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University of Alberta

Monitoring of Biomedical Research in Canada

by

Catherine Susan Miller 

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Laws

Faculty of Law

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ABSTRACT

This thesis discusses the history of human experimentation and the abuse of human subjects of medical experimentation. It traces the international responses to documented cases of abuse of human subjects. The thesis includes discussion of international guidelines for the conduct of research involving human subjects. It then discusses the specific approaches of the United States and Canada in setting up of mechanisms to protect human subjects of biomedical experimentation.

The thesis then focuses on the issue of monitoring of biomedical research. Monitoring (or continuing review) is an important issue because of the invasive nature of many of the procedures, the vulnerable population involved as subjects in biomedical research and the current general lack of implementation of a formal system of monitoring on an international scale. The thesis considers monitoring on two levels: a) monitoring by the members of research ethics boards (REBs) and others, of specific protocols approved by the REB and b) monitoring of the performance of research ethics boards. Monitoring is defined by delineating the components of the monitoring process. The responsibility for each aspect is then discussed. Barriers to implementation of various monitoring processes are set out. Models of monitoring currently being used in Canada are presented as models for others to follow.

The thesis concludes that methods must be developed and sufficient resources (financial and administrative) provided to ensure that monitoring occurs as it is vital for the protection of human subjects of biomedical experimentation.

Dedicated to my grandparents, parents Arliss & Tevie Miller and Raye & Max Dolgoy for their wisdom, love and encouragement as role models in life and community service and to my family, Len, Rebecca, Sarah, Leah, Danielle and Gabrielle for their constant love and support.

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INTRODUCTION

> "The history of liberty has largely been the observance of procedural safeguards."
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> Felix Frankfurter, Justice of the United States Supreme Court [1]

Human experimentation, a foundation of modern biomedicine, depends on one person serving as a means to benefit others.[2] Society grants researchers the privilege of involving human subjects in research. Researchers have the concomitant responsibility of ensuring the safety of research subjects.[3] Public trust and confidence provide the legitimacy and support for human experimentation.[4]

As an introduction, a frame of reference for terminology in this thesis might prove helpful. Although the words "medical experimentation or research," might be utilized, the area being addressed has expanded beyond the focus on medicine and prevention and cure of disease, to "biomedical research," referring to: a) studies designed to increase scientific knowledge about normal or abnormal physiology and development and b) studies intended to assess the safety and effectiveness of a medical product or device, a procedure or intervention.[5] 'Research' is defined as a systematic investigation to establish fact, principles

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[1] R.A. Greenwald, M.K. Ryan & J.E. Mulvihill, eds., *Human Subjects Research–A Handbook for Institutional Review Boards* (New York: Plenum Press, 1982) at i; E.C. Gerhart, *Quote It! Memorable Legal Quotations* (Buffalo, N.Y.: William S. Hein & Co., 1987) at 517.

[2] A.M. Capron, "Human Experimentation–Basic Issues" in W.T. Reich, ed., *Encyclopedia of Bioethics*, vol. 2 (New York: The Free Press, A Division of Macmillan Publishing Co., Inc., 1978) at 692 & 694.

[3] G. Crelinsten, "'Who reviews the reviewers? Issues in Implementing' in Proceedings of the NCEHR Retreat," (1998/99) 9 NCEHR Communiqué 1 at 28.

[4] D.J. Jones, "Conflict of Interest in Human Research Ethics," (1995) 6 NCBHR Communiqué 2 at 6.

[5] NIH, OPRR, *1993, Protecting Human Research Subjects, Institutional Review Board Guidebook*, (Washington, D.C.: U.S. Government Printing Office, 1993) 5-1.

or generalizable knowledge,[6] as differentiated from 'therapeutic,' which is intended to benefit the patient, by improving their condition. A "subject" of research is a human being who bears the risks of research.[7] The reference in the title to Chapter One of "Experimentation" was deliberate, as it connotes a greater sense of the unknown or risk, than "research." It was chosen to highlight the idea (often minimized) that participation in biomedical research involves unknown risks.

We will begin by examining the history of medical experimentation with human subjects, and discuss specific examples of abuse. Early writings on the ethics of experimentation are briefly discussed, followed by international responses (including codes of ethics), to the horrific abuses of human beings by the Nazis and the Japanese during World War II. Specific reference will be made to the American [8] and Canadian[9] responses to ethical

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[6] Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998) 1.1. [hereinafter *TCPS*]

[7] Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects 1987* (Ottawa: Minister of Supply and Services, 1987) 7.

[8] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research* U.S. Department of Health, Education and Welfare, DHEW Publication No. (OS) 78-0012; See generally: B.H. Gray, R.A. Cooke & A.S. Tannenbaum, "Research Involving Human Subjects, The performance of institutional review boards is assessed in this empirical study," (1978) 201 Science at 1095; H. Edgar & D. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation," (1995) 73 Millbank Quarterly 4 at 489; H. D. Aldridge & W. J. Walport, "Ethical issues in clinical research: the role of the research ethics committee," (1995) 76 British Journal of Urology Suppl 2 at 27; P.R. Benson, "The Social Control of Human Biomedical Research: An Overview and Review of the Literature," (1989) 29 Soc. Sci. Med. 1 at 1; R.J. Bonnie, "Research with Cognitively Impaired Subjects, Unfinished Business in the Regulation of Human Research," (1997) 54 Arch Gen Psychiatry at 106.

[9] E.M.. Meslin, "Ethical issues in the substantive and procedural aspects of research ethics review," (1993) 13 Health Law in Canada 3 at 182-183. Canada adopted guidelines, rather than the regulatory approach.

issues in human experimentation–a system of review of proposed research by a multi disciplinary group.

This thesis focuses on the monitoring issue, as it relates specifically to biomedical research, because of the invasive nature of much of the research and the vulnerable individuals who make up the population of research subjects of biomedical research. Monitoring of biomedical research involving humans in Canada is complex, as it takes place in the context of an interdisciplinary endeavour, governed by the *Tri-Council Policy Statement*[10] (which covers research in the areas of health, social sciences and humanities and natural sciences and engineering). Numerous associated groups have mandates to contribute in some way to the research enterprise.

Many issues relating to the complex topic of protection of human subjects of medical experimentation will be referred to only briefly, as the focus of the thesis remains monitoring of biomedical research in Canada. The focus is on common law jurisdictions, though some reference is also made to the research environment in Quebec, which is based on the Civil Code.

The unresolved issue with monitoring remains its lack of implementation worldwide. Most countries with regulations, guidelines and policies relating to human experimentation, require continuing review/monitoring Although it appears that there is general consensus among the many participants in research that monitoring should occur, the reality is that monitoring has not been taken seriously in all its facets, in any country in the world. The

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[10] *TCPS, supra* note 6.

issues concerning monitoring: what is monitoring, who should perform it, and why it is critical for the integrity of the research enterprise, will all be explored.

When we speak of monitoring, we are referring to monitoring at two levels: monitoring of research ethics boards (REBs) regarding their effectiveness and monitoring by REBs of specific protocols presented by investigators.

Monitoring is a concern for the following reasons: the vastness and power of the industry in control of the endeavour, the pressures on researchers, institutions and funders which impact decision-making, the likelihood of bias and error, the vulnerability of the subjects and their trust in the system and the people directing the system, the change of attitude on the part of many members of society from fearing participation in research to demanding it, the pressure from society expecting positive results and enhancement of health from the medical research community, the change in the research environment from the time that the original system of regulation of research was put into place to today, the self regulatory nature of the medical profession who are in charge of the research endeavour, the scarcity of resources and the large number of players in research (subjects, investigators, REBs, institutions, various levels of government and industry) whose responsibilities must all be clearly defined.

A monitoring system established in 1992 in Canada will be discussed as a possible model for others. A second model relating to noninstitutional research will also be presented.

This thesis concludes that the monitoring function should be seen as a continuation of the initial focus of the REB and the entire research establishment–protection of the research subject.

Unethical research can be prevented and researchers educated by establishing monitoring procedures. Monitoring is required to re-establish and maintain public confidence in medical research, following recent revelations of scientific misconduct.[11]

Monitoring has various components. One of the impediments to implementation of monitoring has been the reluctance of the REBs to assume responsibility for all components. Once the components are broken out and responsibility for each is assumed by various sectors of the research enterprise, it is apparent that the REB is not and should not be responsible for implementation of all components. What is required is a dialogue and agreement on a national and local level, of which entity is responsible for which component and a commitment by all parties to the importance of monitoring to the integrity of the system. This commitment must be supported by adequate education, human and financial resources.

A cultural shift is required so that research ethics is seen as contributing to research excellence and not as a hurdle for research. Public accountability of research ethics is especially important in an essentially self-regulating system.

Monitoring is a procedural safeguard which, along with reliance on many other factors, including education, the integrity of the investigator and the review of proposed research, contribute to the recognition of the rights of research subjects and ensuring their safety.

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[11] C. Weijer, S. Shapiro, A. Fuks, K.C. Glass, M. Skrutkowska, "Monitoring Clinical Research: An Obligation Unfulfilled," (1995) 152 Can Med Assoc J. 12 at 1973.

CHAPTER ONE: DEVELOPMENT OF SYSTEMS OF REGULATION OF RESEARCH IN HUMAN EXPERIMENTATION

I. History of Medical Experimentation and Abuse of Human Subjects

1. Ancient

The history of experimentation in humans is as old as that of medicine itself. Every society has had its healers, who attempted to devise better ways to prevent illness and to restore the sick to health.

The ancient Greek physician who swore the Hippocratic Oath, promised to apply his knowledge to benefit the sick. The *Epidemics* contains the famous instruction, "To help or at least to do no harm." The Hippocratic physicians of the 4th century B.C., were not experimental scientists in today's terms. Later, Alexandrian physicians of Egypt condoned vivisection of condemned criminals, as they believed knowledge of anatomy was necessary--torture of a few could benefit many.[1]

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[1] G.H. Brieger, "Human Experimentation: History," in W.T. Reich, ed., *Encyclopedia of Bioethics*, vol. 2 (New York: The Free Press, A Division of MacMillan Publishing Co., Inc., 1978) 684 at 684-685.
See e.g.: P.M. McNeill, *The Ethics and Politics of Human Experimentation* (Cambridge: Cambridge University Press, 1993) at 17 . Historically, the socially powerless and disadvantaged are the most likely to be subjected to unethical research; reference to New Zealand cervical cancer study; H.K. Beecher, "Experimentation in Man," (1959) 169 JAMA 5, 461 at 461 & 470. In 1959, he wrote that there are no specified legal precedents which protect human subjects.
See also: J.V. Brady & A.R. Jonsen, "The Evolution of Regulatory Influences on Research with Human Subjects," in R.A. Greenwald, M.K. Ryan & J.E. Mulvihill, eds., *Human Subjects Research–A Handbook for Institutional Review Boards* (New York: Plenum Press, 1982) 3 at 3-4; D.W. Amundsen, "Medical Ethics: History of Europe" in W.T.Reich, ed. *Encyclopedia of Bioethics, Revised Edition,* vol. 3 (New York: Simon & Schuster MacMillan, 1995) at 1513. 9 [hereinafter *Encyclopedia Revised*]

2. 18th and 19th Centuries

There were few new effective therapies from Hippocrates to the end of the eighteenth century. During that period, research involving humans was conducted in an uncontrolled, unscientific manner.[2]

Medical ethics in the 18th century depended on the personal integrity of the physician. Moral decisions were based on medical knowledge and an internal code of honour, rather than on a professional code of ethics or on the Hippocratic Oath. Doctors in the 18th century usually treated only a few wealthy patients. Barber-surgeons, midwives and lay healers cared for most people. With the industrial revolution and urbanization came an expansion of hospital medicine.[3]

The development of modern medicine in hospitals in Paris and large clinics in Vienna during the 18th century depended on large numbers of poor and working class patients, who provided a ready pool of experimental subjects. The use of human subjects in systematic experimentation established systems of classification of disease (nosology). Doctors began to view disease as pathology in specific organs, rather than as a general imbalance of the humours. Doctors saw the relationship between symptoms and the nature of disease. This led to modern concerns about the ethics of research on human subjects. [4]

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[2] M.A. Grodin, "Historical Origins of the Nuremberg Code," in G.J. Annas & M. A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) 121 at 124. [hereinafter "Historical Origins"]

[3] A.-H. Maehle, "Medical Ethics, History Of: Europe, C. Nineteenth Century," in W.T. Reich, *Encyclopedia Revised, supra* note 1 at 1543-44.
See generally: D.J. Rothman, "Ethics and Human Experimentation, Henry Beecher Revisited," (1987) 317 NEJM 19 1195 at 1196. Clinical investigations began as intimate and directly therapeutic. The turning point in human experimentation in the U.S. was WW II.

[4] Maehle, *ibid.* at 1547 and McNeill, *supra* note 1 at 18.

In Great Britain, from the early 16th century to the end of the 18th century, medical colleges and societies were founded, including the Royal College of Physicians. These bodies did not have a major role in imposing ethical codes on the entire profession, as they had limited jurisdiction (e.g. Royal College possessed jurisdiction over only London).[5] Professional bodies left ethical decisions to individual physicians.[6]

The greatest ethical issues arose in public health. Following Jenner's smallpox experiments, (inoculation of an 8 year old boy with cowpox material in 1776),[7] Parliament made smallpox vaccination compulsory in 1853. Poor Law Doctors who cared for the parish poor, were appointed under the New Poor Law, 1834, and assisted in enforcing the legislation.[8]

Case law related to human experimentation began in England, in the mid-eighteenth century, with *Slater* v. *Baker*, which established that a physician experimented at his peril.[9]

Three early examples of published experiments from the U.S. are: 1)1721 – smallpox inoculation in Boston; 2) 1820's-1830's –Beaumont studied the digestive system and wrote about it; and 3) Major Walter Reed, who in 1900 in Cuba, proved beyond a shadow of a

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[5] R. Porter, "Medical Ethics, History Of: Europe,-- Great Britain," in W.T. Reich, *Encyclopedia Revised, supra* note 1 at 1550.

[6] *Ibid.* at 1551-1552.

[7] Grodin, *supra* note 2 at 124.

[8] Porter, *supra* note 5 at 1552-1553

[9] *Slater* v. *Baker*, 2 Wils. 359, 95 Eng. Rep. 860, (K.B. 1767); Brieger, *supra* note 1 at 689.
The defendant surgeon tried to straighten an improperly healed leg facture by use of a new instrument and method, opposite to the standard practice.

doubt that yellow fever required the mosquito as an intermediate host to spread the infection.[10]

Autoexperimentation is as old as all human experimentation and continues to this day. A danger inherent in this process is the high level of risk which may be imposed on other subjects, as investigators may be willing to expose themselves to high risks, confident of results.[11] [12]

3. Responses -- Early Ethical Statements on Research in Human Experimentation

Medical ethics were not written down until the 1803 publication of Thomas Percival's *Medical Ethics; or A Code of Institutes and Precepts Adapted to the Professional Conduct of Physicians and Surgeons.* Percival's handbook was primarily practical. He was concerned with resolving practical problems among medical men.[13]

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[10] Brieger, *supra* note 1, at 686- 687.
See also: M.E. Evans, "The Legal Background of the Institutional Review Board," in Greenwald, Ryan & Mulvihill, *supra* note 1, 19 at 20; reference to *Carpenter* v. *Blake*, 60 Barb. (481) (N.Y. 1871), a 1871 New York case, where the Supreme Court of New York upheld a jury award to a patient whose elbow was treated unsuccessfully in an unorthodox manner.

[11] Brieger, *ibid.* at 688-689.

[12] See also: Maehle, *supra* note 3, at 1547-1548 for early examples of documented abuse: regarding reference to Hansen in Norway in 1880, inoculating with leprosy without consent and Neisser in Breslau in 1892, injecting syphilitic blood serum into uninformed prostitutes and children, which resulted in the 1900 decree by the Prussian Minister of Religious, Educational and Medical Affairs, (Appendix 2, the earliest official regulation of nontherapeutic research in the Western world), requiring disclosure, informed consent and a prohibition on experimentation with minors and those not fully competent; and reference to Berlin neurologist Albert Moll, who in 1902 argued that medical ethics should concentrate on duties to the patient rather than duties to colleagues and defined the doctor-patient relationship as one of contract; S. Lock, "Research Ethics–a brief historical review to 1965," (1995) 238 Journal of Internal Medicine 513 at 514; J. Vollmann & R. Winau, "The Prussian Regulation of 1900: Early Ethical Standards for Human Experimentation in Germany," (1996) 18 IRB A Review of Human Subjects Research 4 at 9-11; McNeill, *supra* note 1 at 18-20 for examples of unethical studies which were not confined to hospital patients; examples of unethical experiments conducted in 19th century United States, and also reference to Russian physician Smidovich, who in 1910 was one of the few to express humanitarian concern for subjects of experiments

[13] Porter, *supra* note 5 at 1550-51.
See also: R.J. Levine, *Ethics and Regulation of Clinical Research*, 2nd ed. (Baltimore: Urban & Schwarzenberg,

In Percival's view, action should be taken only after consulting with one's colleagues. There was no mention of the need to protect human subjects, nor any discussion of consent. Percival's book was very influential in the United States, which had no standard universal accredited licensing procedures. It served as the model for the American Medical Association's Code of 1847, but was not as influential in Britain, where licensing of practitioners was well entrenched since 1815.[14]

Wilcock first wrote about research ethics, in *Laws Relating to the Medical Profession*, published in 1830. He was amazingly perceptive about the need for informed consent:

> ...If the practitioner performs his experiment without giving the subject information that it is an experiment and obtaining consent, he is liable to compensate in damages any injury.[15]

William Beaumont's code of 1833 is considered the oldest American document dealing with the ethics of human experimentation. Beaumont prescribed a set of principles to guide the researcher. Three of the six principles related to concerns for the subject: voluntary consent of the subject was necessary, the experiment was to be discontinued when it caused distress to the subject and the project must be abandoned when the subject became dissatisfied.[16]

The influential French physiologist Claude Bernard laid down his principles for

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1986) at 322.

[14] Grodin, *supra* note 2 at 124-25 and Porter, *supra* note 5 at 1551.

[15] Lock, *supra* note 12 at 514.

[16] Grodin, *supra* note 2 at 125.; Grodin provides references for his discussion.

ethical human experimentation in his famous text, *An Introduction to the Study of Experimental Medicine*, published in Paris in 1865:

> "....It is our duty and our right to perform and experiment on man whenever it can save his life, cure him or gain him some personal benefit. The principle of medical and surgical mortality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even the though the result might be highly advantageous to science, i.e. to the health of others....."[17]

Grodin compares the writings of these early ethicists as follows: Bernard did not distinguish patient care, innovative therapy and therapeutic experimentation. He appears to prohibit nontherapeutic research by requiring personal benefit for the subject. The codes of Hippocrates, Percival, Beaumont and Bernard all focus on the physician's responsibility to benefit the patient/subject. Hippocrates only deals with the physician-patient relationship, (does not include experimentation); Percival discusses innovative therapies, Beaumont extends to nontherapeutic experimentation and Bernard focuses on the scientific method and therapeutic research. Beaumont and Bernard are also concerned with acceptable experimental risk. Only Beaumont discusses voluntary consent as a necessity for human experimentation.[18] These authors are later referred to by experts at the Nuremberg Doctors Trial and the fact that none of these statements is comprehensive is discussed in later sections.

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[17] Brieger, *supra* note 1 at 689-690.

[18] *Ibid.* at 690 and Grodin, *supra* note 2 at 126.
See also: R.M. Veatch, *The Patient as Partner, A Theory of Human-Experimentation Ethics*, (Bloomington: Indiana University Press, 1987) 16-28 for discussion of above early writers on ethics.

4. 20th Century

"Human experimentation" was rare in the early 1900's. The "investigator-clinician" role was developed in the 1920's. By the early 1930s, Sir Bradford Hill and Sir Ronald Fisher made available statistical tools to design and analyse clinical experiments. The professional clinical investigator and research became important aspects of the hospital system.[19]

Prior to World War II, experimentation on human subjects was conducted on a relatively small scale. While research ethics was not a subject of broad concern, evidence suggests there was considerable abuse of subjects of experiments in the 19th and 20th centuries. Science was not concerned about subjects, who rarely benefited.[20]

Historically, three countries were concerned with medical research ethics: the U.S., the U.K. and Germany. Between the two world wars, there was little discussion about new abuses or old problems in the U.S. or U.K.

During the 1920s in the U.S. and U.K., discussion focussed on the positive achievements of medical research--such as the life saving discoveries of insulin for diabetes and liver extract for pernicious anaemia, and also, local and general anaesthetics, hypnotics, mercurial diuretics, vitamins and sex steroids.[21]

Medicine had achieved much: many lethal infectious diseases were conquered by antiseptic practice, immunization and antibiotics, and pain was conquered by anaesthesia.

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[19] Brady & Jonsen, *supra* note 1 at 4.

[20] McNeill, *supra* note 1 at 19.

[21] Lock, *supra* note 12 at 515-16.

All this came about through research and experimentation. The public and patients who benefited, supported research.[22]

In Germany in the 1920s, reaction was different. The new pharmaceuticals were actively criticized by the media and the German parliament, culminating in 1930 in Lübeck, where over 100 children given BCG vaccine (contaminated with virulent tubercle bacilli), died of tuberculous meningitis. As a result, the German Ministry of the Interior issued a set of guidelines in February 1931.[23] (See Appendix 3; further discussion regarding these guidelines will take place in the section on the Nuremberg Code).

5. World War II

World War II was a "turning point in experimentation on human subjects."[24] The U.S. and U.K. conducted extensive research, targeted at the medical problems experienced by their troops, particularly vaccines and/or treatment for infections like dysentery, influenza, malaria and scrub typhus. Trials were conducted on troops, on children in orphanages, the mentally retarded (both adults and children) housed in institutions and on prison volunteers. The public responded not by asking about informed consent, but by congratulating 'these one-time enemies of society for demonstrating to the fullest extent just how completely this is everybody's war.'[25] The association of medical research with the war, pre-empted the

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[22] Brady & Jonsen, *supra* note 1 at 4-5.

[23] Lock, *supra* note 12 at 516.

[24] McNeill, *supra* note 1 at 20.
See also: Rothman, *supra* note 3 at 1196-97.

[25] Lock, *supra* note 12 at 516.
See: Rothman, *ibid.* at 1197-98, reference to *New York Times*.
See also: McNeill, *ibid.* at 20.

welfare of research subjects and justified putting them at considerable risk without any personal therapeutic advantage.[26]

During the war, funding of research increased significantly and an associated bureaucratic framework developed. Clinical research became centrally funded, well-coordinated and extensive. The U.S. Committee on Medical Research distributed $25 million to universities, hospitals, institutes and companies to find antidotes to dysentery, influenza and malaria.[27]

Funding for research continued after the war. The wartime Committee on Medical Research was succeeded by the National Institutes of Health (NIH). Funding for medical research rose dramatically. The public viewed science as serving society.[28] "Research practices which had been established during the war 'profoundly influenced researchers' behaviour in the post-war era' and their attitude to subjects. It was not until the 1960s that an effective challenge to this ethos was mounted."[29]

6. Germany

German and Japanese physicians and researchers conducted the most detestable experimentation on humans during World War II.[30]

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[26] McNeill, *ibid.* at 20-21.
See also: Rothman, *ibid.* at 1197-98.

[27] Lock, *supra* note 12 at 516.
See also: Rothman, *ibid.* at 1197.

[28] McNeill, *supra* note 1 at 21.
See also: Rothman, *ibid.* at 1198.

[29] McNeill, *ibid.* at 21.

