., what would a reasonable physician disclose?) to a patient

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centered approach. Accordingly, physicians are required to disclose any relevant information that a reasonable person in the patient's position would want to know. What is considered a piece of information worthy of disclosure must be determined through the lens of the patient, not the physician. In the setting of research, the standard for informed consent would be no less exacting than that in medical practice.[28]

What follows from this standard? If correct, this view has important implications for REB review of studies in which a waiver of consent is proposed. As we have said, such studies must be determined to pose no more than minimal risk to prospective subjects. Here minimal risk serves to demarcate between information that must be disclosed in the consent process and information that may not be disclosed (given that other conditions, listed above, are fulfilled). In determining whether a study poses minimal risk the REB should use the lens of the research participant.[29] Thus, the question is not whether an REB or a researcher believes that biobank and cohort research is minimal risk, but whether a research participant is likely to see it that way.

Public and Research Participant Perceptions of Research

Given this new understanding of the role of minimal risk in waiver of consent for large-scale biobank and cohort research, data on public and research participant perspectives on such studies take on a new importance.[30] How do Canadians view large-scale biobank and cohort research? Do they view participation as risky? What features of studies modify support or risk perceptions?

Relevant survey and focus group data tell us that the public, including Canadians, are generally very supportive of this type of research.[31] But they also have many concerns, including concerns about privacy, the impact of commercialization and a loss of control over results.[32] More to the point, there is at least some evidence that individuals view the risks associated with "genetic research with identifiable human tissue as substantially higher than minimal."[33] While there are few studies on the specific issue of minimal risk, the data that does exist should remind us that the perspective of potential research participants might belie the claims of researchers that such studies pose minimal risk.

Further, the risks associated with a research project could, at first, seem minimal in nature but may need to be re-characterized if it turns out that it has the potential to generate clinically relevant information[34] – even if that information is incidental to the goals of the research project. While the purpose of most biobank and cohort studies is often not about the production of clinically relevant data, it is certainly possible that they will stumble across some. Indeed, there is a good deal of recent literature that touches on the issues associated with the handling of incidental findings, especially as they relate to biobank research.[35]

Finally, specific features of large-scale biobank and cohort research may heighten public sensitivity and risk perceptions. For example, the involvement of commercial entities lowers trust (and, by implication, heightens the assessment of risk).[36] Media portrayals of social controversies associated with the relevant research can also shake confidence.[37] From an objective assessment, such events may not substantially alter the risks involved in the research, but when viewed from the participant perspective these developments may raise the risks beyond minimal.

Conclusion

The complexity of large-scale biobank and cohort research makes it very difficult in many cases for researchers to seek informed consent on a project-by-project basis. The use of blanket informed consent has proven a popular solution to this problem in that it involves a one-time consent for all present and future research studies conducted under the umbrella of the biobank or cohort study. However, if this approach amounts to a move away from existing consent norms, the TCPS requires such studies fulfill criteria for a waiver of consent, including the stipulation that study participation pose no more than minimal risk. We suggest that the moral foundation of minimal risk in this context is likely to be different than minimal risk in the context of research involving children. Rather we suggest that the law of informed consent might inform our understanding of the meaning and use of minimal risk in large-scale biobank and cohort research.[38] One implication of this view is that a research participant centered perspective ought to inform the REB's minimal risk determination.

Clearly, much work needs to be done to develop this view. Whether and to what degree the legal doctrine of informed consent may support withholding information from research subjects must be determined. This is complicated by continuing uncertainty regarding the moral and legal nature of the researcher-subject relationship. When researcher and subject have a pre-existing physician-patient relationship, most would agree that the physician-researcher owes fiduciary duties, including one of informed consent, to the patient-subject. But what of cases – and we think them common – of patients who enter clinical research and who have no pre-existing relationship with the physician researcher? Ought we consider this relationship fiduciary in nature? Negative and affirmative views have been argued in the literature recently.[39] Finally, while empirical research on public attitudes to research is suggestive, what precise role should it play in REB deliberations?

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Endnotes

1 Anne Cambon-Thomsen, "The social and ethical issues of post-genomic human biobanks" (2004) 5 Nature Reviews Genetics 866.