[30] *Ibid.*.

The abominable conduct of the German doctors and scientists is widely known due to the publicity of the trial conducted by the Allied Forces after the war. The case is known as *United States* v. *Karl Brandt* (the Doctors Trial). Sixteen of the 23 defendants were found guilty of various crimes including: placing prisoners in low pressure chambers to observe their deaths; exposing prisoners to freezing air and water; infecting prisoners with typhus and malaria to test drugs; sterilization and castration and murdering prisoners (including children) for specimens of their anatomy. Like the Allies, many experiments had military goals. Others were purely evil. The prosecutor invented the word "thanatology" to describe the science of producing death rapidly. Methods of mass extermination were developed through 'research.' "Medical killing" and "euthanasia" were part of the Third Reich's program of "racial hygiene"--the extermination of unwanted groups.[31]

The recent record of experimentation on human subjects demonstrates a continuing neglect for their welfare. The major difference between the Nazi experiments and experimentation on humans elsewhere, is the extent of the atrocities committed by German doctors and the deliberate intention to inflict brutal injury and death.[32]

7. Japan

The atrocities committed by Japanese Kwantung Army doctors against prisoners during World War II in Manchuria and China, were identical to the human experiments, torture and murder conducted by the Nazis. From 1932 to 1945, Japan conducted trials of

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[31] *Ibid.* at 22.
See also: J. Katz, *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972) 292-306 for discussion of *United States v. Karl Brandt.*

[32] McNeill, *ibid.* at 23.

biological warfare with various diseases including anthrax, cholera, typhoid and typhus.[33] The Japanese doctors were reinforced by their racial hygienist views of racial superiority. The subjects of Japanese experiments included Han Chinese, White Russians, Soviet prisoners, Mongolian and Korean political prisoners and the mentally handicapped.[34]

An estimated 12,000 prisoners died as a direct result of Japanese medical experimentation. Field tests by the Japanese accounted for another 200,000 to 250,000 deaths. Deaths attributed to Nazi experiments are estimated at 100,000. After the war, these Japanese physicians avoided prosecution as war criminals in exchange for their data. No Japanese physicians were brought before the 1948 Tokyo war crimes trial.[35]

"Medicalization of military and political ideology leads to an objectification of humans as a means to an end." [36] World War II experiments on U.S. servicemen (such as mustard gas, chemical agents and radiation) were justified, like those of the Nazis and Japanese, as experiments done for the country as a whole. Continued study of these cases is necessary, as we "cannot survive their being repeated."[37] History has demonstrated that

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[33] *Ibid.* at 23-24. The principal testing site, Unit 731, was Ping Fan on mainland China where there were installations for germ warfare, a prison for experimental subjects and a crematorium for human victims. At least 11 Chinese cities were subjected to biological warfare attacks.
See: M.A. Grodin, "The Japanese Analogue," Book Review of *Factories of Death: Japanese Biological Warfare, 1932-1945 and the American Cover-Up* by S.H. Harris (1996) 26 Hastings Center Report 5 at 37. [hereinafter "Japanese Analogue"]

[34] Grodin, *ibid.* Three types of experiments were conducted at the "factories of death"--laboratory experiments on individual subjects; open air experiments to test effectiveness of a prototype biological warfare delivery system and field tests exposing civilians and military personnel to biological pathogens.

[35] *Ibid.* at 37-38. These doctors were given immunity even though identical medical experiments were condemned by the 1947 Nuremberg Tribunal. The U.S. army valued the data from Unit 731 more than prosecuting war crimes and crimes against humanity. Following the war, these physicians became leaders in the Japanese medical establishment.

[36] *Ibid.* at 38.

[37] *Ibid.*

even physicians dedicated to healing can turn to torture and murder in the service of country and ideology.[38]

8. Beecher and Pappworth - U.S. & U.K.

The U.S. Health Service adopted the Nuremberg Code, (Appendix 1) in 1957. The American Medical Association (AMA) did the same. Apart from occasional exceptions, no other institution followed, including the NIH. Few medical researchers took notice of the Nuremberg trials. "It was a good code for barbarians, but unnecessary for ordinary physician-scientists."[39]

The impetus for change in research with humans came principally from the furore aroused by the proselytising of two physicians-- Henry Beecher (U.S.) and Maurice Pappworth. (U.K.).[40] Beecher presented the issues in public, incrementally. He started with an article and his first book, *Experimentation in Man* addressing general principles. Later, he became more direct and identified instances where the ethics of the research were debatable. Beecher chose 22 of 50 ethically questionable published studies, and incorporated them into an article in 1966.[41]

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[38] *Ibid.*

[39] Lock, *supra* note 12 at 517. The NIH may not have introduced guidelines, as it respected the traditions of academic freedom. Ultimate responsibility for standards lay with the university and the principal investigator.
See also: R.R. Faden, S. Lederer, & J. Moreno, "U.S. Medical Researchers, the Nuremberg Doctors Trial and the Nuremberg Code, A Review of Findings of the Advisory Committee on Human Radiation Experiments," (1996) 276 JAMA 20 1667-1670 for discussion of reaction of U.S. researchers to the Nuremberg Code.

[40] Lock, *ibid.* at 516.
See: Faden, Lederer & Moreno, *ibid.* at 1670 reference to Beecher's negative reaction to the first principle of the Nuremberg Code. Rather than informed consent, Beecher believed in the relationship of trust between subject and investigator and in the integrity of a virtuous researcher.

[41] Lock, *supra* note 12 at 517. The article was initially rejected for publication by JAMA and was accepted for publication in 1966, by the NEJM. It described anonymous cases (including the Willowbrook institution).

Beecher wrote that, thoughtlessness and carelessness, rather than a wilful disregard of the patients' rights, accounted for most of the abuse. In many of his examples, the investigators risked the health or life of their patients, i.e. Willowbrook, Jewish Chronic Disease Hospital.[42] [43]

Beecher stated that many of the patients in the 22 examples were never properly informed of the risk and hundreds did not know that they were the subjects of an experiment, although grave consequences resulted from participation in these experiments. Beecher argued the situation must be dealt with urgently.[44]

Beecher believed that although fully informed consent may not be obtainable, it remained a goal for which to aim, for sociologic, ethical and clear-cut legal reasons. There was no option. He cautioned, patients will agree on the basis of trust, to any request their physician may make, if properly approached. For Beecher, a more dependable safeguard

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See: Rothman, *supra* note 3 at 1195. "Beecher's most important and controversial conclusion was that "unethical or questionably ethical procedures were not uncommon," and his 22 examples represented mainstream science."

[42] H.K. Beecher, "Ethics and Clinical Research," (1966) 274 NEJM 24 1354 at 1355-1359. Beecher gave 22 examples of unethical experimentation in published journal articles. Examples are: withholding effective treatment for rheumatic fever and typhoid fever; giving medication which was not the most efficacious; using medication (in mental defectives and juvenile delinquents who were inmates in childrens' centres and suffering from no disease), which caused hepatic dysfunction; artificial induction of hepatitis in an institution for mentally defective children where a mild form of hepatitis was endemic (parents gave consent for administration of the virus, but were not told of appreciable hazards—Willowbrook); live cancer cells were injected into 22 human subjects to study immunity to cancer (in the 1960s, the subjects were told they would be receiving "some cell"-the word cancer was entirely omitted; consent was not obtained from subjects and the protocol was not submitted to the hospital's research committee for review –Jewish Chronic Disease Hospital) and many high risk cardiac experiments.
See also: Evans, *supra* note 10 at 22-23. Reference to Jewish Chronic Disease Hospital; Levine, *supra* note 13 at 70 & 71 for discussion of Willowbrook and the Jewish Chronic Disease Hospital studies; Katz, *supra* note 31 at 9-65 for discussion of Jewish Chronic Disease Hospital case; Board of Regents Decision- revocation of certificates to practice medicine of investigators.

[43] Beecher, *ibid.* at 1360. In Beecher's view, data improperly obtained should not be published. This would discourage unethical experimentation.

[44] *Ibid.* at 1354-1355.

than consent, is the presence of an intelligent, informed, conscientious, compassionate and truly *responsible* investigator.[45]

Maurice Pappworth, a physician in London, U.K., did not hold a major academic post and was a prickly and difficult outsider. He collected examples of published research that he considered unethical. In 1962 he published an article which was expanded into his book *Human Guinea Pigs*, in 1967. "Unlike Beecher, Pappworth named names."[46] Like Beecher, he achieved much angry discussion among colleagues and realized that self-regulation by the individual experimenter was not sufficient.[47]

The pressure from Beecher and Pappworth, was augmented by judicial concern with individual rights, resulting in additional pressure on the U.S. federal government to develop a regulatory system designed to protect human subjects of biomedical research.[48]

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[45] *Ibid.* at 1355 & 1360. The statement that consent was obtained has little meaning unless the subject comprehends and the hazards are made clear.

[46] Lock, *supra* note 12 at 518.
See: M.H. Pappworth, *Human Guinea Pigs, Experimentation in Man,* (London: Routledge & Kegan Paul, 1967).

[47] Lock, *ibid.* Pappworth was the best freelance teacher in the country for the higher medical diploma. He learned of the anxieties of young doctors regarding the ethics of the research then going on, which they were forced to take part in or risk losing their jobs.

[48] Evans, *supra* note 10 at 23; Reference to: the 1973 case of *Kaimowitz* v. *Department of Mental Health*, Civil No. 79-1934 AW, Circuit Court for the County of Wayne, State of Michigan, July 10, 1973 dealt with the a patient who had agreed to participate in a study designed to evaluate the relative efficacy of psychosurgery and hormonal treatment in controlling aggression. The patient and his parents signed consent forms. Although the project had been approved by scientific and human rights committees, due to the high risk involved and the uncertainty of the results, the court held the patient's consent to surgery was invalid; *Wyatt* v. *Stickney*, 344 F. Supp. 373 (M.D. Ala. 1972) one of the early cases that recognized the rights of the institutionalized mentally infirm not to be subjected to experimentation without their consent.
See: G. J. Annas, L.H. Glantz, & B.F. Katz, *Informed Consent to Human Experimentation: The Subject's Dilemma* (Cambridge, Mass.: Ballinger Publishing Company, 1977) at 9. The *Kaimowitz* case is the only case in the U.S. where the Nuremberg Code is cited as authority in the experimental context. The court held: the Nuremberg Code was a proper standard against which to judge the sufficiency of the consent for the proposed experimental brain surgery.
Appellate court decisions regarding human experimentation were rare after WWII, with the exception of a series of cases involving tissue transplants from minor donors.

Prior to World War II, the U.S. courts found human experimentation a deviation from medical practice and evidence of malpractice. The U.S. courts did not consider nontherapeutic experiments prior to World War II. By World War II, experimentation done with the patients' informed consent was seen as legitimate. The Nazi experiments were rarely mentioned in U.S. courts. Human experimentation was viewed as mainstream and legitimate. Clinical trials with new drugs were conducted to find new treatments, rather than to assist individuals.[49]

Another example of unethical experimentation in the U.S., (which came to light following Beecher's article), was the Tuskegee Syphilis Study conducted from 1932- 1972 involving two groups of subjects, one suffering from the disease and the other disease free. No treatment of the disease was provided to either group-- even following the discovery of antibiotic therapy.

The ad hoc committee appointed in 1973 to study the Tuskegee project determined that informed consent had not been obtained from the participants and that standardized evaluation measures had not been utilized.[50]

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[49] G. J. Annas, "The Nuremberg Code in U.S. Courts: Ethics versus Expediency," in Annas & Grodin, *supra* note 2, 201 at 217.

[50] Evans, *supra* note 10 at 20. Subsequent litigation on behalf of the participants resulted in settlements ranging from, $37,000 for survivors who had syphilis to $5000 for estates of deceased participants who did not contract the disease.
See: E-H. W. Kluge, *Biomedical Ethics in a Canadian Context* (Scarborough, ON: Prentice-Hall Canada, Inc., 1992), at 180. The study, which took place in Tuskegee, Alabama over 40 years, is the longest study in the history of modern medicine. It was designed to study the course of untreated syphilis. Participants were not informed of the nature of the study or that treatment was available; H. Gurdon, "Clinton Apologizes to Blacks," *The Daily Telegraph* reprinted in *The Edmonton Journal* (17 May, 1997). This was Clinton's second apology on behalf of the U.S. government in 18 months. In October 1995 he apologized officially to victims of radiation experiments in the 1940s and 1950s; C.K. Yoon, "Silent Victims of a Monstrous Lie," *The New York Times* reprinted in *The Edmonton Journal* (25 May, 1997).
See also: Levine, *supra* note 13 at 69 for discussion of Tuskegee study.

The U.S. Cold War radiation experiments are a further example of abuse of research subjects. An Advisory Committee on Human Radiation Experiments was established in 1994 by President Clinton to examine the history of human radiation experiments between 1944 and 1974, to evaluate the degree to which these experiments were ethically acceptable and scientifically valid, to examine specific cases of known research involving exposure of humans to radiation and make recommendations for improving protection of subjects.[51] "The 1995 Final Report provided evidence of how easy it was to administratively dismiss the moral (if not legal) requirements for obtaining informed consent from individuals."[52]

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[51] E.M. Meslin, "Adding to the Canon, The Final Report," Report Review of *Final Report: White House Advisory Committee on Human Radiation Experiments* (1996) 26 Hastings Center Report 5 at 34.
See: Advisory Committee on Human Radiation Experiments, R.R. Faden, Chair, *Final Report of the Advisory Committee on Human Radiation Experiments,* (New York: Oxford University Press, 1996) xxi-xxiii [hereinafter *Final Report*].

[52] Meslin, *ibid.* at 34-35. Examples of human radiation experiments where individuals were treated as mere means for other's ends are: a study co-sponsored by the Quaker Oats Company in the 1940s-50s at the Fernald School in Massachusetts where mentally retarded boys were given oatmeal containing radioactive iron and calcium, as part of a "science club;"; a study at the Wrenthan State School, where mentally retarded children were administered radioactive iodine; uranium miners in the western United States who worked in underground mines with inadequate ventilation; inhabitants of the Marshall Islands in the South Pacific who were prematurely returned to their island following the detonation of nuclear weapons at Bikini Atoll between 1946 and 1954; and groups of Alaskans who, in 1956-57, were subjects of a study in which iodine was administered to determine the effect on the thyroid gland of extreme cold. The uranium miners were the group most seriously at risk of harm with often-fatal consequences.
See also: A.A. Skolnick, "Discovery of 50-year old Naval Logbook May Aid Follow-up Study of Radium-Exposed Veterans," (1996) 276 JAMA 20 at 1628-1630; A. Buchanan, "Judging the Past, The Case of the Human Radiation Experiments," (1996) 26 Hastings Center Report 3 at 27-28 for a discussion of examples of radiation experiments at universities and medical centres; T. Beardsley, "The Cold War's Dirty Secrets, Radiation Experiments Ignored Ethics Guidelines," (1995) 272 Scientific American at 16 Subjects were deceived about the likely side effects and the true purpose. The Atomic Energy Commission insisted on informed consent in 1947, so researchers could not argue that ignoring consent was the accepted ethical practice. Risks in most experiments were not excessive and led to current medical procedures.
See generally: McNeill, *supra* note 1 at 4. Other cases of review by IRBs, which raise ethical concerns: Baby Fae (implantation of a baboon heart), Barney Clarke (implantation of an artificial heart) and ethics approval of a New Zealand study on women with carcinoma *in situ* which was left untreated; many of the women died when timely treatment would have saved their lives.
See also: for articles discussing examples of current abuse of subjects or the related topic of scientific misconduct: Orange County Register, "Cancer patients sued in unapproved tests,," *The Edmonton Journal* (5 December, 1998) G.6 University of California, Irvine researchers conducted unapproved experiments on cancer patients in the mid-1990s; Eliot Marshall, "San Diego's Tough Stand on Research Fraud," (1986) 214 Science at 534-35 Discussion of Dr. Slutsky whose fraud was discovered in 1985 and resulted in 15

9. Canada

Two cases in Canada following the Nuremberg Code dealt with issues surrounding research ethics.

Halushka v. *University of Saskatchewan*[53] is significant as it is the only post-Nuremberg case dealing with a healthy volunteer. A student, looking for $50 income, volunteered to be a subject at the University Hospital at the University of Saskatchewan. He was told that the test involved a new drug, but that it was "perfectly safe" and "had been conducted many times before." He was informed that it involved an incision in his arm and insertion of a catheter into his vein.

In fact, the catheter was inserted into his arm and threaded through his heart and out into the pulmonary artery. His heart stopped after 45 minutes. His chest was cut open, and his heart beat restored by manual massage. He was unconscious for 4 days and was in hospital for 10 days. He received $50 from the investigators.[54] Halushka sued and was awarded $22,500 by a jury. The Court of Appeal held that the duty of disclosure of investigators to their subjects was "'at least as great as, if not greater than' the duty of disclosure in a doctor-patient relationship. They continued, *"the subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent."*[55]

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published papers being withdrawn; A.S. Relman, "Lessons from the Darsee "Affair," (1983) 308 NEJM 23 at 1415 for discussion of Darsee, a cardiologist who fabricated a large number of published findings.

[53] *Halushka v. University of Saskatchewan*, (1965), 53 D.L.R. (2d) 436 (Sask. C.A.) [hereinafter *Halushka*].

[54] Annas, Glantz, & Katz, *supra* note 48 at 18 & 19.

[55] *Ibid.* at 18 & 19; *Halushka, supra* note 53 at 443-444. The court held: " There can be *no exceptions* to the ordinary requirements of disclosure in the case of research as there may well be in ordinary medical practice.

The court found that the subject was not told that the new drug was an anaesthetic, that there were specific risks, or that this particular anaesthetic had never been tested before. Therefore, his consent had not been properly obtained.

Weiss v. *Solomon*[56] is the second Canadian case ruling on biomedical research ethics with human subjects. The Quebec Superior Court found a researcher and a teaching hospital responsible for not disclosing the risks of a non-therapeutic intervention that led to the death of a patient. The court held both parties responsible for not screening the subject and for failing to have proper resuscitation equipment quickly available. This case raises concerns

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The researcher does not have to balance the probable effect of lack of treatment against the risk involved in the treatment itself. The example of risks being properly hidden from a patient when it is important that he should not worry can have no application in the field of research. The subject of medical experimentation is entitled to a full and frank disclosure of all the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent."
See also: C. Bernard, "Legal Case Briefs on Medical Research," (1992) 3 NCBHR Communiqué 1 at 13-14. Halushka sued the physicians/researchers and their employer, the university hospital. The Appeal Court held that the researchers were liable as they both withheld information and provided incorrect information. This information did not relate directly to the cause of the injury, but should have been disclosed as it could have influenced the subject's consent. *Halushka* has been interpreted as holding, that in the case of research, the duty of disclosure is higher than in medical treatment.
Two other cases, although not directly related to research protocols, dealt with experimental therapy. The Court imposed a greater duty of disclosure when a therapeutic treatment is experimental, than when it has been previously tested: *Cryderman* v. *Ringrose* [1977] 3 W.W. R. 109 (Alta. Dist. Ct.) aff'd [1978] 3 W.W.R. 481, (1978) 89 D.L.R. (3d) 32 (Alta. C.A.) and *Zimmer* v. *Ringrose*, [1981] 4 W.W.R. 75, (Alta. C.A.), 124 D.L.R. (3d) 215 aff'g (1978) 89 D.L.R. (3d) 646; leave to appeal to SCC denied (1981) 28 A.R. 92 Both dealt with the same experimental sterilization technique. In the first, the court held that the patient was not told that the technique was experimental. When a treatment is experimental, the physician must use a high degree of care and bears the duty to disclose to the patient that the treatment is new and risky. The court relied on three factors to conclude, that the procedure was experimental: 1) the novelty of the procedure; 2) the lack of general acceptance by the medical profession and 3) the lack of sufficient proof of its efficiency and reliability. In the second case, the court held that the physician breached his duty to disclose by withholding information regarding both the risks and the alternative treatments and the novelty of the procedure. The patient was denied damages as the Court found that had the patient been fully informed, a reasonable person in her position would have consented to the experimental procedure. The Court did not apply the full disclosure standard of *Halushka*, as these were not situations of pure medical experimentation. See also: *Coughlin* v. *Kuntz* (1987), 17 B.C.L.R. (2d) 365 (S.C.) where a physician was conducting his own case control. The Court applied the standard of disclosure for therapy.

[56] *Weiss* v. *Solomon* [1989] R.J.Q. 731 (Qué. S.C.); (1989) 48 C.C.L.T. 280 (Que. C.S.).

for the research community, as it is the first Canadian judgment dealing with the issue of institutional liability for the negligent action of an REB.[57]

A further example of unethical research in Canada is the case of "psychic driving" and of "depatterning" experiments done by Dr. Ewen Cameron in Montreal, in the 1950s-60s. Dr. Cameron developed psychiatric techniques which involved subjecting patients to unusual, (and scientifically apparently quite questionable procedures), performed without consent. Several people suffered irreversible destruction of fundamental parts of their personalities.[58]

A more recent incident of research misconduct involved the case of scientific fraud of Dr. Roger Poisson of Montreal, who admitted forgery and falsification of dates and other fabrications in the records of a number of patients (St.-Luc Hospital) which he entered into the National Surgical Adjuvant Breast and Bowel Cancer Project (NSABP) of the National

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[57] *Weiss* v. *Solomon*: "Researcher and Hospital Found Legally Responsible," (1992) 3 NCBHR Communiqué 1 at 18. Weiss agreed to participate in a drug trial after his successful cataract operation, which involved a fluorescein angiogram. He knew he would not receive any therapeutic benefit. He died of cardiac arrest immediately following his first injection. The researcher was negligent in his failure to advise the patient of every known risk regardless of how rare. The hospital was also held responsible because it allowed the trial to be conducted without adequate subject screening and because it did not foresee means to prevent or rescue victims of cardiac arrest. The court held that the hospital's REB did not assure the subject's security and integrity during the clinical trials. The court did not refer to the MRC Guidelines in its decision, but did cite the Declaration of Helsinki.
See also: B. Freedman, "Multicentre Trials and Subjects Eligibility: Should Local IRBs Play a Role?" (1994) 16 IRB A Review of Human Subjects Research 1 & 2 at 1-6 for a discussion of responsibilities of REBs.

[58] Kluge, *supra* note 50 at 178-79.
See e.g. for other examples of unethical conduct in Canada: J.Bronskill & M. Blanchfield, "Military backed LSD trials in 1960s" *The Edmonton Journal* (7 December, 1998) A3 The Canadian military funded LSD experiments on students and musicians in Montreal in the early 1960s and secret experiments with even more powerful hallucinogens in rural Alberta. The tests were part of a larger military research program during the Cold War. During WW II, in Suffield Alberta, Alberta scientists played a role in the Allied effort to develop and test biological and chemical weapons; M.Blanchfield & J. Bronskill, "LSD tests on inmates unethical–report," *The Edmonton Journal* (31 October, 1998) B7 Testing LSD on vulnerable Canadian prison inmates at Kingston's Prison for Women, in 1961, was unethical even by the standards of the day, says a new federal report.

Cancer Institute (NCI), which was comparing the results of radical mastectomy to lumpectomy.[59]

10. Summary

As a result of the revelations about Nazi experiments on concentration camp prisoners and the reactions to the articles by Henry Beecher and Maurice Pappworth, demands for action were forcefully communicated to the funders of much of the biomedical research enterprise, the members of the U.S. Congress. In less than a decade, human experimentation, formerly heavily supported by the general public, was transformed into 'suspect activity' that required the approval of governmentally constituted authority for each project.[60]

The history of unethical experimentation is an appalling account of "man's inhumanity to man." In McNeill's view, the lesson to be learnt from this historical account is that there should be *no* privilege extended to scientists to conduct experiments on human subjects without adequate protective measures.[61]

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[59] Statement of S. Broder M.D. Director, National Cancer Institute, on Scientific Fraud at NSABP, Before the Subcommittee on Oversight and Investigations Committee on Energy and Commerce, April 13, 1994 at 1-7. The Office of Research Integrity found that Dr. Poisson falsified data on 115 separate breast cancer cases from 1977-1990, in St.-Luc Hospital. Although the misconduct took place in Canada, it was followed up by American regulatory authorities as Dr.Poisson and his subjects were part of a U.S. multi-centre protocol. NCI initiated action to recover funds awarded to St. Luc's Hospital. Dr. Poisson was barred from receiving NIH (U.S.) federal funds or contracts and prohibited from serving on NIH committees for eight years. Media reports appeared on March 13/14, 1994.
See e.g.: D. Sanger, "Second Cancer Study Investigated," *The Ottawa Citizen* (30 March, 1994) Reference to discrepancy at St. Mary's Hospital, Montreal.
See: J. Crewdson, "Pittsburgh Institution Handled Research Fraud by Montreal Physician by Doing Nothing," *Chicago Tribune* reprinted in *The (Montreal) Gazette* (3 April 1994); J. Cohen, "The Poisson Case: Battle over Auditing,"(1994) 264 Science at 1537. Dr. Poisson had first submitted false reports to NSABP 13 years previously. One might question whether the policy of reviewing only eight patient records when over 400 patients were entered over 3 years, contributed to the delay in detecting significant data irregularities.

[60] Brady & Jonsen, *supra* note 1 at 6.

[61] McNeill, *supra* note 1 at 35-36.

II. Development of International Guidelines Regarding Medical Research with Human Subjects

Given the history of human experimentation and the enormous growth and development of pharmaceuticals, medical treatment and research, a movement developed worldwide, to respond and establish standards to regulate the health research enterprise for the purpose of protecting the human subjects of research.

Medical experimentation involving human subjects is a worldwide activity. It is regulated by national and state/provincial laws, regulations and guidelines, by international statements and guidelines, by intraprofessional controls (ethical codes and disciplinary boards), by institutional policies and by the courts. All of these must be taken into account by a researcher when seeking direction regarding the ethical conduct of medical research with human subjects.[62] We will embark on a discussion of the development of international guidelines governing biomedical research with human subjects and will conclude with a discussion of the response of the United States and Canada to the requirement for guidance in this area.

1. Nuremberg Code

"The Nuremberg Code [hereinafter The Code], was an attempt to formulate a universal natural law standard for human experimentation."(Appendix 1)[63] It was the first

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[62] See generally: P.R. Benson, "The Social Control of Human Biomedical Research: An Overview & Review of the Literature," (1989) 29 Soc. Sci. Med. 1 at 1-12; B.H. Gray, *Human Subjects in Medical Experimentation, A Sociological Study of the Conduct and Regulation of Clinical Research* (New York: John Wiley & Sons, 1975) at 7.

[63] G.J. Annas & M.A. Grodin, "Introduction," in Annas & Grodin, *supra* note 2 at 3.

international code to establish ethical standards for human experimentation and is the first authoritative and the most demanding declaration of the rights of research subjects.[64]

The final judgment in the Doctors Trial concluded with the Nuremberg Code, a 10-point statement of rules intended to protect the rights and welfare of research subjects.[65]

The judges based their decision on universal human rights principles, and saw themselves as speaking as the "voice of humanity." The Code provided that human rights in research be protected by the strict requirement of the informed, voluntary, competent, and understanding consent of research subjects, and the right of subjects to withdraw from research at any time. Other provisions of The Code require researchers to protect research subjects.[66]

The Nuremberg Code, as a whole, has not been formally adopted by international treaty or convention as international law, but its consent principle was incorporated into international law in Article Seven of the United Nations International Covenant on Civil and

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[64] J. Katz, "The Consent Principle of the Nuremberg Code: Its Significance Then and Now," in Annas & Grodin, *supra* note 2 at 227. [hereinafter "Consent Principle"]
See also: Vollmann & Winau, *supra* note 12 at 9.

[65] M.A. Grodin & G.J. Annas, "Legacies of Nuremberg, Medical Ethics and Human Rights," (1996) 276 JAMA 20 at 1682. [hereinafter "Legacies"]
See: Annas & Grodin, *supra* note 2 at 4; M. Lippman, "The Nazi Doctors Trial and International Prohibition on Medical Involvement in Torture," (1993) 15 Loy. L.A. Int'l & Comp. L.J. 395 at 422, 424-429. Control Council Law No. 10 defined both war crimes and crimes against humanity. The tribunal held the experiments were unethical as well as illegal under international law. "...human experiments under such conditions are contrary to 'the principles of the law of nations as they result from usages established among civilized peoples, from the laws of humanity, and from the dictates of public conscience." The tribunal rejected the necessity and good motive defences. Superior orders is not recognized as a defence to war crimes and crimes against humanity and will only be considered, if at all, in mitigation of punishment.

[66] Grodin & Annas, *ibid.*, at 1682.
See: Annas, Glantz, Katz, *supra* note 48 at 1. Some state that The Code is the most comprehensive and definitive statement of the law of informed consent in experimentation. None of the cases prior to The Code deal with the standards to apply in experimentation, as they were concerned with malpractice, not experimentation.

Political Rights (adopted by the UN General Assembly in 1974). This ambiguous legal status of The Code may contribute to its marginalization by some, as a medical ethics statement.[67]

"The Doctors Trial was the most important historical forum for questioning the permissible limits of human experimentation. The extent of human experimentation, atrocities and murders that were recorded during the trials is inescapable. Most important was the focus on universal ethical codes within the context of a criminal trial."[68]

The context

How was it possible that physician healers became murderers? This is one of the most difficult questions in medical ethics.[69]

Nazi medicine was supported by a combination of National Socialist ideology, social Darwinism and a theory of racial hygiene that saw some racial and ethnic groups as subhuman. This converted murder into the medical procedures of euthanasia and sterilization.[70]

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[67] Grodin & Annas, *supra* note 4 at 1682.
See: G.J. Annas & M.A. Grodin, "Where Do We Go From Here?," in Annas & Grodin, *supra* note 2 at 309-310 for discussion of reasons for marginalization of The Code; [hereinafter "Where to?"]; Annas, Glantz, Katz, *ibid.* at 6-9. No exceptions were made to full disclosure in the Code. The Code's adoption by the United Nations General Assembly on December 11, 1946, and its use as a basis for other international documents, such as the Declaration of Helsinki could lead to the conclusion that the decision is properly viewed as part of international customary or common law. The legal standing of the Code in the U.S. is discussed.

[68] Annas & Grodin, *supra* note 63 at 3.

[69] *Ibid.*

[70] Grodin & Annas, *supra* note 4 at 1682. Recurrent themes occur in Nazi medicine: the devaluation and dehumanization of segments of society, the medicalization of social and political problems, training of doctors to identify with political goals, fear of the consequences of refusing to cooperate with civil authority, the bureaucratization of the medical role and the lack of concern for medical ethics and human rights. Nazi physicians did not see themselves as physicians first, with an ethic dedicated to healing. They saw the state

"Biomedical scientists and physicians were active leaders in the initiation, administration and execution of each of the major Nazi racial programs."[71] By 1942, about half of all the doctors in the country were members of the Nazi Party and doctors held leading positions in German government and universities.[72] "Medical scientists were the ones who *invented* racial hygiene in the first place."[73]

The practical results of racial hygiene were three main programs: the Sterilization Law,[74] the Nuremberg Laws and the euthanasia program. The argument for forcible euthanasia was economic–to free up beds.[75]

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as their "patient" and extermination of an entire people as "treatment" for the state's health.

[71] R.N. Proctor, "Nazi Doctors, Racial Medicine and Experimentation," in Annas & Grodin, *supra* note 2 at 18.

[72] *Ibid.* at 19.

[73] *Ibid.* at 19.
See: *Ibid.* at 18-20 for background on the eugenics movement in Germany; Lippman, *supra* note 65 at 399-402; J.A. Barondess, "Medicine Against Society, Lessons from the Third Reich," (1996) 276 JAMA 20 at 1657 & 1660. Other major pillars of the German state were also involved, including: the judiciary, the legal system generally, industry and the universities. Medicine differed from these due to a 2000-year-old Hippocratic ideal that placed the sufferer first.
See also: V.W. Sidel, "The Responsibilities of Health Professionals, Lessons from Their Role in Nazi Germany," (1996) 276 JAMA 20 at 1679. Discussion of forces influencing doctors to support Nazism and an example of group resistance; W.E. Seidelman, "The Path to Nuremberg in the Pages of JAMA, 1933-1939," (1996) 276 JAMA 20 at 1694 for an example of German protest.

[74] Proctor, *ibid.* at 20. In July 1933, the Nazi government passed the Sterilization Law, allowing the forcible sterilization of anyone suffering from "genetically determined" illnesses.
See: Lippman, *ibid.* at 403-419 for an explanation of the factors contributing to the participation of the medical profession in the Nazi regime, the effect of legislation promulgated and experiments undertaken.

[75] Proctor, *ibid.* at 23-24. In 1935 Hitler signed the Nuremberg Laws, administered by physicians, which excluded Jews from citizenship and prevented marriage or sexual relations between Jews and non-Jews. In October 1939, Hitler initiated the euthanasia plan.

There were many experiments. Doctors were never forced to perform such experiments; they volunteered.[76] "Physicians assisted the Nazis to *biologize* or *medicalize* a broad range of social problems."[77]

The Nuremberg Code

The Code's ten principles were "an attempt to establish substantive standards and procedural guidelines for permissible medical experimentation with humans. They were not identified as a code of medical ethics but appear as part of the final legal judgment, where it is claimed that they are derived from the "natural law" of all people."[78]

The tribunal focussed on the criminal nature of the Nazi experiments, and more broadly, the ethical concerns in medical research--- specifically the limits of acceptable nontherapeutic human experimentation on adult prisoners. The judges valiantly sought a tradition of medical standards on which to base their judgment of the Nazi physicians and attempted to establish a set of principles of human experimentation that could serve as a code of research ethics. The Nuremberg Code was not the first code of human experimentation, or the most comprehensive. The pre-WW II German codes were more extensive. As the

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[76] *Ibid.* at 26-28 for discussion of the experiments and role of the physicians.

[77] *Ibid.* at 27.

[78] Grodin, *supra* note 2 at 121.
See also: S.Perley, S.S. Fluss, Z. Bankowski, & F. Simon, "The Nuremberg Code: An International Overview," in Annas & Grodin, *supra* note 2 at 149-Note 1. A. Capron remarked that the Nuremberg Code is central to the process of asserting legal control over research on human beings.

Code was drafted in reaction to medical and scientific horrors, protecting human subjects is its primary concern.[79]

The prosecution's two primary medical expert witnesses, Leo Alexander and Andrew Ivy, used the oaths, codes and writings of Hippocrates, Percival, Beaumont and Bernard as a basis of the ethics of human experimentation. None of these was an entirely appropriate statement of the ethical standards of human experimentation.[80] (See earlier discussion)

They also referred to the 1900 Directive by the Prussian Minister of Religious, Educational and Medical Affairs, which may be the first reported regulation dealing with human experimentation (see Appendix 2), [81] and to the 1931 Reich Circular, (issued in response to the deaths of 75 children who were subjects in experiments with tuberculosis vaccinations), entitled, "Regulations on New Therapy and Human Experimentation," (Appendix 3). There is controversy regarding the legal force of the 1931 guidelines.[82]

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[79] Grodin, *ibid.* at 122, 137-138. Evidence of widespread, ethically suspect medical research in countries other than Germany must have disturbed the judges at Nuremberg. The judges realized that although there were existing codes and regulations dealing with standards of human experimentation prior to the Tribunal, there was significant disparity among them.

[80] *Ibid.* at 122-127 & 137.
See also: J. Katz, "The Nuremberg Code and the Nuremberg Trial, A Reappraisal," (1996) 276 JAMA 20 at 1665. [hereinafter "Nuremberg Code: A Reappraisal"]

[81] Grodin, *supra* note 2 at 127-128. This document may be the first to specifically recognize the need for the protection of uniquely vulnerable populations such as minors or incompetents. It demands unequivocal consent and requires disclosure. This 1900 document is critical in the history of human experimentation guidelines. It goes beyond setting standards for ethical conduct of research, and provides procedural mechanisms to ensure responsibility for experimentation.

[82] *Ibid.* at 129 & 131. Some argue that these guidelines are more inclusive than The Code, as they demand that the medical profession take complete responsibility for carrying out human experimentation.
See: Perley, Fluss, Bankowski & Simon, *supra* note 78 at 151; H.-M. Sass, "The Nuremberg Code, German Law and Prominent Physician-Thinkers," (1997) 277 JAMA 9 at 709.
See also Levine, *supra* note 13 at 69 referring to: Sass, H.M., "Pre-Nuremberg German Regulations Concerning New Therapy and Human Experimentation," (1983) 8 J. Med. Philosophy at 99-111.

Despite the existence of the 1931 Guidelines, the Nazi physicians were either unaware of them or their force of law, or chose to disregard them. Whatever the status of the prewar standards–whether based on medical ethics, statutory, or administrative law-- all of these codes were violated. Perhaps the judges at Nuremberg incorporated the Nuremberg Code as part of their legal judgment to ensure its place in common law, hoping that once established in international criminal law, The Code would be widely disseminated and, if followed, would guard against future atrocities. [83]

Criticism of the Code

Criticisms of The Code include: 1) inapplicability to modern research which is therapeutic; the judges may not have envisioned The Code as a universal statement of ethics, as they focussed on competent, unconsenting prisoners and deleted reference to incompetent patients and proxy consent in Alexander's memorandum;[84] 2) The Code does not differentiate between clinical research on healthy subjects for the advancement of scientific knowledge and clinical research with therapeutic objectives; 3) there are no mechanisms to review a researcher's actions and 4) The Code has been ignored (Tuskegee, Jewish Chronic Disease Hospital). A set of "universal principles" with no legal or professional authority, will only succeed if researchers choose to comply;[85] 5)The Code has seldom been cited;

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[83] Grodin, *supra* note 2 at 138.

[84] *Ibid.* at 139.
Contra Katz, *supra* note 16 at 1662. Katz argues that the judges did intend The Code to apply to the practice of human experimentation generally, and was not restricted to the issues in the case before them and provides reasons for his view.

[85] Perley, Fluss, Bankowski, & Simon, *supra* note 78 at 156-157.

where it has, it is in the dissent; it has not been used as the basis for awarding monetary damages to a victim of human experimentation and has not formed the basis for a criminal charge in the U.S [86] "The Nuremberg Code remains more of a statement of ethics than of law in the United States."[87] [88] [89]

The Code's Impact

The Nuremberg Code is often cited as a leading influence on later international and national codes on the ethics of research involving human subjects.[90] The Code raised the consciousness of the world and stimulated public debate regarding human experimentation.[91]

Principle 1, concerning voluntary, uncoerced, informed and comprehended consent, may be its most important contribution. National and international codes have adopted the

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[86] Annas & Grodin, eds., *supra* note 2 at 148.
See also: Annas, *supra* note 49 at 217-218. Even though The Code is rarely cited, Principle One is the primary justification for therapeutic experimentation and informed consent.

[87] Annas & Grodin, *ibid.*

[88] Faden, Lederer, Moreno, *supra* note 39 at 1667 & 1669. The Doctors Trial received limited coverage in the popular press.

[89] L.H. Glantz, "The Influence of the Nuremberg Code on U.S. Statutes and Regulations," in Annas & Grodin, *supra* note 2 at 198. U.S. Federal regulations relating to fetal research come the closest to adoption of the Nuremberg principles. See reference for discussion of federal and state laws relating to fetal research.

[90] G.J. Annas & M.A. Grodin, eds. "The Role of Codes in International and U.S. Law," in Annas & Grodin, *supra* note 2 at 147 . [hereinafter "Role of Codes"] The Code did have a profound effect on the U.S. regulation of research on prisoners and on fetuses.

[91] Perley, Fluss, Bankowski & Simon, *supra* note 78 at 152.

principle of informed consent.[92] "In some respects, it has become the *sine qua non* for human experimentation."[93]

The Code's principles are divided into two areas, by differing approaches to the issue of protection of human subjects: 1) the first, protecting the rights of subjects; 2) the second eight provisions, directed at the researcher, protecting the subjects' welfare. The Code's requirements are directed at the researcher, and not at the institution that sponsors the research or in which the research is conducted. The Code does not require the involvement of any review board or similar bureaucratic entity. The Code contains 10 statements about human decency, requiring no special training in law, ethics, or medicine to formulate. Putting these standards in writing, ensured that future researchers could not claim to be unaware of them.[94]

The standard of the Nuremberg Code has not been fully attained in the United States or elsewhere in the world. National security and "medical progress" have relegated human rights to a secondary position.[95] However, the power of The Code's declaration, to respect persons, was too strong and prevailed, though diluted, in later codifications and regulations.[96]

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[92] *Ibid.* at 155.

[93] *Ibid.* This principle is criticised as it is phrased in absolute terms. Beecher and others stated that adherence to this provision effectively curtails the study of mental illness and children's diseases, as neither population (the mentally ill or children) has the legal capacity to give consent.
See also: Katz, *supra* note 80 at 1665.

[94] Glantz, *supra* note 89 at 197.

[95] Annas, *supra* note 49 at 219.

[96] Katz, *supra* note 64 at 228.
See also: Katz, *supra* note 80 at 1663.

The Code's steadfast first principle was soon removed from its lofty position by the 1964 Helsinki Declaration of the World Medical Association and in the U.S., by the Rules and Regulations for the Protection of Human Research Subjects promulgated by the Department of Health and Human Services. Physician-scientists in the West distanced themselves from Nuremberg. They praised the Code as a fitting response to an unprecedented aberration of medical experimentation and rejected it as irrelevant to research practices in the rest of the Western world. "The spirit of the Nuremberg Code was not, and perhaps could not be taken seriously."[97] Its language was too uncompromising and too restrictive to the advancement of science. Later codes re-introduced the idea of giving physician-scientists the responsibility of balancing patient-subject's interest against the advancement of medicine. The first principle requiring voluntary consent establishes the significance of the Nuremberg Code then and now. Auschwitz revealed, more starkly than ever, human's capacity for aggression.[98]

The Code prohibits the objectification of the research subject by requiring their voluntary, competent, informed and understanding consent. The challenge after Nuremberg is to "protect the individual humanity of the human subject of medical research while permitting medical experimentation, and thus, progress."[99]

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[97] Katz, *supra* note 64 at 235.

[98] Katz, *ibid.* at 227-28, 231, 235-237.
See also: Perley, Fluss, Bankowski & Simon, *supra* note 78 at 150; W.K. Mariner, "AIDS Research and the Nuremberg Code," in Annas & Grodin, *supra* note 2 at 286. The Helsinki Declaration and WHO/CIOMS Guidelines (details to follow later), shifted the focus from voluntary consent to independent review of the risks and benefits of research, due in part, to increased opportunities for therapeutic research.

[99] Annas & Grodin, *supra* note 67 at 307-308.

Summary

The Nuremberg judges did not rely on the existence of "civilized standards" among future professionals-- doctors or government officials. They provided the individual patient/subject with the principle of self-determination as a first line of defence against future abuse.[100]

The Doctors Trial is a historical landmark in the application of international criminal law. The decision established that medical professionals have ethical and international legal duties which go beyond domestic law.[101]

The Doctors Trial resulted in making new international law. The Nuremberg Principles (which recognize crimes against humanity and war crimes), when combined with the 1948 Universal Declaration of Human Rights, can be seen as the birth of the international human rights movement. "Human rights law and medical ethics are both universal and aspirational, and since the Nuremberg trials, both have been unenforceable."[102] International human rights law and codes of medical ethics are not sufficient to prevent human rights abuses by physicians. The authors proposed an international human rights court to adjudicate and punish violators of human rights.[103]

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[100] R.A. Burt, "The Suppressed Legacy of Nuremberg," (1996) 26 Hastings Center Report 5 at 31.

[101] Lippman, *supra* note 65 at 395.

[102] Grodin & Annas, *supra* note 65 at 1682-1683.

[103] *Ibid.* The authors set out the responsibilities of physicians and lawyers in preventing violations of human rights. Since this article was published in 1996, many countries in the world have established the International Criminal Court which does have authority to indict, try and punish war criminals.

Medical ethics was forever changed after the Holocaust. " The Nuremberg Tribunal attempted to light the way to a reconstituted moral vision... It is this vision that makes the Nuremberg Code the cornerstone of modern human experimentation ethics."[104]

Some authors argue that the Declaration of Helsinki and peer review have eclipsed informed consent as a *sine qua non* of ethical research throughout the world, but others argue that the Nuremberg Code remains the foundational document and retreat from it will come only at the expense of the experimental subject's human rights.[105] Physicians have special responsibilities to protect human rights. Medical ethics without human rights is no more than hollow words.[106] Annas and Grodin do not think that The Code is irrelevant to modern medical research and believe efforts to marginalise it are due to the belief that if research is important to society, ways should be found to circumvent consent.[107]

The Nuremberg Code was formulated decades before the immergence of bioethics. It was the field of law and not bioethics, which first incorporated the concept of consent in medicine. [108]

"Moral lessons are quickly forgotten. Medical ethics is more fragile than we think."[109] Pellegrino states that medical power is too great to be left unregulated. "Perhaps above all,

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[104] Grodin, *supra* note 2 at 140.

[105] Annas & Grodin, eds. *supra* note 2 at 147.

[106] Grodin & Annas, *supra* note 65 at 1683.

[107] Annas & Grodin, *supra* note 67 at 309-310.

[108] Katz, *supra* note 80 at 1665.

[109] E.D. Pellegrino, "The Nazi Doctors and Nuremberg: Some Moral Lessons Revisited," (1997) 127 Annals of Internal Medicine 4 at 307.

we must learn that some things should *never* be done."[110] We must never forget the lessons of Nuremberg, if we want to be sure that the moral abyss revealed there never occurs again.[111]

"The Nuremberg Code stands alone as the most eloquent and principled statement of the significance of human rights in the conduct of research involving human subjects."[112]

2. **Declaration of Helsinki** (Appendix 3)

The influence of the Nuremberg Code is reflected in the activities of the World Medical Association (hereinafter WMA) founded in 1947. Revelations at the Doctors Trial and formulation of The Code, led the founding physicians to decide that professional ethical codes and guidelines were immediately required.[113]

The international medical community participated in a "global attempt to bring the standards enunciated in the Nuremberg Code into line with the realities of medical research."[114]

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[110] *Ibid.* at 308.

[111] *Ibid.* at 307-308.

[112] Faden, Lederer, Moreno, *supra* note 39 at 1670.

[113] Perley, Fluss, Bankowski & Simon, *supra* note 78 at 154.
See also: P. Riis, "Research ethics--a widening of the scope and extrapolation into the future," (1995) 238 Journal of Internal Medicine at 521; Gray, *supra* note 62 at 7. The ethics of human experimentation has resulted in at least thirty different guidelines and codes of ethics since World War II.

[114] Faden, Lederer & Moreno, *supra* note 39 at 1670.