2 UK Biobank, "Improving the health of future generations," online: UK Biobank <http://www.ukbiobank.ac.uk/>.

3 Sylvia Rumball & Alexander McCall Smith, International Bioethics Committee, *Human Genetic Data: Preliminary Study by the IBC on its Collection, Processing, Storage and Use* (Paris: UNESCO, May 15, 2002) at 16.

4 Bernice S. Elger & Arthur L. Caplan, "Consent and Anonymization in Research Involving Biobanks: Differing Terms and Norms Present Serious Barriers to an International Framework" (2006) 7:7 EMBO reports 661.

5 See e.g. Blair H. Smith *et al.*, "Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability", online: (2006) 7 BMC Medical Genetics 74 <http://www.biomedcentral.com/1471-2350/7/74>.

6 Vilhjámur Árnason, "Coding and Consent: Moral Challenges of the Database Project in Iceland" (2004) 18 Bioethics 27; Timothy Caulfield, "Biobanks and Blanket Consent: The Proper Place of the Public Good and Public Perception Rationales" (2007) 18 King's Law Journal 209; Deborah Mascalzoni *et al.*, "Informed consent in the genomics era" (2008) 5:9 PLoS Medicine e192 (where it is argued that: "[A] detailed analysis of the rationale behind broad consent shows that "broad consent" is seldom if ever justified" at e192).

7 Elger & Caplan, *supra* note 4 at 663.

8 Timothy Caulfield, Russell Brown & Eric M. Meslin, "Challenging a Well Established Consent Norm?: One Time Consent for Biobank Research" (2007) 4 Journal of International Biotechnology Law 69.

9 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 and 2005 amendments)* (Ottawa: Public Works and Government Services Canada, 2005) at art. 2.1(c) [*TCPS*].

10 Laura M. Beskow *et al.*, "Informed Consent for Population-Based Research Involving Genetics" (2001) 286 JAMA: the journal of the American Medical Association 2315 at 2318.

11 See e.g. UK Biobank, *UK Biobank Ethics and Governance Framework – Version 3.0* (October 2007) at s. I(C) at 10, online: UK Biobank <http://www.ukbiobank.ac.uk/docs/EGF20082_000.pdf>.

12 *TCPS*, *supra* note 9 at art. 1.5.

13 *Ibid.* at art. 2.5.

14 Charles Weijer & Paul B. Miller, "When are research risks reasonable in relation to anticipated benefits?" (2004) 10 Nature Medicine 570.

15 *TCPS*, *supra* note 9 at arts. 1.5, 1.11.

16 *Ibid.* at art. 1.6.

17 *Ibid.* at art. 1.5 (a), (c).

18 *Ibid.* at art. 2.1(a).

19 *Ibid.* at art. 2.1(c).

20 U.S., The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research on the Fetus* (DHEW Pub. No. (OS) 76-127) (Washington, D.C: United States Government Printing Office, 1975); U.S., The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Prisoners* (DHEW Pub. No. (OS) 76-131) (Washington, D.C.: United States Government Printing Office, 1976).

21 U.S., The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *Report and Recommendations: Research Involving Children* (DHEW Pub. No. (OS) 77-0004) (Washington, D.C: United States Government Printing Office, 1977).

22 Benjamin Freedman, Abraham Fuks & Charles Weijer, "*In Loco Parentis*: Minimal Risk as an Ethical Threshold for Research upon Children" (1993) 23:2 Hastings Center Report 13.

23 See e.g. Henry Silverman, Sara Chandros & Jeremy Sugarman, "Variability among institutional review boards' decisions within the context of a multicenter trial" (2001) 29 Critical Care Medicine 235; Loretta M. Kopelman, "Minimal Risk as an International Ethical Standard in Research" (2004) 29 Journal of Medicine and Philosophy 351; Weijer & Miller, *supra* note 14.

24 Freedman, Fuks & Weijer, *supra* note 22 at 16.

25 *Ibid.* [emphasis added].

26 *Ibid.*

27 *Reibl v. Hughes*, [1980] 2 S.C.R. 880, 114 D.L.R. (3d) 1 (the *Reibl* standard of disclosure has been

consistently applied and, indeed, expanded. See e.g. *Huisman v. MacDonald*, [2005] O.J. No. 2332, 139 A.C.W.S. (3d) 1103, aff'd 2007 ONCA 391, 280 D.L.R. (4th) 1).