The WMA's Committee on Medical Ethics began discussing human experimentation in 1953. They recognized that there was a need for *"professional* guidelines designed by physicians for physicians" (as opposed to The Code, drafted by jurists in a legal trial).[115]

Physicians saw The Code as applying to the Nazi atrocities and found it too legalistic and irrelevant to their therapeutic experiments. The most successful and influential alternative code has been the WMA's Declaration of Helsinki, (hereinafter Declaration), subtitled "Recommendations Guiding Doctors in Clinical Research," adopted in 1964 and amended four times since. [116]

The Declaration set out the rules for "Clinical Research Combined with Professional Care" (physicians were required to obtain consent from patient-subjects only when 'consistent with patient psychology'), and "Non-therapeutic Clinical Research," (where the consent requirements were more absolute). Another deviation from The Code is the Declaration's allowance (in both types of research) for third-party authorization from a legal guardian.[117]

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[115] Perley, Fluss, Bankowski & Simon, *supra* note 78 at 154-155 & 157. In 1949 the WMA's General Assembly adopted the International Code of Medical Ethics. While human experimentation is not referred to, one can detect the principles of The Code in the WMA documents.
See: Mariner, *supra* note 98 at 289.

[116] Annas, *supra* note 86 at 204-205.
The latest draft of the Declaration ratified in 1996 is in Appendix 4.

[117] Faden, Lederer & Moreno, *supra* note 39 at 1670
See also: O. Dale & M. Salo, "The Helsinki Declaration, research guidelines and regulations: present and future editorial aspects," (1996) 40 ACTA Anaesthesiologica Scandanavica at 771.

The Declaration met with widespread approval among researchers in the U.S. Compared with the idealized language of The Code, the Declaration offered rules that took into account actual research practice in the clinical setting.[118]

Helsinki I provides for consent of a legal guardian. The requirement of informed consent is less stringently worded in Helsinki I than in The Code.[119]

The Declaration was first revised in Tokyo in 1975, following consultation with the World Health Organization. Helsinki II, (1975) further revised in 1983, 1989 and 1996, is recognized as providing fundamental guiding principles for the conduct of biomedical research with human subjects. It has been adopted, in modified form, in international texts and national legislation and by medical organizations throughout the world. The revised Declaration corrects problems noted in the Nuremberg Code. The most significant change from Helsinki I to Helsinki II is the addition of ethics review committees. Helsinki II requires that the protocol for each experimental procedure "be transmitted to a specially appointed independent committee for consideration, comment and guidance."[120] Helsinki II emphasizes informed consent and (like Helsinki I), differentiates between research with potential therapeutic value and research for the advancement of scientific knowledge.[121]

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[118] Faden, Lederer, Moreno, *supra* note 39 at 1670.

[119] Perley, Fluss, Bankowski & Simon, *supra* note 78 at 158.
See also: Katz, *supra* note 80 at 1665. The quality of consent in the Declaration was left ambiguous and not as stringent as that articulated in The Code.

[120] Perley, Fluss, Bankowski & Simon, *ibid.*, at 159.
See also: Levine, *supra* note 13 at 322 for discussion of peer review.

[121] Perley, Fluss, Bankowski & Simon, *ibid.*

Although highly influential, neither The Code nor the Declaration of Helsinki has any legally binding authority. Their rules are unaccompanied by any controls, traditional sanctions or means of enforcement. The general nature of these codes highlights the need for national legislation and/or international documents with binding authority.[122]

The 1989 Declaration stresses "medical progress" over "interests of subjects."[123]

The Declaration of Helsinki reflects a more modern attitude toward biomedical research than The Code. The Declaration confirms faith in science.[124]

In summary, attitudes are more important than specific wording of guidelines, or national legislation. If the scientist respects the patient, guidelines help to structure and reaffirm the ethical aspects. Without respect for the individual, no rules can adequately control the situation.[125]

3. Council for International Organizations of Medical Sciences (CIOMS)/World Health Organization (WHO) & Council of Europe

CIOMS established by UNESCO and WHO in 1949, is an international nongovernmental scientific organization which coordinates medical congresses and provides

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[122] *Ibid.*, at 160.
See also: Annas, Glantz, Katz, *supra* note 48 at 9 for a discussion of how these documents might be viewed as "law" when adopted as standards of care and establishment of duty to the subject.

[123] Katz, *supra* note 64 at 231 & 234-235. The U.S. Rules and Regulations for the Protection of Human Research Subjects promulgated by the Department of Health and Human Services set out the basic elements of informed consent. They are more consistent with the Declaration than The Code. However, there are wide exceptions.

[124] W.K. Mariner, *supra* note 98 at 289-290. The U.S. Food and Drug Administration (FDA) adopted the Declaration and not The Code for its regulations.

[125] P. Riis, *supra* note 113 at 527.

an international forum for the discussion of scientific and theoretical questions relating to new advances in biomedicine. It sponsors annual Round Table Conferences to facilitate an exchange of opinions on the social, moral, administrative, legal and ethical aspects of new developments in biology and medicine. Many conferences have dealt with medical ethics.[126] The WHO's "Proposed International Ethical Guidelines for Human Experimentation" were issued in 1982. They attempt to assist developing countries establish a system of scientific and ethical review of research projects and to protect potential subjects. The Nuremberg Code and Declaration of Helsinki define international standards for medical ethics, but they are quite broad and difficult to apply. The developed countries have additional safeguards, such as research ethics committees to protect the rights and welfare of subjects.[127] The word *Proposed* does not mean they are in draft form, but that they are proposed to countries as guidelines to consider as national standards. The Guidelines suggest the means for actually implementing ethical principles on a national level, remedying the problems endemic to international codes. [128]

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[126] E. Miller, "International Trends in Ethical Review of Medical Research," (1981) 3 IRB A Review of Human Subjects Research 8 at 10 for examples of topics covered.
See also: Perley, Fluss, Bankowski, & Simon, *supra* note 78 at 161.

[127] Miller, *ibid.* at 9.

[128] Perley, Fluss, Bankowski, & Simon, *supra* note 78 at 160-161.
See: CIOMS, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, (Geneva, Switzerland: CIOMS/World Health Organization, 1993) at 5.

The 1993 CIOMS guidelines, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* supercede the 1982 *Proposed International Guidelines.* The revised guidelines have similar objects to the 1982 Guidelines.[129]

The CIOMS guidelines are based on U.S. standards of ethical review and on international codes, utilizing the principle of informed consent and prior scientific and ethical assessment of protocols by an independent body.[130]

The Nuremberg Code and the Declaration of Helsinki designed by Westerners and based on Western ethical principles are not necessarily applicable to other cultures. Like The Code and Declaration, the Guidelines do not have the force or specificity of a legal text. They are designed to provide an operational approach to the ethics of medical research, for countries without a regulatory requirement for the ethical review of research protocols.[131]

The Guidelines differ from previous international codes in advocating training of local health personnel to carry out similar research projects independently and discussing compensation for injury, of research subjects. The fundamental underlying principle of the Nuremberg Code--protection of the research subject's rights and welfare--has not changed.[132]

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[129] CIOMS, *ibid.* at 6-7.
See: M.T. Claessens, J.L. Bernat and J.A. Baron, "Ethical issues in clinical trials," (1995) 76 British Journal of Urology Suppl 2 at 31. The CIOMS Guidelines are guidelines, not regulations.

[130] Miller, *supra* note 126 at 9.

[131] Perley, Fluss, Bankowski & Simon, *supra* note 78 at 162.

[132] *Ibid.* at 165.

Council of Europe

In 1990, the Council of Europe's Committee of Ministers adopted Recommendation (No. R. (90) 3) which sets out principles to protect the human rights and health of persons undergoing medical research, emphasizing the absolute necessity of obtaining informed consent. It marks a definitive turn away from the Declaration of Helsinki and the WHO/CIOMS Guidelines and it resembles the Nuremberg Code much more than any other international document in relation to consent.[133]

Ethical guidelines for biomedical research involving human subjects will not resolve all the moral and ethical issues, but they will raise sensitivities of investigators, sponsors and ethical review committees to the need to consider the ethical implications and contribute to high scientific and ethical standards of research. [134]

4. Good Clinical Practice Guidelines (GCP)

"Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance

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[133] Council of Europe, Recommendation No. R (90) 3 of the Committee of Ministers to member states concerning medical research on human beings. Strasbourg: 1990 in (1990) 41 "Int'l Dig. Hlth. Legis" at 461-465, Principle 10; Council of Europe document CAHBI (89) 11 at 17.
See: Perley, Fluss, Bankowski & Simon, *ibid.* at 167.
See also: Council of Europe, Convention for the Protection of Human Rights & Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Strasbourg: Directorate of Legal Affairs), November 1996

[134] CIOMS, *supra* note 3 at 7.
For references to other international documents see: NCBHR, (1995) 6 Communiqué 2 at 10; WHO (1995) Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products

that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible."[135]

World Health Organization (WHO) - GCP

"The WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products provide global standards for the conduct of biomedical research on human subjects. The Guidelines are directed to investigators, REBs, pharmaceutical manufacturers and other sponsors of research and drug regulatory authorities."[136]

The WHO GCP Guidelines set out the prerequisites for a clinical trial and for the protection of trial subjects. Independent assurance that subjects are protected can only be provided by an ethics committee review and freely-informed consent. The aims of the REB are to ensure protection of the rights and welfare of human subjects involved in research and to reassure the public by reviewing trial protocols. The REB and the investigator should be guided by the Declaration of Helsinki and governed by national and other relevant regulations. The document sets out the REB's ongoing responsibilities for the ethical conduct of research. [137]

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[135] Health Canada, *Good Clinical Practice: Consolidated Guideline, ICH Harmonised Tripartite Guideline, Therapeutic Products Directorate Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (Ottawa: Minister of Public Works and Government Services Canada, 1997), at 1. [hereinafter Health Canada *ICH-GCP*]

[136] Juhana Idänpään-Heikkilä, "WHO Views on Responsibilities of Research Ethics Boards and Good Clinical Practice (GCP)," (1993) 4 NCBHR Communiqué 2 at 7.

[137] *Ibid.* at 7-9.

International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline-Good Clinical Practice: Consolidated Guideline

The International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use has developed statements of Good Clinical Practice, (ICH-GCP) and other related topics. The ICH-GCP and other international statements have been adopted by the Therapeutic Products Directorate of Health Canada. ICH-GCP was adopted by Health Canada in September 1997. It supercedes the Drug Directorate's 1989 guideline entitled "Conduct of Clinical Investigations." The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions and to reduce product approval process time and associated barriers.[138]

The ICH-GCP Guidelines focus on industry funded research and the Tri-Council Policy Statement (detailed discussion follows) is directed to Council funded research. Most investigators and institutions are doing both. Health Canada has adopted the ICH-GCP guidelines, broadening their impact. One must be in compliance with ICH-GCP to obtain Health Canada approval.

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[138] Health Canada, *supra* note 135 at i, 7-9, 13, 15-17 & 19. ICH-GCP sets out the responsibilities of the investigator and sponsor; composition and procedures of the REB; includes a definition of monitoring; it provides detail on the responsibilities of the REB, including continuing review. Health Canada has adopted the ICH-GCP, but they have not been incorporated into regulation. According to the Director of the Therapeutic Products Program of Health Canada, the intent is to create a 'made-in-Canada' Good Clinical Practice Guideline. (Response to question at a meeting of a committee of MRC).

III. American Model – Regulations

1. Development of Regulations and a System of Institutional Review Boards (IRBs)

The regulation of the research process, its structures and current issues in research involving human subjects in the U.S. is presented as the U.S. is the leader in grappling with the issues in research. The issues in human experimentation in the U.S. today are relevant to research with human subjects generally, regardless of the form of regulation of the research enterprise.

Social control mechanisms are an important element of human medical research in the U.S. Controls over research with humans, began as intraprofessional. They became external, administered by bureaucrats and governed by regulation because internal controls were not effective in ensuring ethical conduct of researchers. However use of external controls also presents problems.[139]

Specialization, advances in medical knowledge and technology and extensive support from government for biomedical research contributed to increasing external controls. Extraprofessional controls responded to examples of unethical use of subjects and were required due to the historic unwillingness of the medical research community to regulate itself. Governmental regulation of medical research will likely continue.[140]

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[139] Benson, *supra* note 62 at 1-3 & 8. Some sociologists assume that science is based on widely held moral norms: universalism, disinterestedness, organized skepticism and communality. Evidence shows that this is not the case. Peer influence in and of itself, is largely ineffectual in promoting and maintaining high ethical standards.

[140] *Ibid.* at 8.

Although necessary, ultimately government regulations are of limited value. External procedures and restrictions cannot impose ethical behaviour on biomedical researchers. It is up to researchers themselves to act ethically.[141]

The history of federal control of drugs illustrates that government responded only following tragedies and the exposure of corporate negligence. The 1906 Food and Drug Law, (the first federal food and drug law), was a response to the publication of *The Jungle*, Upton Sinclair's exposé of the disgraceful conditions in the Chicago stockyards. For the first time, foods and drugs had to be "pure." The safety of these "pure" drugs was not then an issue. In 1937, 107 people died when the Massengill Drug Company produced a drug with a chemical similar to antifreeze as a solvent. The manufacturer did not test the toxicity of the product before putting it on the market. The government responded with the 1938 Food, Drug and Cosmetic Act, which required a manufacturer to prove the "safety" of a new drug before it could be marketed.[142]

Drug studies may be the most common examples of advances in biomedical research. Development of synthetic drugs began after WW II. Before the war, most drugs produced were derived from plants, i.e. opium, quinine, digitalis and salicylates. Insulin, penicillin and the sulfonamides, are examples of the few drugs developed before the war.[143]

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[141] *Ibid.*

[142] M.K. Ryan, L. Gold & B. Kay, "Research on Investigational New Drugs," in Greenwald, Ryan & Mulvihill, *supra* note 1 at 92.

[143] Mariner, *supra* note 98 at 287.

Following the Food, Drug and Cosmetic Act of 1938, there was rapid development of new synthetic chemical drugs. The greatest growth in synthetic drugs and understanding their interaction with disease was in the 1950s-1960s.[144]

Experimental testing of new drugs in humans developed after WW II and was widely accepted by the 1960s. The gold standard in drug research became the randomized clinical trial (RCT), comparing the effects of an experimental substance to results achieved without the drug.[145]

From 1938 to 1962 there were many drug-related safety problems, which culminated with thalidomide.[146]

It was obvious after a series of highly publicized events in the 1960s, (thalidomide, Willowbrook and later, Tuskegee), that a professional code would not sufficiently protect human subjects from abuse.[147]

The most detailed codification of the regulation of research occurred at the federal level in the United States (See Appendix 7 for details of development of regulations in the U.S.).

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[144] *Ibid.* at 288. Cortisone, chloroquine, polio vaccine, tranquilizers, anticholinergics, antihypertensives and diuretics were introduced. The public supported regulating potentially harmful chemicals to avoid the exploitation of the public.

[145] *Ibid.* Subjects in RCTs receive the experimental drug and their responses are compared with those of controls, subjects who received placebo or nothing at all. The preferable method to achieve accuracy in research is the double-blind, randomized clinical trial, where neither the subject nor the researcher knows which of the drugs being compared, a particular subject is receiving. This is done to avoid researcher and subject bias in looking for specific results.

[146] Ryan, Gold & Kay, *supra* note 142 at 93 .

[147] Faden, Lederer & Moreno, *supra* note 39 at 1670.

The Clinical Centre of the National Institutes of Health (NIH) adopted guidelines that applied to the use of normal volunteers in 1953. Beginning in 1962, the federal government became more formally involved in the regulation of research.[148]

Federal law in the 1960s, forbid interstate distribution and marketing of new drugs until they had federal Food and Drug Administration (FDA) approval regarding safety and effectiveness. Approved drugs, licensed by the federal government were accepted therapies; those not formally approved, were experimental.[149]

The view that experimental drugs were beneficial became prevalent in the 1960s. New drugs were intended to treat or prevent illness. People understood that testing new drugs in humans was a necessary step in preventing, alleviating, or even curing disease, that experimentation may have unforeseeable serious adverse reactions or side effects, and that the only way to find out whether a drug was safe and effective was to test it on people. Testing experimental drugs in human subjects is now generally considered desirable.[150]

Access to experimental drugs prior to FDA approval is through clinical trials. Patients wanting access to these drugs must participate in trials as subjects. The patient views the purpose of the experimental drug the same as an approved drug–as a method of

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[148] Benson, *supra* note 62 at 4.

[149] Mariner, *supra* note 98 at 289.

[150] *Ibid.*

treatment, leading to recovery. The distinction between treatment and experimentation is blurred.[151]

2. State Regulation

There is little state regulation of research as so much research is regulated by the federal government, due to federal funding and regulations. Research with human subjects that is not federally regulated remains unregulated if there is no state law. The extent of unregulated research is unknown. Prior to 1970, there was no state law to protect human subjects. In the 1980s, a number of states enacted legislation relating to human subject research, which closed gaps in federal regulations. State law usually included informed consent.[152] California, New York and Virginia have legislation relating to human research, which is not included in federal regulation.[153]

3. Case Law

The limited number of court decisions involving human experimentation make it difficult to consider the "common law" of human experimentation. As a result, codes, especially judicially drafted codes like the Nuremberg Code, are significant.[154]

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[151] *Ibid.* at 290. Experimental drugs are sometimes provided by physicians to patients who have not responded to any accepted treatment, for "compassionate use," (ie. AIDS, HIV and cancer)
See also: Ryan, Gold & Kay, *supra* note 142 at 95. Reference to compassionate use of investigational new drugs outside of organized research projects, for patients who have not responded to conventional therapy. Medical staff committees in hospitals have a role relating to drug utilization.

[152] Benson, *supra* note 62 at 7 .

[153] Glantz, *supra* note 89 at 194.

[154] Annas, *supra* note 86 at 202.
See: Benson, *supra* note 62 at 6-7 for references to cases in 1970s and 1980s dealing with issues of research. The courts' influence in development of legal controls in human subjects research has been limited, but cases dealing with research have increased in recent years.

U.S. courts first cited the Nuremberg Code in 1973, decades after The Code was promulgated. Reasons for the delay in adopting The Code as the minimum standard of care in human research are: 1) there was little opportunity to do so, as almost no experiments resulted in lawsuits in the 1940s, 1950s and 1960s, and 2) the Nazi experiments were considered so extreme as to be irrelevant to the U.S., (despite many U.S. examples discussed earlier, of abuse of vulnerable populations, especially during WW II). Utilitarianism was the prevalent philosophy.[155]

Today, we consider research necessary for progress, and view therapeutic research as simply therapy. Many people demand research as a right. Even Phase 1 cancer drug research and first-of-their-kind transplants and implants, (traditionally viewed as nontherapeutic), are considered by some as simply therapy, or innovative therapy. The Nuremberg Code has not even been applied to situations of nontherapeutic experimentation where individual rights have been outweighed by national security concerns, with dire consequences for subjects.[156]

4. Organization and Regulation of the IRB

Since 1971, all federal guidelines and regulations have mandated that a local, institutionally supported committee, be responsible for protecting the rights and safety of human subjects of biomedical research. Succeeding federal regulations have increased IRB responsibility. The 1981 Department of Health and Human Services (DHHS- formerly

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[155] Annas, *ibid.* at 204.

[156] *Ibid.* at 218-219. Refer to earlier discussion of radiation experiments conducted by the government/army during the Cold War.

Department of Health, Education & Welfare - DHEW) regulations apply to all research it funds or controls.[157]

The IRB is the cornerstone of the regulation of human subjects research in the U.S. IRBs provide professional control through a combination of "centralized government oversight and decentralized peer review."[158] They focus on prospective review and evaluation of the ethics of proposed human subjects research. The IRB system is a decentralized system of institutionally controlled review boards. [159]

The regulatory structure for overseeing biomedical research is on two levels---local (research institutions-IRBs) and federal. Both levels must ensure that researchers and institutions conducting research projects funded federally, comply with federal laws and regulations governing human subjects protection.[160]

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[157] Evans, *supra* note 10 at 24-25 for discussion of initial and added responsibilities of IRBs. The 1981 regulations give the IRB the explicit authority to suspend or terminate approval of research which is not conducted according to the IRB's requirements or that has resulted in unexpected harm to subjects, as well the responsibility for reporting noncompliance to HHS's Office for the Protection from Research Risk (OPRR).

[158] Benson, *supra* note 62 at 5.
See Appendix 7 for details of U.S. regulatory development. IRB was legislated in 1974, consistent with National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report, Ethical Principles & Guidelines for the Protection of Human Subjects in Research*, 1978, DHEW Publication No. (OS) 78-0012 which recommended that ethical review take place locally. [hereinafter *The Belmont Report*].

[159] *Ibid.* at 4-5. Federal regulations direct that IRBs: a) ensure that subjects' rights and welfare are adequately protected; b) risks to subjects are minimized and are reasonable in relation to anticipated research benefits and c) subject informed consent is obtained by adequate and appropriate means.

[160] J.Bell, J. Whiton & S. Connelly (James Bell Associates), *Final Report, Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects*, Prepared for the Office of Extramural Research, National Institutes of Health, June 15, 1998; online: National Institutes of Health <http://www.nih.gov> i-x, 1-86 at 3. [hereinafter *Bell Study*] See Appendix 17 for detailed descriptions of findings and recommendations of most current reviews of the adequacy of current oversight of human subjects protection in the U.S.
IRB judgments reflect institutional values, institutional pressures and community standards.

The IRB system is based on two sets of federal regulation. The first is the Department of Health and Human Services (DHHS: National Institutes of Health- NIH-and Office of Protection from Research Risks-OPRR), which has promulgated regulations and policies governing the protections for human subjects participating in Federally-supported research. The DHHS regulations (*45 CFR 46*) are under the *Public Health Service Act* as amended. Further policy guidance is provided in *Protecting Human Research Subjects, Institutional Review Board Guidebook* (1993) and in periodic "Dear Colleague" letters issued by the OPRR.[161] To receive federal funding from the DHHS, institutions must provide assurance to the DHHS that an IRB has reviewed and approved the research and that it

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At the federal level of review, the NIH OPRR negotiates and approves Assurances of Compliance (AOC) –contract-like agreements that must be entered into by research institutions before conducting federally-funded human subjects research.

The *Bell Study* refers to the General Accounting Office (GAO) report [*Scientific Research-Continued Vigilance Critical to Protecting Human Subjects,* GAO-HEHS-96-72 March 1996] which focussed on the DHHS's oversight of its $5 billion investment in research involving human subjects. At page 82, the GAO report voiced concerns about the continuing/annual review process, including the superficiality of the reviews (if performed at all).

[161] *NIH Regulatory Burden v. Human Subjects Protection, Workgroups Report*, April 15, 1999, at 1-4 online: National Institutes of Health <http://www.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm>[hereinafter *NIH Workgroups*] Subpart A of these regulations governs the programs of 17 Federal agencies which support or conduct research with human subjects and is referred to as the "Common Rule" or "Federal Policy." Subparts B-D of the regulations apply only to research supported by DHHS.

DHHS regulations require among other things: written procedures for initial and continuing review, the IRB must conduct continuing review of protocols at intervals appropriate to the degree of risk but not less than once a year, that the IRB must be satisfied that the investigator made appropriate provision for monitoring to ensure subject safety.

See: H. Edgar & D. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation," (1995) 73 The Millbank Quarterly 4 at 490-491. DHHS (NIH-OPRR) requires various U.S. government agencies to obtain IRB approval (from an institutionally based committee), before research is conducted on human subjects, either in house or through grants they fund for outside projects (45 Code of Federal Regulations 46.101 et seq.). Although the federal regulations apply only to federal activities and federally funded grants, many states require IRB review for all research performed within their jurisdiction, regardless of funding source. Most academic institutions choose to review all their research protocols through an IRB, without regard for how they are funded. IRB regulations do not require the review of all innovations in medical practice. The IRB is responsible for activities intended to gain generalizable knowledge (research).

adheres to federal regulations.[162] The first three DHHS requirements in the regulations, deal with the nature of the research. The remainder deal with informed consent. The three major principles underlying IRB review are: scientific merit, subject selection and risk/benefit ratio.[163]

The Federal government also regulates human subjects protections through the Food and Drug Administration (FDA). FDA regulations are different from DHHS regulations as their application does not depend on federal financial support. They apply to any FDA-regulated article and require that protocols involving human subjects and new drugs or medical devices must be approved by IRBs. The FDA regulations, *21 CFR 50 and 56*, apply to Informed Consent and Institutional Review Boards. These regulations are under the *Federal Food, Drug and Cosmetic Act*, as amended.[164] FDA oversight differs from DHHS

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[162] R.A. Greenwald, "General Principles of IRB Review," in Greenwald, Ryan & Mulvihill, *supra* note 1 at 52.
See: *NIH Workgroups*, *supra* note 161 at 2 & 3.

[163] Greenwald, *ibid.* at 52.

[164] *NIH Workgroups*, *supra* note 161 at 1 & 4. The FDA published its own regulations for IRBs and Informed Consent for evaluation of FDA-regulated test articles. Generally, these regulations are consistent with the Common Rule, but differences do exist. beyond those dictated by the different missions of the agencies. The FDA goal is to inspect each IRB every five years. See more detailed discussion in Appendix 8.
See also: B. Gordon & E. Prentice, "Continuing Review of Research Involving Human Subjects: Approach to the Problem and Remaining Areas of Concern," (1997) 19 IRB A Review of Human Subjects Research 2 at 8. Neither the DHHS or FDA regulations specify either criteria or procedures for IRB reapproval of ongoing research. Neither FDA or OPPR focussed on the quality of continuing review until 1994. Discussion of University of Nebraska Medical Centre system of continuing review, utilizing data submitted by investigator, rather than review of records by IRB; R.B. Weiss, N.J. Vogelzang, B.A. Peterson, L.C. Panasci, J.T. Carpenter, M. Gavigan, K.Sartell, E. Frei III, O.R. McIntyre, "A Successful System of Scientific Data Audits for Clinical Trials, A Report from the Cancer and Leukemia Group B (CALGB), (1993) 270 JAMA 4 at 459-464. FDA performs audits of clinical trials sponsored by drug manufacturers, but does not do so for trials funded by National Cancer Institute, which are mostly conducted by cooperative groups. U.S. regulations and enforcement of monitoring by FDA are not as extensive and complete as one would anticipate.

in several important respects.[165] The FDA procedures do provide some degree of national oversight for clinical research. However, many human experiments do not fall under FDA or NIH supervision. This leaves decisions about the ethics solely in the hands of the IRB.[166] Industry funded clinical research (relating to drugs or medical devices) falls under FDA regulation. Other research with human subjects not involving drugs, medical devices or federal funding, is not covered by federal legislation, though institutions may apply the same standards as for federally funded research.

Federal government regulations provide general specifications about membership, quorum requirements, and the principles that IRBs must follow in making their decisions, but do not give direction on the organizational structure and functioning of the board.[167] Each IRB then implements the regulations in the context of its institution.[168]

Appointment to the IRB should be made by a person of stature and credibility in the institution, as the appointment process affects how the IRB is viewed in the institution.[169] In Levine's opinion, the most important factor contributing to the success of the IRB, is its credibility within the institution.[170] The layman's role on the IRB is to bring community

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[165] See Appendix 8 i.e. FDA reviewers determine the merits of the protocol; not all decisions left to the IRB.

[166] Edgar & Rothman, *supra* note 161 at 491.

[167] M.K. Ryan, "General Organization of the IRB," in Greenwald, Ryan & Mulvihill, *supra* note 1 at 29. For discussion of specific issues not dealt with in the regulations, i.e. no legislative direction regarding selection of IRB members, leadership responsibilities of the board, lay or community representatives and organization of the board for purposes of review.

[168] Greenwald, *supra* note 162 at 51.

[169] Ryan, *supra* note 167 at 29-30.

[170] Levine, *supra* note 13 at 341-347. Levine discussed factors relevant to IRB credibility.
See also reference on page 347 to: Caplan A.L.," Random Auditing–A Modest Proposal for Reforming the

perspectives and concerns to the discussion and to identify incomprehensible consent forms.[171]

Most institutions require departmental chairmen to sign the IRB application for review, providing evidence of scientific review and support. The credentials of the investigator are also an important and integral part of the review.[172]

To be effective, an IRB must include interested, knowledgeable persons, supported by adequate staff, with sufficient time to conduct such reviews. The institution must provide all the resources (financial and administrative) required to adequately perform the job.[173]

A creditable IRB, supported by administration and a monitoring system is required to prevent unapproved research being conducted, subjects being enrolled without giving consent or investigators failing to comply with IRB directions.[174]

Regulation of Research," (1983) 31 Clin. Res. 142-143 Caplan proposes a system of random IRB audit, where only a small number of protocols would be required to submit to the IRB review process. Researchers who fail to comply with regulations, would lose their exemption from the randomization process and all their subsequent protocols would require IRB review; Greenwald, *supra* note 162 at 60.

[171] Ryan, *supra* note 167 at 36.

[172] Greenwald, *supra* note 162 at 54-55.

[173] *Ibid.* at 56.
See: Medical Research Council of Canada (MRC), Natural Sciences and Engineering Research Council of Canada (NSERC) and Social Sciences and Humanities Research Council of Canada (SSHRC), *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998) at 1.2. [hereinafter *TCPS*].

[174] Greenwald, *ibid.* at 60.

Following the enactment of the Food, Drug and Cosmetic Act, the U.S. has not experienced tragedies on the scale of the Massengill Drug Company (1937).[175] [176]

5. Monitoring in the U.S.

Ideally, review boards conduct continuing review to protect human subjects and further ethical research. Monitoring untoward events, morbidity and mortality on a regular basis can detect trends suggesting that alteration or termination of a study is necessary. Compliance with the federally mandated continuing review process should be seen as a way to improve academic research providing the appropriate approach and individuals are utilized. Researchers and the IRB can learn of collective or individual problems regarding research ethics.[177]

The regulations governing the IRB do not provide a strong framework to protect subjects' interests over institutional ones. The regulations cannot protect against bodies that are negligent, inept or subservient to the institution. The quality of the IRB's work depends enormously on the conscience and commitment of its volunteer members. OPRR does not have the funds or personnel to conduct regular and ongoing examinations of how individual IRBs normally function. If OPRR does learn about a particular case (either through the

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[175] Ryan, Gold and Kay, *supra* note 142 at 104.
A contrary view has merit when considering Tuskegee and the Cold War Radiation experiments.

[176] M.K. Ryan, "Research Involving Medical Devices," in Greenwald, Ryan & Mulvihill, *supra* note 1 at 107, 109 & 111. Government regulation of medical devices was in response to the increasing complexity of technology, increasing numbers of therapeutic and diagnostic devices on the market and a general atmosphere encouraging regulation, rather than a response to a major incident of abuse. IRB approval is necessary prior to investigation of a medical device.

[177] S. Wollman & M.K. Ryan, "Continuing Review of Research, " in Greenwald, Ryan & Mulvihill, *supra* note 1 at 129.

institution, the press or the grapevine), it will investigate the incident. In 1994, the office made only 10 site visits.[178] [179]

Most researchers are aware that consent forms and prior review of projects are required, but few universities teach the history of human experimentation or the requirement for continuing review. [180]

Federal regulations permit different levels of accountability and surveillance. At a minimum, the investigator's assurances of compliance are required. In addition, IRB staff could review records and consent forms, either comprehensively or by sampling. Subjects could be interviewed to determine their understanding of the research protocols and that they had agreed to participate in research. Due to limited resources, the comprehensiveness of review procedures should relate to the magnitude of risk in the project. Where potential risks of harm to patients are more than minimal, more effort is required to protect subjects. The

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[178] Edgar & Rothman, *supra* note 161 at 493.

[179] D.F. Phillips, *"Institutional Review Boards Under Stress: Will They Explode or Change?"* (1996) 276 JAMA 1624-1626. Phillips enumerates criticisms of the IRB review process and suggests public policy direction. OPRR Director Ellis recognizes that roadblocks interfere with an IRB's ability to improve the research review process, particularly the lack of adequate support of institutional officials for their own IRBs. Phillips quotes R. Levine who offers nine suggestions to decrease the IRB workload. The OPRR has only a handful of full time staff who cannot closely supervise the thousands of ongoing experiments. Federal agencies are not prepared to oversee research themselves, so they will continue to rely on IRBs.
See also: Edgar & Rothman, *supra* note 161 at 489, 502-505 for discussion of a national ethics committee; C. Marwick, "Bioethics Advisory Commission Holds First Meeting to Define Governing Principles of Ethical Research," (1996) 276 JAMA 20 at 1627 Mandate of the National Bioethics Advisory Commission (NBAC) in the U.S, is the development of recommendations to ensure the well-being, autonomy and privacy of human subjects undergoing experimental treatment, as well as recommendations for the appropriate use of genetic information. The mandate includes appropriateness of governmental programs, policies and guidelines and regulations relating to bioethical issues and identification of broad overarching principles to govern the ethical conduct of research. The Commission shall not be responsible for the review and approval of individual projects

[180] Wollman & Ryan, *supra* note 177 at 129.

level and frequency of review required should be determined at the initial IRB review. All approved protocols must be annually reviewed; those involving more than minimal risk, more frequently.[181]

6. Critique of the Current IRB System

Findings from recent studies conducted by government agencies and consultants in the U.S. are discussed as research environments are similar in Canada and the U.S.

IRBs have generally proven successful. They have set the international standard for reviewing clinical research.

IRBs have been effective for the past couple decades because of the guidance of federal regulations. Since the formation of the IRB system in 1974, no new major transgressions in human investigations have occurred. The presence of the IRB has likely contributed to a rise in the nation's consciousness and insight into ethical issues of human subjects research. Today, IRBs are under pressure from increasing paperwork, federal regulators and economic constraints from their institutions. This situation has created a "pressure-cooker atmosphere within the IRB system, which has led government officials, university administrators, research sponsors and IRB members to wonder whether the IRB system will crack of reform."[182] Current "federal oversight of IRBs provides little basis for determining effectiveness of IRB's continuing review of approved research."[183]

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[181] *Ibid.* at 133. At initial review, the IRB should assess potential risks to subjects, rate of accrual of subject and decide on an appropriate time for review.

[182] Phillips, *supra* note 179 at 1623-1624.

[183] Department of Health and Human Services, USA, Office of Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research*, June 1998, OEI-01-97-00190, Executive Summary at iii.

The OPRR oversight focuses on upfront assurances. OPRR rarely does on-site assessments of IRB performance. FDA oversight involves on-site inspections which stress procedural compliance, not assessment of IRB effectiveness.[184]

Edgar and Rothman suggest that there should be more effective oversight mechanisms. It would be feasible for an NIH office to sample protocols from all research settings (universities, industry and government). Interviews with the subjects of the research should be included. The existence of such a procedure may help improve IRB performance.[185]

In relation to IRB oversight, Jay Katz argues against another advisory commission and in favour of a national commission with authority to regulate all research involving humans.[186]

IRBs rarely assess their own effectiveness regarding protection of research subjects. The assessment depends on the number of complaints or problems brought to their attention.[187]

[hereinafter *IRBs: Their Role in Reviewing Approved Research*]

[184] *Ibid.* FDA conducted just over 200 inspections in 1997. OPRR can assess an IRB's performance regarding protecting subjects when it conducts for-cause site visits, but due to resource constraints, it conducted only one for-cause visit between April 1997 and May 1998.

[185] Phillips, *supra* note 179 at 1626.
See also: Edgar & Rothman, *supra* note 161 at 505.

[186] J. Katz, "Do We Need Another Advisory Commission on Human Experimentation?" (1995) 25 Hastings Center Report at 29-31. [hereinafter "Another Advisory Commission?"]

[187] Department of Health and Human Services, USA, Office of Inspector General, *Institutional Review Boards: A Time for Reform*, June 1998, OEI-01-97-00183, Executive Summary, at iii. [hereinafter *IRBs: A Time for Reform*]

The first study in 1994 was the Advisory Committee on Human Radiation Experiments established to respond to allegations of abuses of human subjects in government sponsored research conducted during the cold war, and to make specific recommendations for improving the current system for protecting human subjects in research.[188] [189]

The committee found serious deficiencies in the current system for the protection of the rights and interests of human subjects. They recommended: 1) changes to the IRB system by setting out clearly the IRB's responsibilities; 2) providing subjects with meaningful information so they can differentiate between research and treatment and full disclosure of potential harm, discomfort or inconvenience , which will provide additional protection; 3) that the appropriateness of sanctions for violations of research ethics be reviewed and 4) that the system of protection be extended to non-federally funded research.[190]

Regulations and policies cannot guarantee ethical conduct. In order to avoid repeating the past, it is essential for the research community to value the ethics of research involving human subjects. Nationally, efforts must be taken to ensure the centrality of ethics in the conduct of scientists who conduct research with human subjects, as the culture of the institutions and professions controlling the enterprise, runs counter to rules demanding

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[188] Faden, Lederer & Moreno, *supra* note 39 at 1667.
See also: Meslin, *supra* note 51 at 34.

[189] Buchanan, *supra* note 52 at 27. The committee found that the so-called "national security exception" was not invoked to justify any of the morally dubious actions undertaken in any of the human radiation experiments. Deception and manipulation was justified on the basis of avoiding legal liability and public scorn.

[190] R. Faden, "The Advisory Committee on Human Experiments, Reflections on a Presidential Commission," (1996) 26 Hastings Center Report 5 at 8. The article sets out the specific committee recommendations.
See: *Final Report, supra* note 51 at 510-511, 522-529.

ethical conduct. The committee called for changes in public policy. Its strongest recommendations were for changes in the culture of human subjects research and in values and commitments of biomedical scientists.[191]

The General Accounting Office (GAO), performed a study of the IRB system at the request of the Senate Government Operations Committee, and published their findings *Scientific Research, Continued Vigilance Critical to Protecting Human Subjects,* in 1996.[192]

The Inspector General of the DHHS conducted a study of the challenges facing IRBs resulting in a four volume report in 1998: *Institutional Review Boards: Promising Approaches,*[193] *Institutional Review Boards: Their Role in Reviewing Approved Research,*[194] *Institutional Review Boards: The Emergence of Independent Boards,* [195]and *Institutional Review Boards: A Time for Reform.*[196]

The *IRBs: Their Role in Reviewing Approved Research* report concluded that the IRB's limited activity in continuing review of approved research is a critical national issue.

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[191] Faden, *ibid.* at 8 & 10. The President responded to the Final Report by issuing an endorsement of the findings and recommendations, making a public apology and establishing the National Bioethics Advisory Commission.
See also: J.D. Moreno, "The Only Feasible Means The Pentagon's Ambivalent Relationship with the Nuremberg Code," (1996) 26 Hastings Center Report 5 at 11-17; Beardsley, *supra* note 52 at 16.

[192] GAO, *Scientific Research–Continued Vigilance Critical to Protecting Human Subjects, supra* note 22. 1996

[193] Department of Health and Human Services, USA, Office of Inspector General, *Institutional Review Boards: Promising Approaches,* June 1998, OEI-01-91-00191. online: DHHS <http://www.dhhs.gov/progorg/oei> [hereinafter *IRBs: Promising Approaches*]

[194] *IRBs: Their Role in Reviewing Approved Research, supra* note 183.

[195] Department of Health and Human Services, USA, Office of Inspector General, *Institutional Review Boards: The Emergence of Independent Boards,* June 1998, OEI-01-97-00192 [hereinafter *IRBs: Independent Boards*].

[196] *IRBs: A Time for Reform, supra* note 187.

It decreases their ability to protect subjects by reducing their ability to identify and deal with situations where risks are unacceptable, where research results are too favourable to continue as research, or where protocols are expanded beyond their approval conditions. It also decreases the IRB capacity to ensure that subjects understand the risk. The report concluded that there are not widespread abuses in the system; that IRBs have made and continue to make valuable contributions due to the conscientious investigators and IRB members who strive to protect human subjects. However, they warn, the system is in need of reform.[197]

IRBs: Promising Approaches made recommendations regarding review of approved research.[198]

IRBs: A Time for Reform concluded that IRBs (some 3000-5000 boards) are currently incapable of adequately protecting research subjects.[199] The report reviews the weaknesses inherent in the system. Research and medicine have changed dramatically in the past decade. The system for protecting human subjects has not kept pace with these changes.[200]

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[197] *IRBs: Their Role in Reviewing Approved Research, supra* note 183 at iii.

[198] *IRBs: Promising Approaches, supra* note 193 at ii, 12 -14 Recommendations included: the IRB may use a third party to observe the research process; use of patient advocates in risky and /or complex protocols, i.e. gene therapy, Phase I studies; develop a continuing review form and establish a re-review mechanism.

[199] Washington Fax, "Moderate Reforms May Be in Order, But Institutional Review is Not Failing Human Subjects, Witnesses Say (18 June 1998) 1 <online: http//ugsp.info.nih.gov/info_items/info2.htm> [hereinafter "Washington Fax"]
See also: *IRBs: A Time for Reform, supra* note 187 at i The Inspector General offers a warning signal and a framework for response. The report does not suggest that widespread harm is being done to human subjects.

[200] *Testimony Before the Committee on Government Reform and Oversight, Subcommittee on Human Resources, United States House of Representatives, Statement of George Grob, Deputy Inspector General for Evaluation and Inspections, Institutional Review Boards: A Time for Reform*, June 11, 1998, Office of Inspector General, Department of Health and Human Services, online: DHHS <http://www.dhhs.gov/progorg/iog/testimony/irb/irbtest.pdf> at 1 [hereinafter "Testimony"]

The IRB system is founded on trust. IRBs work closely with researchers, and assume the best of intentions on their part. This is one of the strengths of the system. IRBs have important responsibilities and authorities for monitoring human subject protections.[201] Federal regulations require IRBs to conduct continuing reviews of approved research "at intervals appropriate to the degree of risk, but not less than once a year." Other groups such as clinical audit teams, clinical trials coordinators, research sponsors, contract research organizations, parts of the institution and a data safety monitoring committee (in some multicentre trials and federally funded cooperative group trials), have responsibilities in overseeing the research process. However, IRBs are the sole bodies whose core mission is the protection of human subjects.[202]

The system is in need of reform, based on the following six main findings: 1) IRBs face major changes in the research environment; 2) IRBs conduct minimal continuing review of approved research; 3) IRBs review too much, too quickly, with too little expertise; 4) neither IRBs nor DHHS devote much emphasis to evaluating IRB effectiveness; 5) IRBs face conflicts that threaten their independence and 6) IRBs and their institutions provide little training for investigators and members.[203]

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[201] *Ibid.* at 3.
See also: *IRBs: A Time for Reform*, *supra* note 187.

[202] "Testimony," *ibid.* at 4.

[203] *Ibid.* at 5 - 11.

The capacity of IRBs to accomplish all that is required is in question. It is time for reform. [204]

The recommendations aim to streamline human subject protections at both the local and Federal levels, with more emphasis on accountability, performance and results.[205] [206]

Some leaders in the biomedical research community agreed that moderate reforms were in order, but stated that IRBs are still nowhere near failing in the protection of human research subjects. Others argued that the system is in jeopardy.[207] [208]

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[204] *IRBs: A Time for Reform*, *supra* note 187 at iii; See also Appendix 17 The Inspector General's recommendations are directed to the OPRR (NIH) and FDA, the two DHHS agencies responsible for IRB oversight. These agencies with different jurisdictions must work together.

[205] "Testimony," *supra* note 200 at 12-16.

[206] "Washington Fax," *supra* note 199. The recommendations stress giving overworked IRBs more flexibility and also holding them more accountable for ensuring protection of human subjects. Recommendations call for a national registry of all private and public IRBs and for more representation on the boards by non-scientific and non-institutional members as one way to avoid potential conflicts of interests.

[207] *Ibid.* at 2. Problems cited included: 1)there is no central registry for all IRBs operating in the nation (OPRR has a list of 3,700 boards, which does not include an unknown number of private IRBs); 2) there is no registry or certification for private researchers whose work on human subjects fall outside of any federal review; 3) the OPRR office has meagre resources given the effort needed to monitor the 3,700 IRBs under its review (OPRR has just one full-time investigator).
See also: P.J. Hilts, "In Tests on People, Who Watches the Watchers?" *The New York Times* (25 May 1999) D1 & D4 Research was shut down at Duke University Medical Centre in May 1999 when its license to conduct human experiments (all 2,000 of them), was suspended due to violations of ethics and safety rules. Duke was the third major research institution in six months to have its work suspended. OPRR has frequently found informed consent documents understate or misstate the risks. Duke's problems included: informed consent documents which failed to give full information to subjects and failure of the IRB to follow up to see if any harm had come to patients, (20 violations in all). OPRR has the equivalent of only three full-time employees to monitor 16,000 to 20,000 human experiments.

[208] See also: E. Marshall, "Review Boards: A System in Jeopardy?" (1998) 280 Science at 1830. The Report urged the federal government to: certify all IRBs, give members less paperwork, but more substantive assignments, establish new educational programs for IRB members, address conflicts of interest and institute stronger federal oversight.

A third review by James Bell Associates, under contract with NIH, issued their report entitled *Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects.*[209] It concluded that IRBs are providing an adequate level of protection at a reasonable cost.[210] The *Bell Study* found that the IRB-based human subjects protection program has been implemented consistent with the regulations. The IRB system provides an adequate level of protection at a reasonable cost. There is a near-unanimous view that human subjects protection can be improved by honing IRB structures and procedures and providing increased education and training. The program is working well and not in need of major adjustments.[211]

Attendees at a workshop in April 1999 focussed their discussions on NIH Regulatory Burden v. Human Subjects Protection and suggested ways for the IRB to provide more efficient and effective monitoring. [212] [213]

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[209] *Bell Study*, *supra* note 160; See Appendix 17 for detailed descriptions of findings and recommendations.

[210] *NIH Workgroups*, *supra* note 161 at 2.

[211] *Bell Study*, *supra* note 160 at vii & viii;

[212] *NIH Workgroups*, *supra* note 161 at 5-9. Issues discussed were: 1) off-site adverse events reports, overall coordination between and within FDA and NIH is required as the differences between OPRR and FDA in administration, results in regulatory burden; 2) timing of IRB review of new grant proposals; 3) continuing review of proposals; 4) assurance process; 5) education programs are undervalued and underfunded and 5) ensuring adequate resources for IRBs.

[213] *Ibid.* at 10-14 Recommendations included: 1) assure that IRBs receive useful off-site adverse event data by coordination between institutions, the FDA, NIH, NIH-supported cooperative groups and data safety monitoring boards; Off-site reporting of adverse events should be limited to those which are "both serious and unexpected;" the FDA should require establishment of Data Safety Monitoring Boards (DSMBs) and develop methods to communicate the DSMB's deliberations to IRBs; DSMBs should provide aggregated and interpreted data to the IRBs at regular and defined times; on-site reporting of adverse events should continue to be provided to the local IRB; 2) eliminate the requirement for annual review and replace it with a system of random audits, resulting in fewer reviews, but more intensive reviews. The *Bell Study* found that 85% of grants submitted to NIH are eventually funded by some source; 3) develop an expanded and comprehensive training program for all members of the research enterprise; 4) encourage additional resources for the IRBs,

Summary

The conclusion to be drawn from this section is that some recent studies in the U.S. reveal a system governed by regulations which is not working at optimum capacity to ensure the welfare of human subjects in medical experimentation. Having laws and regulations "on the books" does not appear to ensure implementation. Rules and regulations do not guarantee ethical conduct.