28 Ellen I. Picard & Gerald B. Robertson, *Legal Liability of Doctors and Hospitals in Canada*, 3d ed. (Toronto: Carswell Legal Publications, 1996) at 150. See also *Halushka v. University of Saskatchewan*, (1965), 53 D.L.R. (2d) 436, 52 W.W.R. 608 (Sask. C.A.) and *Weiss v. Solomon*, [1989] R.J.Q. 731, 48 C.C.L.T. 280 (C.S. Qué.).

29 It is interesting to note that not all research ethics guidelines have a reference to the participant perspective in the definition of minimal risk, thus emphasizing its significance in the Canadian context. The relevant American regulations, for example, adopt a definition that could be interpreted to be more objective in nature. See *Protection of Human Subjects*, 45 C.F.R. § 46.102 (2005) ("Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"). Some scholars have pushed for an even more objective, and quantifiable, approach. See e.g. D. B. Resnik, "Eliminating the daily life risks standard from the definition of minimal risk" (2005) 31 Journal of Medical Ethics 35.

30 We are not saying that perceptions of risk and consent policy should be based on survey data. However, this research gives us a sense of the degree to which the public, or a reasonable person in the participant's position, may view the risks as minimal.

31 Michael Burgess, Kieran O'Doherty & David Secko, "Biobanking in British Columbia: discussions of the future of personalized medicine through deliberative public engagement" (2008) 5:3 Personalized Medicine 285; Jill M. Pulley *et al.*, "Attitudes and perceptions of patients towards methods of establishing a DNA biobank" (2008) 9 Cell and Tissue Banking 55; David Kaufman *et al.*, "Subjects matter: a survey of public opinions about a large genetic cohort study" (2008) 10:11 Genetics in Medicine 831.

32 Burgess, O'Doherty & Secko, *ibid.*

33 Jon F. Merz, "Psychosocial Risks of Storing and Using Human Tissues in Research" (1997) 8 Risk: Health, Safety & Environment 235. Timothy Caulfield, "Perceptions of Risk and Human Genetic Databases: Consent and Confidentiality Policies" in Gardar Arnason, Salvor Nordel and Vilhjálmur Arnason, eds., *Blood and Data: Ethical, Legal and Social Aspects of Human Genetics Databases* (Reykjavik: University of Iceland Press and Centre for Ethics, 2004) 283-9, where Caulfield first discussed the issues associated with perception and minimal risk in this context.

34 Helen M. Sharp & Robert D. Orr, "When "Minimal Risk" Research Yields Clinically-Significant Data, Maybe the Risks Aren't So Minimal" (2004) 4:2 The American Journal of Bioethics W32.

35 Susan M. Wolf *et al.*, "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations" (2008) 36:2 Journal of Law, Medicine & Ethics 219.

36 See e.g. Christine R. Critchley, "Public opinion and trust in scientists: the role of the research context, and the perceived motivation of stem cell researchers" (2008) 17:3 Public Understanding of Science 309. Also, research has shown that people want to know about commercialization/conflicts of interest. Kevin P. Weinfurt *et al.*, "Views of Potential Research Participants on Financial Conflicts of Interest: Barriers and Opportunities for Effective Disclosure" (2006) 21:9 Journal of General Internal Medicine 901.

37 Clive Seale *et al.*, "Effect of media portrayals of removal of children's tissue on UK tumour bank" (2005) 331 BMJ: British Medical Journal 401.

38 Indeed, it could be argued that when a researcher has clinical duties to a research participant, they would be required to comply with informed consent norms regardless of the research ethics spin on the notion of minimal risk. In other words, they would need to follow the "reasonable patient" standard.

39 E. Haavi Morreim, "The clinical investigator as fiduciary: discarding a misguided idea" (2005) 33:3 Journal of Law, Medicine & Ethics 586; Paul B. Miller & Charles Weijer, "Fiduciary obligation in clinical research" (2006) 34:2 Journal of Law, Medicine & Ethics 424.