IV. Canadian Model – Guidelines

1. Introduction

Systems for review of research protocols involving humans have been established in many countries through law (U.S.) or guidelines (Canada). Research ethics boards (REBs-Canada; research ethics committees -U.K. or institutional review boards, IRBs-U.S.), perform the prospective review to ensure the proposal complies with international and national standards for ethical research. To qualify for government funding in Canada, research must comply with these standards. A considerable proportion of research in Canada is affected by this condition. Additional protection is provided, as most universities require

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providing additional federal funds when the Federal government increases IRB duties; include in regulations that provision be made for adequate space and funding for effective IRB operation; 5) the current assurance-based system is considered onerous. Consider a third-party accreditation of IRBs, as long as such a system provides at least an equal or better program of protections.

all research (however funded), to comply with these national guidelines and most scientific journals require REB approval before publishing research.[214]

Legislation in Canada is federal or provincial. Legislation focussed on issues of health is generally provincial, as health is a provincial jurisdiction. This results in different legislative requirements across Canada, as well as the differing authority of the Civil Law in Quebec and the Common Law in the remainder of the country.

In Canada, no comprehensive legislation exists which regulates all research involving humans, (i.e. no legislation establishes the authority of the REB). Health care research is governed by the Common Law, or in Quebec, by the *Civil Code* (C.C.Q.) (Appendix 11) and federal and provincial legislation governing issues which affect particular aspects of research. In addition, national voluntary codes, guidelines and policies affecting research, developed by governmental agencies, professional organizations and local institutions, also contribute to ensuring ethical research, as the primary focus of these documents is protection of human research subjects.[215] For the most part, the Canadian research environment exists as a nonstatutory system of self-regulation.[216]

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[214] K.C. Glass, "Research Involving Humans," in Jocelyn Downie and Timothy Caulfield, eds., *Canadian Health Law and Policy* (Toronto: Butterworths, 1999) at 379.
See also L.N. Fortin and T. Leroux, "Reflections on Monitoring Ethics Review of Research with Human Subjects in Canada," (1997) 8 NCBHR Communiqué 1 at 11-23.

[215] Glass, *ibid.* at 375.
See also: S. Verdun-Jones & D.N. Weisstub, "The Regulation of Biomedical Research Experimentation in Canada: Developing An Effective Apparatus for the Implementation of Ethical Principles in a Scientific Milieu," (1996-97) 28 Ottawa Law Review 2 at 317. REBs have no independent power to require that research protocols involving human subjects be submitted to them for prior approval.

[216] Glass, *ibid.* at 380.

Common Law in the areas of contract and tort (negligence) and some specific legislative provisions, (such as the C.C.Q.), impact on the relationship of research subjects and researchers. The Common Law allows subjects injured due to participation in research, to seek compensation from the physician investigator and/or the institution for damages resulting from research participation.[217] Criminal law and the *Charter of Rights and Freedoms*[218] also have the potential to affect medical research. In Canada, to this point, the role of the civil courts has been minor and the *Criminal Code*[219] has not been used to regulate biomedical research.[220]

In the absence of legislation, guidelines, codes or policy statements may set the standard by which an individual or institution will be judged.[221] As no Canadian case has referred to Canadian guidelines or policy statements governing the ethical conduct of

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[217] *Ibid.*

[218] *Canadian Charter of Rights and Freedoms, Part I of the Constitution Act, 1982, being Schedule B to the Canada Act 1982* (U.K.) 1982, c. 11. [hereinafter *The Charter*]; *Elderidge v. B.C. (A.G.)* [1977] 3 S.C.R. 624 is a case where a deaf patient in labour required sign language interpretation. The court held that the B.C. Health Care Act infringed the Charter, Section 15. This section could be used if certain groups are excluded from research.

[219] *Criminal Code of Canada*, R.S.C., 1985 c. C-46. [hereinafter *Criminal Code*]

[220] S. Verdun-Jones & D.N. Weisstub, *supra* note 215 at 305.
See also: Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects, 1987*, (Ottawa: Minister of Supply & Services, 1987) [hereinafter *MRC 1987 Guidelines*] at 11 Research governed by guidelines is subject to legal scrutiny through federal and provincial legislation and common law.

[221] Glass, *supra* note 214 at 380-381.

research, to establish the standard of practice acceptable in Canada, the question remains unanswered. The court in *Weiss* v. *Solomon*[222] referred to the Declaration of Helsinki.[223]

2. Development of Guidelines - 1978, 1987, 1998

The Medical Research Council (MRC), in the mid to late 1960s, requested that research it funded be reviewed by local ethics review committees. By the 1970s, MRC required formal certification as a condition of funding and several universities and teaching hospitals developed systems of ethics review. Some complied with U.S. standards, especially if they were seeking U.S. research funding.[224] A summary of the successive guidelines developed for governing the conduct of medical research involving human subjects follows.

Ethics in Human Experimentation, Report No. 6, 1978, Medical Research Council

Canada's response to abuses of subjects in human experimentation in Canada and to the Nuremberg Code, Declaration of Helsinki and the regulation of human experimentation in the U.S. and elsewhere, was the establishment of a Working Group on Human Experimentation by the MRC, which issued their Final Report in 1978, entitled *Ethics in Human Experimentation, Ethical Considerations in Research Involving Human Subjects, Report No. 6.*[225]

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[222] *Weiss* v. *Solomon*, (1989), 48 C.C.L.T. 280 (Que. C.S.) *supra* note 57.

[223] Glass, *supra* note 214 at 393.

[224] J. N. Miller, "Ethics Review in Canada: Highlights from a National Workshop, Part I," (1989) 22 Annals RCPSC 7 at 519.

[225] Medical Research Council of Canada, *Ethics in Human Experimentation, Ethical Considerations in Research Involving Human Subjects, Report No. 6* (Ottawa: Minister of Supply and Services Canada, 1978) (Appendix 9) [hereinafter *Report No. 6*].

Up until 1978, there was no comprehensive Canadian statement which clearly set out the ethical considerations regarding research on human subjects, so that these could be uniformly applied across the country.[226]

The Working Group concluded that the same ethical standards should be applied to all research with human subjects, regardless of the availability or source of funding.[227]

The Report was consistent with the U.S. National Commission[228] in recommending setting of ethical standards by the local institution. Implementation of guidelines was left to committees whose membership was knowledgeable about local circumstances. The requirement of local REB approval of protocols on ethical grounds is a major contribution of this Report.[229]

Guidelines on Research Involving Human Subjects, 1987[230]

The purpose of the 1987 Guidelines was to set out the MRC's requirements for research involving human subjects which it funded. The 1978 MRC Guidelines were being superseded due to the need to update ethical statements taking into account new developments in research.

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[226] *Ibid.* at 1.

[227] *Ibid.* at 13.

[228] *The Belmont Report, supra* note 158.

[229] *Report No. 6, supra* note 225 at 14-25, 30-37, 39-46; See Appendix 12 for discussion of: a) research involving individuals incompetent to consent for themselves, b) comments regarding procedures for implementation of ethical requirements, c) responsibilities of various participants in medical research, d) the MRC's responsibility regarding review of proposals, which is carried out by local REBs and e) the membership and procedures to be followed by the REB.

[230] *MRC 1987 Guidelines, supra* note 220. See Appendix 6 for references to sections relating to monitoring.

The *MRC 1987 Guidelines* were designed to sensitize and give general guidance, rather than giving specific direction about what decisions to make.[231] [232]

The Guidelines briefly review the historical development of research ethics, describe the nature of human research and discuss the various approaches of regulating ethical conduct--guidelines or legislation.[233]

The Standing Committee set out the reasons why it did not consider legislation to be the appropriate response to ethical issues in research with human subjects, (including increased flexibility) and described the relationship between law and ethics.[234] [235]

The Guidelines set out: a) fundamental principles which underlay research with human subjects-- respect for life, concept of autonomy, the duty to beneficence and the duty to justice,[236] b) the factors to consider when evaluating the risks and benefits of research and

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[231] *Ibid.* at xi.

[232] Miller, *supra* note 224 at 522. The *MRC 1987 Guidelines* assign the major responsibility for ethical conduct of research to the investigator, (sensitive to ethical issues), assisted by an REB. Investigators and REBs must undertake continuing review, following the initial consent.

[233] *MRC 1987 Guidelines, supra* note 220 at 3-12.

[234] *Ibid.* at 10
Legislation and regulation under law prescribe standard responses to anticipated scenarios. Research issues are not easily standardized.
Research proposals affect matters such as health, hospitals, universities, majority age and mental competency which fall under provincial jurisdiction. Provincial legislation on tissue donation and release of medical data are also relevant to research, (though most human tissue legislation deals with transplantation and clinical care, rather than research; the Quebec Civil Code does refer to use of tissue for research).

[235] Miller, *supra* note 224 at 519. The *MRC 1987 Guidelines* confirm MRC Report No. 6 recommendations, that implementation occur at the local level due to the advantage of a multidisciplinary REB's ability to reflect local values in interpreting guidelines.

[236] *MRC 1987 Guidelines, supra* note 220 at 12.

discussed particular types of research,[237] c) the issues in research with special populations [238] and d) the issues of confidentiality and implementation of ethical responsibilities.[239] The principles of consent relating to research on human subjects are set out in the Guidelines: to the extent possible, consent should be informed and voluntary.[240]

The procedures recommended in these 1987 Guidelines are more stringent than those in the 1978 Guidelines. All those involved in research, especially the researcher and REB are responsible for the ethical conduct of human research. The MRC's responsibility includes ensuring that public funds are spent only on ethical research.[241]

The Guidelines delineate the responsibilities of the researcher, the institution and the MRC. The institution where the researcher works must ensure that ethical research takes place and acts as trustee for research funds. The REBs are delegated the institution's responsibility for the ethics of research, funded by the MRC (REBs are commonly delegated the responsibility to review and approve of all research carried on in the institution, regardless of the source of funding). Minimal expectations for REB operations, composition and issues for REB consideration are provided in the 1987 Guidelines.[242]

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[237] *Ibid.* at 15-20. E.g. genetic engineering, pilot studies, clinical trials, etc.

[238] *Ibid.* at 27-35. E.g.: distinctive ethnic or cultural groups, research involving legally incompetent subjects, research with children, research involving mentally incompetent adults, research with fetuses and embryos.

[239] *Ibid.* at 37-38, 40-52.

[240] *Ibid.* at 21-35. Ideally, subjects should be fully informed and have time, free from pressure, to decide whether to participate. In reality, this is rarely possible.

[241] *Ibid.* at 41.

[242] *Ibid.* at 43. 45-49. The REB and MRC should ensure that the actual implementation of the project continues to meet the standards of ethics agreed to among the researcher, REB and the MRC.

The institution's monitoring should be more active than simply seeking investigators' assurances. Approved research should be scrutinized. The manner of ongoing review depends on the specifics of the protocols.[243]

The Standing Committee stated that appropriate attitudes towards research are not ensured by monitoring alone. High ethical standards result from sensitivity and personal integrity, not from policing.[244]

The Guidelines conclude by setting out the responsibilities of the MRC in reviewing applications (through Grants Review Committee of peers). [245]

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, 1998[246]

This document represents the first Policy Statement on ethical conduct for research involving human subjects endorsed by all three granting councils. The new Tri-Council statement is the culmination of several years of discussions and consultations involving Canadian researchers in the humanities, social sciences, medicine, natural sciences and engineering who work with human subjects. "Canada is the first country to produce a comprehensive ethical policy statement for research involving humans in all academic

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[243] *Ibid.* at 50. See Appendix 9 for comparison of responsibilities of REBs in 1987 and 1998 documents.

[244] *Ibid.* at 51.

[245] *Ibid.* at 52. The Standing Committee suggested that the MRC establish mechanisms, (involving other agencies), to ensure the effective functioning of the local REBs. Primary responsibility for ethical review is on the REBs, but public accountability requires that MRC monitor the functioning of the REBs which review the work that it funds.

[246] *TCPS, supra* note 173.

disciplines," stated Dr. Henry Friesen, President of the Medical Research Council of Canada.[247]

The *TCPS* demonstrates the commitment of the three Councils to promotion of ethical conduct of research involving human subjects and articulates their standard of ethical conduct. The Councils will fund (or continue funding) only individuals and institutions which comply with standards in the *TCPS*. [248]

The Policy provides the context of an ethics framework, and in prescriptive fashion, sets out the minimum requirements for the process of ethical review, setting out in detail the operations, composition, and processes of deliberation of the REB. The Policy deals specifically with the issues of informed consent, privacy and confidentiality, conflict of interest, inclusion in research, research involving aboriginal peoples (discussion only; no policy), clinical trials, human genetic research, research involving human gametes, embryos or foetuses and human tissue. It discusses review procedures for ongoing review, conflict of interest and a proportionate approach to ethics assessment.[249]

With regard to the issue of monitoring, the *MRC 1987 Guidelines* imposed on REBs

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[247] MRC, NSERC & SSHRC "Joint Policy Statement on Ethics, A First for Canadian Research Councils," News Release (17 September 1998).
See: *TCPS, ibid.;* Appendix 12 for requirements for review procedures for ongoing research and Appendix 13 for a comparison of sections dealing with review procedures in *MRC 1987 Guidelines* and *TCPS*.

[248] *TCPS, supra* note 173 at i.1 - i.3. The description of the development of this document is on i.1. The *TCPS* replaces the SSHRC *Guidelines for Research with Human Subjects,* MRC's 1987 *Guidelines on Research Involving Humans* and MRC's *Guidelines for Research on Somatic Cell Gene Therapy in Humans.* The *TCPS* is intended as an educational resource. It updates some norms and encourages further reflection on other ethical issues. The *TCPS* does not present answers to ethical questions. It offers guiding principles and basic standards from which to develop and implement research ethics policies.

[249] *TCPS, ibid.*

the obligation to monitor ongoing research. This was a problem due to lack of resources. The *TCPS* states the continuing review is a "collective responsibility" involving research institutions, researchers and REBs. The REBs are directed to review annual reports from investigators, research that poses "significant risks" and "specific cases where the REB believes that it is best suited to intervene. As no Canadian court has applied Canadian guidelines to determine an REB's duty of care, it is not clear how the courts would deal with this issue.[250]

Despite the fact that Canada approaches the regulation of research involving humans, specifically, the underlying principles and the system of review of research, through the vehicle of guidelines rather than through legislation and regulation (the U.S. approach), there are numerous activities in the research area in Canada which are governed by legislation and regulation. They are set out below, with reference first to federal and provincial legislation and then to national policy statements and statements from national regulatory agencies.

Presently, no standard exists at the federal government level, as a whole, (similar to the Common Rule for 17 U.S. government departments and agencies), regarding ethics in research. Few departments have policies and procedures in place. The research councils (MRC., National Research Council-NRC, NSERC and SSHRC) have gone the furthest in

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[250] *TCPS*, *supra* note 173 at 1.10 - 1.11.
See: Glass, *supra* note 214 at 394. In a 1995 judgment of the Illinois Appellate Court *Kus* v. *Sherman Hospital*, 644 N.E. 2d 1214 (Ill. App. 2 Dist. 1995) the hospital was held liable for the IRB's omission in failing to follow up to determine whether the approved research protocol and approved consent form were used. The court described checking to ensure use of the IRB approved form as a "minimal duty" of the hospital through its IRB.

establishing policies, guidelines and procedures in research ethics. They serve in many areas, as national standards.

In 1996, there were approximately 400 REBs operating in Canadian universities and medical schools.[251]

3. Federal and Provincial Legislation

Even though there is no overall statutory framework regulating research with humans in Canada, investigators and REBs should know about provincial and federal legislation that governs health care generally and affects research. Examples of provincial legislation are acts regulating the following: access to medical records for research purposes, prohibitions or limitations on research with incompetent adults, psychiatric patients or children, human tissue gift acts which provide for donations for purposes of research, advance health care directives and appointment of substitute decision makers and freedom of information and health information protection. Each of these areas are particular to the individual province.

Because of the international nature of health research and multi-centre trials sponsored by multinational pharmaceutical companies, international guidelines, regulations and American regulations also have direct impact on the way research is carried out in Canada (referred to earlier). If the data from all these centres is being pooled, then the protocol in design and in implementation must be carried out to the highest standards to have the data and results acceptable to all regulatory agencies in all the countries participating (in

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[251] Memorandum to Ministers from Presidents of the Research Councils, *Ethics and Research Involving the Government of Canada* (27 September 1996).

particular, the FDA standard for the U.S. dictates much of the actual requirements for research carried on worldwide).

Federal legislation affecting research involving human subjects includes:

1) *Canadian Charter of Rights and Freedoms*,[252] specifically sections 7--life, liberty and the security of the person; section 8--unreasonable search and seizure; section 9--arbitrarily detained or imprisoned; section 12--cruel and unusual punishment and section 15--equal before the law without discrimination based on race, ethnic origin, colour, religion, sex, age, mental or physical disability (examples of situations where this may be applicable are exclusion from studies of women of child bearing age, visible minorities and economically underprivileged);

2) *Criminal Code of Canada*,[253] specifically section 45–protection from criminal responsibility for performing surgical operations if performed with reasonable care and skill and section 265(1) assault;

3) *Food and Drugs Act*[254]--Section C.08.005.1 sets out requirements for drug manufacturers to divulge extensive information to the Minister in order to sell a new drug to an investigator for purposes of clinical testing to determine the safety, dosage and effectiveness;

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[252] *The Charter*, *supra* note 218.

[253] *Criminal Code*, *supra* note 6.

[254] *Food and Drugs Act*, R.S.C., 1985, c.F-27; *Medical Devices Regulations*, SOR/98-282.
See also: Online: Health Canada <http://www.hc-sc.gc.ca/english/about.htm> The Act applies to all food, drugs, cosmetics and medical devices sold in Canada.

4) *The Corrections and Conditional Release Act*,[255] specifically sections 88 (2) & (4) which could apply to medical experimentation involving inmates and requires review of inmates' consent by an independent committee;

5) legislation relevant to Health Canada (which is important, as Health Canada plays such a critical role in issues relating to biomedical research and approval of drugs and devices through clinical trials) includes, among others, *Department of Health Act*,[256] *Food and Drugs Act*;[257]

4. Joint or National Statements and Case Law

Health Canada has many policies, which are generally directed at the pharmaceutical industry regarding regulations which they must comply with in order to have new pharmaceuticals approved. These relate to documentation, groups which must be included and the process of approval. One exception seems to be the Health Canada *ICH-GCP*, which, as well as being addressed to the pharmaceutical companies, also describes the minimum requirements for REBs (composition, documentation, review and monitoring functions).[258] The second exception appears to be the new proposed regulations relating to Clinical Trials,[259] which discuss:

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[255] *Corrections and Conditional Release Act*, S.C. 1992, c. 20.

[256] *Department of Health Act*, (1996) C.S.C. c. 8, H-3.2.

[257] *Food and Drugs Act, supra* note 254.

[258] As noted earlier, although Health Canada has adopted the ICH-GCP, it is not clear what authority they will have, as they have not been incorporated into regulation.

[259] Canada Gazette, Part I, January 22, 2000, *Food and Drug Regulations, (Schedule No. 1024) Clinical Trials.*

a) *registration* of all Phase I clinical trials, (first time administration with healthy volunteers; if this information is shared with REBs, they can communicate with each other regarding initial review and adverse events; should Health Canada-Therapeutic Products Program be responsible for sharing and interpreting safety data?);

b) *accreditation* of REBs-it is not clear whether the standards articulated in the *TCPS* are sufficiently detailed to act as minimal standards for the purposes of accreditation;

c) *inspection*- it is not clear whether this is intended to refer to a monitoring function and oversight of REB effectiveness; it appears to refer to compliance with ICH-GCP.

Health Canada policy documents include:

1)*Good Clinical Practice: Consolidated Guidelines*[260] (discussed in earlier chapter), which focus on: a) responsibilities, composition, functions and operations of Institutional Review Boards (REBs in Canada); b) investigator's qualifications; c) informed consent of trial subjects; d) records and reports; e) responsibilities of sponsors for quality assurance, trial design and management, monitoring responsibilities and procedures, audits and multicentre trials; f) clinical trial protocol and protocol amendments;

2) *Clinical Trial Review and Approval Policy*, March 1997;[261]

3) *Guidelines on Inclusion of Pediatric Subjects in Clinical Trials;* [262]

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[260] Health Canada, *ICH-GCP, supra* note 135 which supersedes the Drug Directorate's 1989 guideline entitled *Conduct of Clinical Investigations*; adopted by Health Canada, September 1997.

[261] Health Canada, Drugs Directorate, Clinical Trials Working Group, *Clinical Trial Review and Approval* (Health Canada: Ottawa, March 1997) supersedes the Drugs Directorate *Clinical Trial Review and Approval Policy*, November 1995, defines information required by the Drugs Directorate from sponsors of investigational drugs.

[262] Health Canada, Therapeutic Products Directorate, Guidelines, *Inclusion of Pediatric Subjects in Clinical Trials*, (Health Canada: Ottawa, November 1997).

4) *Inclusion of Women in Clinical Trials;* November 1997.[263]

The Pharmaceutical Manufacturers' Association of Canada. (PMAC) has a Code of Marketing Practices, 1997 which governs the operations of many of the sponsors of research. PMAC is also bound by the *ICH-GCP* document adopted by Health Canada.

Other statements and guidelines impacting on health research with human subjects in Canada, include those promulgated by the funding Councils in Canada and by the regulatory agencies of the federal government:

1) The MRC published *Guidelines for the Handling of Recombinant DNA Molecules and Animal Viruses and Cells* in 1977. These were revised in 1979 and 1980. In 1990 Health Canada and the MRC published technical standards on biosafety focussing on known pathogens, including bacteria; these were revised by Health Canada in 1996 and renamed *Laboratory Biosafety Guidelines, Second Edition*; Health Canada now leads in this area.[264]

2) The MRC also published *Guidelines for Research on Somatic Cell Gene Therapy in Humans* in 1990, (superceded by the *TCPS*);[265]

3) The three funding councils (MRC, NSERC & SSHRC) produced a document entitled *Integrity in Research and Scholarship* in 1994 and universities have responded, by ensuring compliance with the requirements, by having policies in place to deal with these issues. This

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[263] Health Canada, Therapeutic Products Programme Guidelines, *Inclusion of Women in Clinical Trials* (Health Canada: Ottawa., April 1997) designed to encourage inclusion of women, especially those of child-bearing potential, at the earliest stages of drug development.

[264] Laboratory Centre for Disease Control, Health Protection Branch, *Laboratory Biosafety Guidelines*, 2nd ed. (Ottawa: Minister of Supply and Services, 1996)

[265] Medical Research Council of Canada, *Guidelines for Research on Somatic Cell Gene Therapy in Humans*, (Ottawa: Minister of Supply and Services, 1990)

policy sets out the responsibilities of the researchers and scholars and the responsibilities of the institutions.[266]

4) In the area of conflict of interest, the government has general policies in this area. The Networks of Centres of Excellence Program developed its own guidelines in this area in 1996.[267] The MRC has developed a working paper on *Guidelines for the Commercialization of Medical Research*,[268] which is now in discussion in the research community.

5) The MRC has a *Report of the Working Group on Liability*,[269] which focuses on the liabilities of the researcher, the REB and its members, the institution and the MRC. This document is currently being updated and revised. The case of *Weiss* v. *Solomon* was referred to in the Liability document as well as elsewhere in this paper.[270]

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[266] MRC, NSERC, SSHRC, *Integrity in Research and Scholarship, A Tri-Council Policy Statement* (Ottawa: Minister of Supply and Services, 1994)
The MRC has received a number of allegations of scientific misconduct. Pursuant to the Integrity document, these are referred to the institutions for investigation. The National Research Council approved a policy generally consistent with this policy in 1995/96.

[267] Networks of Centres of Excellence (NCE), overseen by the Tri-Councils and Industry Canada, is a partnership among industry, universities and government to develop the economy and improve our quality of life through nation-wide networks.
There are 14 centres of excellence, involving 46 Canadian universities, 350 Canadian companies, over 100 provincial and federal departments and over 250 other organizations involved.
For more information, see: Online: NCE <www.nce.gc.ca/ncepublications/nce2000programguide/AppendixAConflictofInterestPolicyFramework>; each particular centre of excellence adapts the general framework of principles to their specific area.

[268] MRC Working Group, *Draft Document, Guidelines for the Commercialization of Medical Research, Report of the Working Group on Conflict of Interest in Intellectual Property and Commercialization*, (Ottawa: MRC, 7 February 1996)

[269] Medical Research Council of Canada, *Report of the Working Group on Liability*, (Ottawa: MRC, 1989).

[270] *Weiss* v. *Solomon*, 1989, R.J.Q. 731 (C.S.); (1989) 48 C.C.L.T. 280 (Que. C.S.) *supra* note57.
In this case the court held the fault of the researcher resulted in the liability of the hospital, even though there was a contract between the subject and the researcher. The research institution in Quebec can be liable for the negligence of its REB in approving a protocol or consent form that is inadequate. The hospital was further held liable for its failure to have appropriate emergency equipment available. The individual REB members were not sued in *Weiss*.

Another Canadian case dealing with issues relating to REBs is *Maziade* v. *Parent et Complexe hospitalier de la Sagamie.* [271] The case deals with the issue of REB and institutional autonomy and authority. This case is important as the authority of the Director was severely circumscribed to ensuring confidentiality. He could not legally require the prior approval of the ethics committee. This resulted in the medical institution having no ethical screening or oversight of research on its premises. Where initial approval is given to a protocol, it appears that all subsequent protocols fall under its ambit. The legislation being interpreted in this case was Article 125 of the *Law respecting Access to Documents*

See: Glass, *supra* note 214 at 386-387, 392-393.
The hospital's REB in *Weiss,* required modifications to the investigator's consent document to provide information on possible side effects of the fluorescein angiograms. Reference to minor allergic reactions was added.
The Canadian cases of *Halushka* and *Weiss* highlight that the standard of disclosure is even more demanding for research than it is for therapy: requiring "full and frank disclosure" of all risks, no matter how rare or remote. Other material information about the research is also required
In *Halushka* and *Weiss*, both investigators and institutions were held liable for negligence and in *Weiss,* the hospital was liable for the faults of its REB concerning both inadequate disclosure of risk and failure to require the exclusion of prospective participants who might be at greater risk in undergoing fluorescein angiography.
See: Bernard, *supra* note 55 Canadian courts have decided cases involving research with intended therapeutic benefit, which did not have protocol review for scientific or ethical merit.
See also: S. Clarke, *Can the Medical Research Council Be Liable for Damages or Liable to Criminal Prosecution, Because of its Guidelines on Research?* prepared for the MRC (which is currently being reviewed along with the Liability document)

[271] *Maziade* v. *Parent et Complexe hospitalier de la Sagamie* [1998] A.Q. no 1867; [1998] R.J.Q. 1444 (C.A.) No. 200-09-001445-097 aff'd Cour supéieure, district de Chicoutimi, April 14, 1997, Dossier: 150-05-000641-979 The case dealt with a physician who received authorization from the Director of Professional Services of a psychiatric hospital to access some patient files in 1991 for research. The original hospital merged with another. The trial court held that the original authorization by the Director of the psychiatric hospital was unconditional and did not specify a time limit. Thus, it was valid for all subsequent protocols. The Director could not limit access to records, based on the interests of the research subjects or of the public, nor can the Director legally require prior scientific or ethical review. In *obiter*, the judge added that ethical review already takes place before research is funded by the funding agencies and that a physician is already bound by the Code of Ethics for Physicians. The Court of Appeal denied the appeal by the new Director as he had denied the physician/researcher access to records without legal basis to do so.

held by Public Bodies.[272] As the case focussed on interpretation of Quebec legislation and was heard in Quebec, it is not clear how much impact it will have on REBs in other parts of the country.

5. Authority and Organization of REBs

Canadian REBs are delegated their authority by the governing body of the local institution. Consistent with ethics committees worldwide, their membership is multi-disciplinary, including both scientific and non-scientific representation. REBs have the discretion to approve or disapprove of a protocol, or to suggest modifications to ensure scientifically and ethically sound research. Many Canadian REBs are responsible for the evaluation of all aspects of a protocol, including its scientific merit, balancing the risks of harm and the potential for benefits, selection of participants, ensuring disclosure of the type and extent of interventions proposed, the consent process, ensuring confidentiality, evaluating potential conflicts of interest and monitoring the implementation.[273] Some institutions have separate scientific review committees.

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[272] *Law respecting Access to Documents held by Public Bodies and the Protection of Personal Information*, R.S.Q., c. A-2.1, s. 125.

[273] Glass, *supra* note 214 at 380.

6. Associated Organizations providing guidance and support regarding ethics and research involving humans

National Council on Bioethics in Human Research (NCBHR)[274]

The origins of Council began in the mid-1980s, when the MRC reviewed its guidelines on research involving human subjects. MRC recognized that an ethics review system relying on autonomous review by local REBs required ongoing support and information exchange. In 1989, at the request of the MRC and with funding/support from the MRC and Health Canada, the Royal College of Physicians and Surgeons of Canada established the National Council on Bioethics in Human Research as an arm's- length body to assist REBs.[275] NCBHR was established to support the interpretation and implementation of ethical guidelines on research involving human subjects.[276]

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[274] See Appendix 11 for NCEHR current terms of reference and Appendix 14 for reference to recommendations relating to monitoring, from the NCBHR study, based on site visits to 16 universities with medical faculties.

[275] National Council on Ethics in Human Research (NCEHR); sponsored by: Health Canada, The Medical Research Council of Canada (MRC), The Natural Sciences and Engineering Research Council of Canada (NSERC), The Royal College of Physicians and Surgeons of Canada (Royal College) and The Social Sciences and Humanities Research Council of Canada (SSHRC); Fifth Edition, 1998, at 1–NCBHR has expanded its mandate and changed its name to NCEHR.
See also: *MRC 1987 Guidelines*, *supra* note 220 at 52.

[276] Council News, "An Expanded NCBHR Mandate," (1995) 6 NCBHR Communiqué 2 at 1. See article for discussion of development of NCBHR, a multidisciplinary group, its activities and terms of reference. NCBHR undertook a variety of activities to assist Canadian REBs, researchers, granting agencies, governments and research institutions in meeting their ethical obligations in research with human subjects, including a study of the REBs associated with medical faculties across Canada. NCBHR's original mandate was expanded beyond biomedical research, to include the ethics of health and social science research involving humans. The 1995 terms of reference of NCBHR include: providing assistance to REBs in establishing and implementing procedures for evaluating and monitoring the performance of research involving human subjects. In 1995, NSERC and SSHRC joined the founding group. In 1997, the Council changed its name to the National Council on Ethics in Human Research (NCEHR) as its mandate now extends to all areas of research involving human subjects.

Canadian Council on Animal Care (CCAC)[277]

The Canadian Council on Animal Care was founded in 1968 by the MRC and NSERC and is funded jointly. It has an accreditation mechanism and operates on a voluntary basis, although institutions receiving Council funding are required to comply with CCAC guidelines. CCAC through monitoring and assessment systems, has achieved almost complete country wide effectiveness in monitoring research involving use of animals.[278] CCAC has developed a number of sets of guidelines which set out the principles of good animal care and use and are utilized by CCAC to assess institutional animal care.[279]

The CCAC developed a system to monitor its local committees. CCAC does not have the authority of legislation, but no research may begin until the local committee has approved the protocol. Periodic assessment visits are made by assessment panels of three scientists and a member of an animal welfare group. The institution has six months to implement the panel's recommendations and if the CCAC is not satisfied with the results, it may bring the situation to the attention of MRC and NSERC, which may apply financial or other sanctions. As the sanctions are real, institutions generally comply with its recommendations. The sanction for non-compliance is not the responsibility of the CCAC and involves only the institutions receiving funding from the granting agencies and the

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[277] CCAC Mandate and Guidelines, Online: CCAC <http://www.ccac.ca>
See: CCAC, *Guide* Vol. 1, 2nd ed., 1993 For terms of reference see Appendix 16.

[278] Fortin & Leroux, *supra* note 214 at 12-13 & 19.
See: G. Crelinsten, "'Who reviews the reviewers?' Issues in implementing, in Proceedings of the NCEHR Retreat," (1998-99) 9 NCEHR Communiqué at 28-29; CCAC Guide, *ibid.* at 3.

[279] CCAC Mandate and Guidelines, *supra* note 61.

granting agencies. All institutions (including private sector companies and government departments, independent of granting agencies), support and cooperate with CCAC programs.[280]

The CCAC monitoring system is presented as a possible model for monitoring of biomedical experimentation involving human subjects, with further detailed discussion to follow.

Health Protection Branch (HPB)

Health Canada is the federal department responsible for assisting Canadians to maintain and improve their health. Its policies (mentioned previously), and its departments impact directly on health research in Canada.

Health Canada has a number of branches including the Health Protection Branch (HPB), whose purpose is to assess the safety, effectiveness and quality of drugs and medical devices. HPB has responsibility for the following areas: Environmental Health Directorate, Laboratory Centre for Disease Control and Therapeutic Products Programme. Although other areas of the HPB impact on research involving human subjects, the prime area is that of the Therapeutic Products Programme which is made up of: the Office of the Director General, the Bureau of Pharmaceutical Assessment, the Bureau of Medical Devices, the Bureau of Biologics and Radiopharmaceuticals , the Bureau of Drug Surveillance, the Bureau of Compliance and Enforcement, the Bureau of Policy and Coordination and Drug Analysis Services. The Therapeutic Products Programme has the responsibility to evaluate

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[280] Fortin and Leroux, *supra* note 214 at 12-13, 19.
See: CCAC Guide, *supra* note 277.

the safety of new pharmaceuticals and is part of the government agency (HPB) which performs similar functions to the FDA in the U.S. Health Canada monitors health and safety risks related to the sale and use of drugs, food, chemicals, pesticides, medical devices and certain consumer products. New drugs and medical devices cannot be marketed without complying with Food and Drugs Act Regulations, and a Notice of Compliance from Health Canada.[281]

There are currently major draft revisions to the Food and Drugs Act, Regulations on Clinical Trials being proposed. There are suggestions regarding shortening the review time for applications, registration of all Phase I clinical trials, certification (accreditation) of REBs and inspection (monitoring) of REB performance, to ensure good clinical practice.[282]

There is also currently a major review of health protection legislation, affecting Health Canada and the more than one dozen pieces of legislation which affect its mandate (including the Food and Drugs Act), possibly resulting in the Health Protection Act.[283]

7. Critique of Current REB System and Monitoring

A critique of the current REB system generally and the state of monitoring of approved research, in particular, will be presented in the following chapter. The overview of the system is presented in the discussion of the NCBHR study. A full discussion will

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[281] Health Canada, Online: Health Canada <http://www.hc-sc.gc.ca/english/about.htm>

[282] These amendments are set out in the Canada Gazette, Part I, January 22, 2000, Food and Drug Regulations-Amendment, (Schedule No. 1024) Clinical Trials and the Regulations are to come into force on September 1, 2000.

[283] Health Canada, Online: Health Canada <http://www.hc-sc.gc.ca/hpb/transitn>

follow regarding the issues in monitoring, barriers to implementation, who should perform monitoring and how (several models and recommendations are proposed).

CHAPTER TWO: MONITORING OF BIOMEDICAL RESEARCH

I. Introduction

This chapter will examine the rationale behind monitoring of human subject research and will describe the functions which make up the monitoring process. The varying responsibilities of the individuals and groups involved in the research enterprise will be analyzed. We will discuss the current state of monitoring in Canada and the U.S. and examine barriers to monitoring, and outstanding issues in the area of monitoring, which must be addressed. Finally, various models of monitoring which have been or are currently being utilized in Canada are presented as possible models for others to adopt.

II. Two Levels

Two levels of monitoring could and should occur in human experimentation. Monitoring in biomedical research involving humans frequently refers to monitoring of specific protocols (previously approved by a REB), which focus on a particular hypothesis to be tested on individual subjects. The monitoring would be performed or supervised by the local REB or its delegate (subcommittee or research office staff).

The second level is review of the performance of the very bodies which have the responsibility to monitor the proposed research–the REB itself.

Some discussion will follow regarding issues related to how best to "monitor the monitor," but the major focus is on the issue of monitoring *by* REBs (and other bodies), of research.

III. Why is Monitoring Needed?

A significant gap exists "between ideal and reality"[1] in human subjects research. Public norms are not realized in practice, despite an elaborate administrative structure for doing so.[2] Comprehensive monitoring is practised in word and not deed. Monitoring is required for the following reasons:

a. protection of research subjects and integrity of the process

Protection of research subjects is most effectively achieved by following through the review of proposed research, to the implementation of actual research and overseeing the subject's welfare throughout. Protection of subjects extends beyond security from physical or psychological harm, to protection of information, especially in the current environment of databases and banking of information and tissue samples for several decades and generations. Current processes focus on antecedent review. Review of proposed research only, is insufficient to detect changes in implementation of research, to that which was approved, and to ensure compliance with ethical standards.[3] Guidelines/policy in Canada and legislation

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[1] J.A. Robertson, "Taking Consent Seriously: IRB Intervention in the Consent Process," (1982) 4 IRB A Review of Human Subjects Research 5 at 1.

[2] *Ibid.*

[3] See: P.M. McNeill, *The Ethics and Politics of Human Experimentation* (Cambridge: Cambridge University Press, 1993) at 10. [hereinafter *Ethics and Politics*] This focus on proposals places too much emphasis on the researcher's intention and not on their practice. Adherence to protocol and protocol "creep" (going beyond the protocol approved by the REB by enrolling greater numbers of subjects, altering the exclusion/inclusion criteria, altering dosages of study medication) will only be discovered by monitoring of approved research. Protocol creep denies the basic concept of research ethics review.
See: B.H. Gray, *Human Subjects in Medical Experimentation, A Sociological Study of the Conduct and Regulation of Clinical Research* (Toronto: John Wiley & Sons, 1975) at 14-16. [hereinafter *Sociological Study*] An important difference between antecedent and continuing review, is that funding is contingent primarily at the initial review. The requirements following approval are not taken seriously. Gray demonstrated noncompliance with or evasion of review committee directives in a national sample of medical institutions. Therefore a review mechanism is needed.

(regulation) in the U.S., mandate monitoring; international guidelines and Health Canada policy require monitoring.[4] This legislation and policy was developed in response to the history of abuse of human subjects in experimentation.[5] Investigators are human and make mistakes, which could lead to injury or invalidated conclusions. Error can better be discovered by an audit of the process. Science and medicine must acknowledge that error is part of the system. Admission of error, attempting to identify and correct it, is the appropriate response.[6] Many clinical trials are substandard as researchers lack training in clinical trial design and execution.[7]

The solution to these issues may be to reward (rather than punish), admission of error, and to provide education to researchers regarding the research process, design and ethics.

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[4] Medical Research Council of Canada, 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*, (Ottawa: Public Works and Government Services Canada, 1998).[hereinafter *TCPS*]; U.S. *Code of Federal Regulations; Title 45, Public Welfare Department of Health and Human Services, National Institutes of Health, Office for Protection From Research Risks, Part 46 - Protection of Human Subjects*, Revised June 18, 1991 (45 CFR 46);(Appendix 5). *FDA Regulations 21 CFR 50 and 56.* (See Appendix 8 for comparison of HHS and FDA approaches). Reference to international guidelines and policies and to Health Canada policies was made earlier.
See also: N.A. Christakis, "Should IRBs Monitor Research More Strictly?" (1988) 10 IRB A Review of Human Subjects Research 2 at 8.

[5] Reference to Chapter One- I. History of Medical Experimentation with Human Subjects.
See also: Gray, *Sociological Study, supra* note 3, at 16, 46, 238-239. Focussing only on proposals, presents great opportunity for abuse, intentional or unintentional.

[6] B. Freedman & C. Weijer, " 'Monitoring Of and By REBs,' in Proceedings of a National Workshop organized by the National Council on Bioethics in Human Research on The Ethics of Human Experimentation: REinventing the Research Ethics Board," (1996) 7 NCBHR Communiqué 1 at 23. [hereinafter "Monitoring REBs][hereinafter "NCBHR Workshop"]
See also: Christakis, *supra* note 4 at 9. Administrative errors, such as using an outdated consent form, rather than the REB approved form, negate the efforts of the REB review of specific wording in consent forms

[7] R. Nowak, "Problems in Clinical Trials Go Far Beyond Misconduct," (1994) 264 Science at 1538.
Even in the absence of misconduct, poor design leads to ambiguous, contradictory or misleading results.
See also: R. Nowak, "Ignorance is not Bliss," (1994) 264 Science at 1538. The most prevalent form of misconduct is ignorance rather than situations of fraud.

The risk/benefit assessment performed by the REB must be ongoing, requiring the most current information (an initial assessment prior to the study is inadequate).[8] Positive results may pose a problem as they may indicate one arm of the study is clearly more effective and the study should be terminated.[9] This will not be apparent to REBs without monitoring. A further result of the absence of monitoring procedures is that investigators can evade IRB/REB recommendations with impunity.[10] An REB cannot apply lessons learned in one study to future studies without monitoring.[11] IRBs/REBs must monitor actual enrollment in protocols to ensure fair access and generalizability of results.[12]

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[8] Gray, *Sociological Study, supra* note 3, at 254. i.e. adverse events, morbidity, mortality, preliminary results may alter risk/benefit assessments
See also: S. Wollman & M.K.Ryan, "Continuing Review of Research," in R.A.Greenwald, M.K. Ryan & J.E. Mulvihill, eds. *Human Subjects Research–A Handbook for Institutional Review Boards* (New York: Plenum Press, 1982) at 130 for description of the goals of IRB review.

[9] L.Friedman & D. DeMets, "The Data Monitoring Committee: How It Operates and Why," (1981) 3 IRB A Review of Human Subjects Research 4 at 6.
See also: B. Freedman, "Equipoise and the Ethics of Clinical Research," (1987) 317 NEJM 3 at 141-145 for a discussion of clinical equipoise (where there is genuine uncertainty within the expert medical community-not just the investigator- regarding which is the preferred treatment).

[10] Gray, *Sociological Study, supra* note 3, at 39-40.

[11] B.H. Gray, "An Assessment of Institutional Review Committees in Human Experimentation," (1975) XIII Medical Care 4 at 326. [hereinafter "Assessment of IRBs"] The REB can learn, for example, that the recruitment setting is important.

[12] S.C. Mitchell & J. Steingrub, "The Changing Clinical Trials Scene: The Role of the IRB," (1988) 10 IRB A Review of Human Subjects Research 4 at 3. To ensure that not only the poor and ill-informed or the wealthy are enrolled, as that would fail to comply with the principle of justice; recent U.S. regulations encourage inclusion of women and minorities in protocols; they were being excluded, resulting in the inability to generalize results.
See also: K.H. Rothenberg, "The Institute of Medicine's Report on Women and Health Research: Implications for IRBs and the Research Community," (1996) 18 IRB A Review of Human Subjects Research 2 at 1-3. Justice is not achieved when the national research agenda does not address women's health issues;
R. J. Levine, *Ethics and Regulation of Clinical Research*, Second Edition (Baltimore: Urban & Schwarzenberg, 1986) at 67. The principle of justice requires equitable distribution of burdens and benefits of research; K.H. Rothenberg, E.G. Hayunga, J.E. Rudick & V.W. Pinn, "The NIH Inclusion Guidelines: Challenges for the Future," (1996) 18 IRB A Review of Human Subjects Research 3 at 12. A clinical study without appropriate numbers of women or minority subjects may be scientifically flawed. Most IRBs do not collect data on study

b. the system relies on trust and the presumption of honesty

Research subjects trust doctors, and the research enterprise. Subjects have a difficult time distinguishing the different role responsibilities of their treating physician who is also the principal investigator. Patient/subjects do not carefully read over consent/information sheets. They trust that their doctor and the system will not involve them in a situation of harm;[13] The investigator-subject relationship is a fiduciary one.[14] The subject's signature on the consent form does not assure that informed consent has occurred. The solution is for the doctor to clearly explain that his responsibilities as an investigator go beyond primary concern for the welfare of the patient and to have a mandatory waiting period following the

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population composition. Inclusion criteria may comply with NIH inclusion guidelines, but are they being implemented? C. Weijer, "The IRB's Role in Assessing the Generalizability of Non-NIH-Funded Clinical Trials," (1998) 20 IRB A Review of Human Subjects Research 2-3 at 1-5. The new *NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research* for the first time, explicitly directed IRBs to assess the generalizability of clinical trials.

[13] N.E. Kass, J. Sugarman, R. Faden & M. Schoch-Spana, "Trust – The Fragile Foundation of Contemporary Biomedical Research," (1996) 26 Hastings Center Report 5 at 28. The researcher's primary loyalty is to the research process and future patients, not present ones.
See also: H. K. Beecher, "Experimentation in Man," (1959) 169 JAMA 5 at 465. The physician and investigator have different aims and ends. The physician accepts patients and is primarily concerned with their welfare. The investigator selects subjects and though responsive to the patient's interest, is primarily focussed on solving the scientific problem; D.J. Jones, "Conflict of Interest in Human Research Ethics," (1995) 6 NCBHR Communiqué 2 at 5. Discussion of multiple roles and responsibilities of professionals; K.C. Glass, "Research Involving Humans," in J. Downie & T. Caulfield, eds., *Canadian Health Law and Policy* (Toronto: Butterworths, 1999) at 375, for discussion of the confusion in roles of physician/investigator and expectations regarding therapy/experimentation; J. Sugarman, N.E. Kass, S.N. Goodman, P. Perentesis, P. Fernandes & R.R. Faden, "What Patients Say About Medical Research," (1998) 20 IRB A Review of Human Subjects Research 4 at 1-7. Discussion of: the trust of patient/subjects in relation to medical research; the terminology used by investigators to describe research is perceived differently by patients i.e. 'medical experiments' is seen as riskier than 'clinical investigations;'the difficulty for subjects of distinguishing between research and treatment; the weight given to doctors' opinions regarding research participation.

[14] A.R. Holder, "Do Researchers and Subjects Have a Fiduciary Relationship?" (1982) 4 IRB A Review of Human Subjects Research 1 at 6-7. J. Katz and R. Levine both conclude that the investigator-subject relationship is a fiduciary one. The article explains this concept in further detail.
See also these cases for discussion of physician's fiduciary relationship: *Norberg v. Wynrib* [1992] 2 S.C.R.226 at 275; *McInerney v. MacDonald* [1992] 2 S.C.R. 138 at 149 and *Hodgkinson v. Simms* [1994] 3 S.C.R. 377 at 405-415, 421.

subject receiving the explanation, to permit time to consider the request to participate and consult with family members and family doctor (especially with Phase 1 and 2 studies in cancer patients). Subjects cannot clearly distinguish research from clinical care. There is a potential conflict when physician/investigators recruit their own patients, so research nurses are employed to enrol subjects. Patients assume that there will be a personal benefit, or if no benefit, then at the very least, no harm.[15] The perception is that research offers new and improved treatment, rather than understanding that the research is occurring to determine *if* the newer drug or procedure is an improvement over the accepted mode. Many subjects view participation in research as another treatment option. Subjects considered the consent process as "a formality," as they did not believe the intervention would be offered unless it was of benefit.[16] A solution is for investigators to explain that research is not therapy.[17] Subjects expect that the system will ensure that only safe research is conducted and that

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[15] B.H. Gray, R.A. Cooke & A.S. Tannenbaum, "Research Involving Human Subjects," (1978) 201 Science at 1099-1101. The most common reason for subjects to participate was the expectation of medical, psychological or educational benefits. Review boards are ineffective at simplifying consent forms.
See: Kass, Sugarman, Faden & Schoch-Spana, *supra* note 13 at 26; Advisory Committee on Human Radiation Experiments, R.R. Faden, Chair, *Final Report of the Advisory Committee on Human Radiation Experiments* (New York: Oxford University Press, 1996) 510, 527-528; The Committee recommended steps be taken to improve three areas of the federal system for protecting human subjects: oversight (mechanisms to assess outcomes and performance), sanctions (appropriateness of sanctions for violations) & scope (extension of human subjects protection to nonfederally funded research).

[16] Kass, Sugarman, Faden & Schoch-Spana, *ibid.* at 26 & 28.
See also: Robertson, *supra* note 1 at 1-3; W.K. Mariner, "AIDS Research and the Nuremberg Code," in G.J. Annas & M. A. Grodin, eds., *The Nazi Doctors and The Nuremberg Code, Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) at 290-291. [hereinafter *Nazi Doctors*].

[17] J. Katz, "The Nuremberg Code and the Nuremberg Trial, A Reappraisal" (1996) 276 JAMA 20 at 1666. [hereinafter "Nuremberg Code-A Reappraisal"].

there are systematic checks and balances to ensure safety.[18] The system emphasizes autonomy, leaving choices to subjects, based on informed consent. However, frequently, subjects do not read or if they read, do not comprehend the consent forms; they tend to rely on advice and direction from their physician. Investigators, IRBs/REBs and all those responsible for evaluating and regulating research, must take this trust into account and be sure that it is justified.[19] Obtaining voluntary informed consent becomes a problematic goal when considering issues of: competence of the subject, comprehension, nature of the information and method of presenting it; readability and length of time between presentation and signing.[20] The format of presentation is also a factor.[21] Informed consent was developed to "set out minimum disclosure obligations that physicians must fulfill to escape *legal* liability for alleged non-disclosure."[22] The legal doctrine of informed consent was not

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[18] Kass, Sugarman, Faden and Schoch-Spana, *supra* note 13 at 26 & 28

[19] *Ibid.* at 26-28. Emphasis in research ethics on analysis of benefits/risks and on subjects' autonomous decision making is insufficient; the profound trust of participants in researchers and the research enterprise, must also be considered. A paternalistic attitude of IRBs is expected. Many nonmedical results of research, such as quality of life, interference with home and work, must be considered.

[20] M.C. Silva & J.M. Sorrell, "Enhancing Comprehension of Information for Informed Consent: A Review of Empirical Research," (1988) 10 IRB A Review of Human Subjects Research 1 at 1-3; H.A. Taub, "Comprehension of Informed Consent for Research: Issues and Directions for Future Study," (1986) 8 IRB A Review of Human Subjects Research 6 at 7; B. Heinze-Lacey, C. Saunders & A. Sugar, "Improving the Readability of Informed Consent Documents, (1993) 15 IRB A Review of Human Subjects Research 3 at 10-11. Discussion of ways to increase understanding of consent forms other than reducing reading level; Robertson, *supra* note 1, at 1. IRBs now play a limited role in the consent *process*. The ethical legitimacy of human subjects research relies on the informed consent of subjects, but IRBs focus almost exclusively on review and revision of consent forms. REBs rarely change the timing, setting, or consent process, even if these actions are required to allow/provide for autonomy of the patient/subject.

[21] G.L. Barbour & M. Blumenkrantz, "Videotape Aids Informed Consent Decision,"(1978) 240 JAMA 25 at 2742; For example, videotape: ensures uniformity; allows for varying educational levels and repetitious presentation; is well accepted by patients and is not time consuming for physicians.

[22] J. Katz, "'Ethics and Clinical Research' Revisited: A Tribute to Henry Beecher," (1993) 23 Hastings Center Report 5 at 35. [hereinafter "Tribute to Beecher"]

designed to serve as a set of rules governing the relationship of patients/physicians or subjects/investigators. The *idea* of informed consent in the medical context is broader. A solution is for physicians, patients, investigators and subjects to make joint decisions.[23] There is little Canadian research assessing the adequacy of consent to participation in hospital research. Studies elsewhere, demonstrate a failure to meet basic information and comprehension requirements of informed consent.[24] Much REB review of informed consent forms remains essentially a charade as the process of informed consent is often not implemented.[25] In practice, full, informed consent is not feasible most of the time . Failure to achieve voluntary, informed consent today is due, in part, to the public expectation favouring active screening and intervention, (encouraged by physicians) and the media barrage regarding the benefits of research. The difficulty in obtaining informed consent does not justify the failure to do so. The physician's ethical responsibility is a most important factor in achieving high ethical standards in research. There are conflicts between the roles of clinician and researcher, especially when they are commonly performed by the same individual. Beecher stated that a conscientious investigator may be a more reliable safeguard

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[23] *Ibid.*

[24] A. Estey, G. Wilkin & J. Dossetor, "Are Research Subjects Able to Retain the Information They Are Given During the Consent Process?" (1994) 3 Health Law Review 2 at 38.

[25] Robertson, *supra* note 1 at 1.

than informed consent in assuring ethical human research.[26] Tracking rates of refusal is important to ensure proper informed consent is occurring.[27]

Summary

The system assumes patients can be autonomous and protect themselves through informed consent. Realistically, consent rarely occurs in the fullest sense. We rely on the integrity and conscientiousness of the investigator, who experiences many kinds of pressures and on institutional checks and balances. Strategies include: a) implement a system of review of ongoing research to ensure that directions given by the REB are being carried out and b) interview subjects to be sure they knew they were in research and were enrolled voluntarily. This could be done through random checks of subject comprehension by way of formal questionnaires or personal or telephone interview.

c. Subjects, investigators, institutions and sponsors all have different perspectives, interests and conflicts of interest

There exist many conflicting loyalties and pressures for: a) income (institutions receive overhead funding and perhaps, licensing or patenting income; investigators may receive salary, benefits, laboratories and equipment or have entrepreneurial interests in products tested); b) prestige (both investigators and institutions benefit from association with important research) and c) promotion (career implications for individuals are significant).

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[26] M. T. Claessens, J. L. Bernat and J. A. Baron, "Ethical issues in clinical trials," (1995) 76 British Journal of Urology, Suppl. 2, at 34-35.
See also: Christakis, *supra* note 4, at 8; Gray, *supra* note 3, at 238, 241, 244-45.

[27] D.S. Shimm & R.G. Spece Jr., "Rate of Refusal to Participate in Clinical Trials, (1992) 14 IRB A Review of Human Subjects Research 2 at 7-9 The authors recommend that investigators keep records of eligible potential subjects and those who agree to participate. If more than anticipated agree, more investigation may be needed.

Conflict is inherent in the process.[28] The IRB/REB itself is part of the research apparatus which supports, promotes and funds research, and its membership is largely medical researchers. One could argue the IRB/REB already has a bias in favour of research and in protecting the institution, the investigator (colleague) and its own legitimacy. By its very nature, a peer review requirement is biased in favour of doing research.[29] "... Actions with regard to *proposals* are quite distinct from actions that affect the *conduct* of research."[30] A solution is to ensure effective lay representation on the REB (both in numbers and authority/credibility of the individual appointed). Performance of REBs themselves must be assessed. The concern about monitoring does not imply that investigators lack moral integrity. It recognizes that ethical requirements are often ambiguous, that situational

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[28] See: Jones, *supra* note 13, at 5-10 for detailed discussion of conflict of interest including definition, examples and cases. Research funding guidelines and policies articulate explicit conflict of interest standards and procedures for all those involved in the research enterprise-investigators, institutions and REBs; K.C. Glass & T. Lemmens, "Conflict of Interest and Commercialization of Biomedical Research: What is the Role of Research Ethics Review?" in T.A. Caulfield & B. Williams-Jones, eds., *The Commercialization of Genetic Research: Ethical, Legal and Policy Issues* (New York: Kluwer Academic/Plenum Publishers, 1999) for discussion of the conflicts in the research system: researchers, institutions, commercial sponsors and REBs, the role of the REB in dealing with conflicts of interest and approaches to manage conflict of interest; *TCPS*, *supra* note 4 Article 1.12 and Article 4.1 "Researchers and REB members shall disclose actual, perceived or potential conflicts of interest to the REB. REBs should develop mechanisms to address and resolve conflicts of interest."
See also: T. Lemmens & P.A. Singer, " Conflict of interest in research, education and patient care," (1998) CMAJ 159 at 960-965 Studies have shown an association between the source of funding and the outcome of research studies. Trials funded by drug companies are less likely to find that traditional therapy is better than the new drug; M. Day, "He Who Pays the Piper....." (1998) 158 New Scientist 2133 at 18-19. A discussion of Betty Dong commissioned by a drug company to compare drugs and found no difference with cheaper drugs. The paper was withdrawn by the company from publication, (finally published 8 years later). As we cannot eliminate conflict of interest altogether, the researcher must disclose the conflict. E. Marshall, "The Mouse that Prompted a Roar," (1997) 277 Science 24 DuPont has a patent on a powerful method of manipulating genes in the Cre-loxP mouse. Report of the NIH Working Group on Research Tools, "Summary of Problems," Executive Summary, Presented to the Advisory Committee to the Director, June 4, 1998, There are increasing problems and delays in obtaining access to research tools.

[29] Gray, *Sociological Study, supra* note 3 at 50 & 52.
See also: McNeill, *supra* note 3, at 184-206, 207-222, 222-223, 225, 239-246.

[30] Gray, *ibid.* at 52.

pressures impinge on investigators and that medical researchers belong to a self governing profession. Visibility of performance is the key to social control of professionals. Medical research has very low visibility, as interaction is visible only to individual patient/subjects. The only visible aspect of the investigator's ethical performance is the consent form. The REB focuses primarily on an editing the consent form, rather than assessing of the consent process. Scientific results receive peer scrutiny in scientific literature, but scrutiny of the ethical *performance* of the investigator is not carried out.[31] Research suggests that intraprofessional controls (including medical training, peer influence, ethical codes and disciplinary boards), are, on their own, inadequate to ensure ethical conduct of investigators. Studies of external controls over biomedical research (government regulations, IRBs/REBs, judicial and state law), suggest that extraprofessional regulations are often ineffective. Decreasing public and legislative confidence in the ability of biomedical science to regulate itself has resulted in increased use of extraprofessional (governmental) controls.[32] Even the perception of wrongdoing may be enough to lose public trust.[33] Because of benefits which

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[31] *Ibid.*, at 246.
See also: E. Marshall, "Journals Joist Over Conflict of Interest Rules," (1997) 276 Science at 524.
Journals have policies regarding disclosure of conflict of interest from full disclosure of the author's financial interests to the modest requirement for self-disclosure; E. Marshall, "Secretiveness Found Widespread in Life Science," (1997) 276 Science at 525. Scientists have delayed publishing their data by more than six months for commercial reasons (amongst others).

[32] P.R. Benson, "The Social Control of Human Biomedical Research: An Overview and Review of the Literature," (1989) 29 Soc. Sci. Med. 1 at 1.
Some authors argue that current procedures are ineffective and call for stricter government controls over biomedical research. Others question whether government regulation is effective in protecting research subjects.
See: B. Barber, J.J. Lally, J.L. Makarushka & D. Sullivan, *Research on Human Subjects, Problems of Social Control in Medical Experimentation,* (New York: Russell Sage Foundation, 1973) 181-183, 187-189.

[33] P.R. Lichter, "Our System, Our Responsibility: Research and the Public Trust," (1994) 101 Opthamology 7 at 1163-1164.

investigators stand to gain, they may try to reduce practical problems in research (e.g. recruitment of subjects, by noncompliance of ethical standards).[34] Investigators have admitted evading review committees, so the assumption of good faith being universal amongst investigators is not accurate.[35] The high value society gives to medical research allows researchers to rationalize their non compliance with ethical standards, in the pursuit of this higher goal.[36] The physician-investigator may tend to treat subjects as patients and use the discretion and authority of a treating physician, who might make decisions for, rather than consulting with, their patients.[37] Doctors tend to exaggerate the benefits of research and underestimate the risks.[38] The solution regarding conflict of interest (on the presumption that it can not be avoided altogether), is to acknowledge it honestly, initially and to design ways to prevent or minimize bias.[39]

See also: A.S. Relman, "Lessons from the Darsee Affair," (1983) 308 NEJM 23 at 1415-1417.

[34] Gray, *Sociological Study, supra* note 3, at 248-249. Existing control measures do not suffice, due to the role expectations and career interests of investigators and systemic pressures they face. Professional positions, depend primarily on publishing research results.

[35] *Ibid.* at 39.
See: Barber, Lally, Makarushka & Sullivan, *supra* note 32 at 149-150.

[36] Gray, *ibid.* at 249.
See: Gray, "Assessment of IRBs," *supra* note 11 at 324-325.

[37] J. Katz, "Do We Need Another Advisory Commission on Human Experimentation?" (1995) 25 Hastings Center Report 1 at 30. [hereinafter "Another Advisory?]

[38] Kass, Sugarman, Faden and Schoch-Spana, *supra* note 13 at 27.

[39] C. K. Gunsalus, "Institutional Structure to Ensure Research Integrity," (1993) 68 Academic Medicine 9, September Supplement, at S37.
See also: Glass, *supra* note 13 at 378 Currently, there is little institutional oversight of conflicts of interest in the form of policies or monitoring. Increasing academe/industry ties create potential for conflicts of interest.

d. Changes in the research environment from the point it was established to the present

Clinical research began decades ago, with one researcher formulating a hypothesis and testing it on a patient population in one institution. Today, multi-centre clinical trials are so large and involve so many investigators that they are vulnerable to careless practices and scientific misconduct. Monitoring in multicentre trials is critical for accountability.[40] Today, biomedical research is seen as a benefit to subjects and society, rather than as a risk to subjects.[41] New therapies and clinical trials involve patients with life-threatening diseases, who cannot and will not wait for the outcome of traditional controlled clinical trials. Regulators have increased the speed of approval, so that a treatment use becomes an uncontrolled treatment trial. Benefits shown in treatment trials may not be repeated in controlled trials, but these benefits may be impossible to refute, as they have already been accepted as therapy. The result could be less controlled clinical trials, which could expose patients to ineffective, risky treatments.[42]

The business of testing experimental drugs on people is a multibillion-dollar industry with hundreds of testing and drug companies working with thousands of private physicians. Patients have become commodities. The number of private physicians doing research in the

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[40] J. Cohen, "Clinical Trial Monitoring: Hit or Miss?" (1994) 264 Science 1534.
See also: H. Edgar & D. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation,"(1995) 73 Millbank Quarterly 4 at 497-501 for discussion of the evolution of the research environment.

[41] CIOMS/WHO, International Guidelines for Biomedical Research Involving Human Subjects, (Geneva, 1993) at 9.

[42] Mitchell and Steingrub, *supra* note 12 at 1-3.
See also: Benson, *supra* note 32 at 8, reference to FDA allowance of treatment use of investigational drugs.

U.S. has tripled from 1990-99. There has been little public debate as the full scope of the situation is hidden. The system is fraught with conflicts of interest as it places a premium on speed and meeting quotas. Many physicians have little experience as clinical investigators. Current monitoring systems do not detect these problems. The tremendous growth of the industry has left experienced study monitors in short supply.[43]

Another reason to monitor in Canada is to avoid being regulated by government. If the research establishment does not act in a responsible and accountable manner by fulfilling all the requirements in the voluntary guidelines/policy statement, there is a risk that control of the enterprise will fall into the less flexible and less responsive hands of government.[44]

Increased volumes of research and multicentre trials result in obstacles to performing adequate *initial* review. This makes ongoing monitoring even more important. In the last 10-15 years, the U.S. research environment has doubled expenditures for health research, seen a 30% increase in research applications, experienced a huge increase in the non-government sponsorship of health research to at least 50% and an extension of research to non-traditional research sites, (such as community hospitals, clinics and private physicians' offices). There are also new opportunities such as genetic engineering and human reproductive interventions. These changes have altered the research scene

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[43] K. Eichenwald & G. Kolata, "Drug Trials Hide Conflicts for Doctors," *The New York Times* (16 May 1999) 1, 28-29 See article for full discussion of the issues, such as incentives for physicians; changes in the process and development of new structures, for discovery and testing of new pharmaceuticals; focus of ethics review boards on small payments to subjects and lack of review of larger payments to investigators.

[44] *Canada Gazette, Part I of January 22, 2000, Schedule No. 1024.* This is currently taking place with proposed amendments to the Food and Drug Regulations dealing with Clinical Trials-relating to accreditation of REBs, a registration system for Phase I trials, a 30 day default system and an inspection system.

dramatically.[45] Many of these factors are present in Canada, although the extent of government funding has been well below the levels in the U.S.

Once it is accepted that monitoring should take place, decisions about monitoring should be determined based on proportionate review according to the *TCPS* and U.S. regulations, and each institution should establish a system to identify research protocols which require monitoring.[46] There is a danger that having a committee responsible for ethics review will allow investigators and the institution to feel less responsible for ethics concerns.[47]

Summary

Continuing review can serve as a key safety net for human subjects. This protective role is particularly significant as many individuals agree to participate in research trials with little understanding of the risks involved or of the distinction between research and established therapy. It becomes more important as the research environment becomes increasingly influenced by marketplace pressures and potential harms to human research subjects increase. Access to experimentation and experimental drugs is now seen as a right.[48]

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[45] J. Bell, J. Whiton & S. Connelly, (James Bell Associates) *Final Report, Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects*, Prepared for the Office of Extramural Research, National Institutes of Health, June 15, 1998, online: NIH <www.nih.gov> at 1; See Appendix 17 for detailed descriptions of findings and recommendations [hereinafter the *Bell Study*]

[46] Christakis, *supra* note 4 at 9. Monitoring is required where: i) dealing with vulnerable populations (young, infirmed); ii) permissive researchers (prone to take risks and neglect appropriate consent procedures); iii) high risk research.

[47] Gray, "Assessment of IRBs," *supra* note 11 at 328.

[48] DHHS, Office of the Inspector General, *Institutional Review Boards: Their Role in Reviewing Approved Research*, June 1998, OEI-01-97-00190 at i [hereinafter *IRBs: Their Role in Reviewing Approved Research*] See also: Mariner, *supra* note 16 at 290; CIOMS/WHO, *supra* note 41 at 14. The deliberate exclusion of

Monitoring as an issue focusses on both subject safety and ethical conduct of researchers.

Developments such as the movement of research from single site to multicentre and multinational studies and the large numbers of players involved in research (subjects, REBs, investigators, institutions, government and industry) call for a clear definition of roles and responsibilities. Pressures on researchers, institutions and sponsors impact decisions for example: pressures from society for positive results and better health, a scarcity of resources (creating other pressures, such as competition for research income for institutions and researchers and competition for subjects to enrol in protocols) and pressure from industry which sets the research agenda based on market forces. All these considerations result in the requirement for a more vigilant and effective system of monitoring, both of the system and the safety of subjects. In many cases, everyone but the subject, benefits personally from the research enterprise.

The current level of continuing review conducted by IRBs is limited in scope and impact. Reviews of annual reports, adverse event reports and protocol amendments are often hurried and superficial. Continuing review is almost always entirely limited to paperwork reviews. It is rare to visit the research site to see how the consent process is actually working or to review records of active protocols. Other parties do on-site monitoring (such as pharmaceutical company data auditors). However, they do not have the protection of human

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pregnant women or women capable of becoming pregnant is being questioned as it denies them the right to decide for themselves. U.S. regulations state that the researcher must provide justification for exclusion.

subjects as their central mission. Protection of human subjects, *is* the fundamental reason for the establishment of the IRB system.[49]

IV. How to Best Protect the Research Subject

Writers disagree about what is the most important element in protecting research subjects –the investigator's commitment to voluntary consent as a first principle or the integrity and good character of the researcher. There seem to be weaknesses in each approach. As discussed above, there are many pressures and challenges to the integrity of the researcher. Evidence shows that although subjects are given an opportunity to make an autonomous choice, they rely heavily on the advice and perceived recommendations of their physician. Many subjects are not physically or mentally capable of making a meaningful autonomous choice, yet they are still enrolled in research protocols. The research enterprise, its supporting structures and institutions must ensure that all subjects are fully protected.[50] Authors have stated that the single most important component in an institutional culture of research integrity is institutional leadership committed to ethical conduct.[51]

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[49] DHHS, Office of the Inspector General, *ibid.* at i & ii. It appears that industry sponsored research is more closely monitored than Council funded research, but in fact, industry research is not peer reviewed, as is Council funded research. Industry research is market driven.

[50] Katz, "Nuremberg Code-A Reappraisal," *supra* note 17 and Katz, "Tribute to Beecher," *supra* note 22. Katz advocates that the investigator's adherence to the principle of voluntary consent is the best protection for the research subject. Beecher was convinced in many cases, it was impossible for a patient/subject to give voluntary consent, and therefore the best protection for the patient/subject was the integrity and good character of the investigator.
See also: R. J. Levine, "The IRB and the Virtuous Investigator," (1985) 7 IRB A Review of Human Subjects Research 1 at 8. Levine agrees with Beecher that the IRB should take trustworthiness into account. This was the rationale for the National Commission recommendation of local review.

[51] Gunsalus, *supra* note 39 at S33 The institution should: focus on prevention and education; develop codes of ethics and misconduct review processes. Increasing demands for accountability are increasing pressures on institutions to monitor conduct of their members.
See also: R.A. Greenwald, "General Principles of IRB Review," in Greenwald, Ryan & Mulvihill, *supra* note

In both the U.S. and Canada, initial review and monitoring of specific protocols has been fixed at the local level, because of the advantages of knowing the circumstances locally, the subject population and the qualifications and practices of the investigators. The REB also has an important role in protecting the research subject by: a) reviewing the scientific validity of the proposal, b) evaluating its value (its impact on practice and whether significant knowledge will result, which may alter clinical practice); c) assessing risks and benefits and assuring that by enrolling, the subject is not receiving less than standard care; d) assessing the qualifications and track record of the investigator (this is a primary function of peer review regarding the *scientific* validity of the proposal and should also play a more important role in the assessment of the *ethics* of the proposal); e) ensuring subject selection will allow generalizability of results; f) assessing the informed consent process and g) determining protocol adherence and monitoring of approved research. However, all parties involved in review–institutions, REBs, REB members and investigators-- have conflicting interests and pressures which must be acknowledged.[52]

V. Who Should Be Responsible for Monitoring?

There are those who argue against monitoring, specifically as a function to be performed by the IRB. Robert Levine argues that having the IRB monitor protocols, would transform the IRB from a review and advisory board into a police force, for which it is ill-equipped. The policing approach would indicate to researchers that the system is operating

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8 at 59 where Greenwald refers to Robert Levine's comment that the most important factor in the success of an IRB is its credibility within the institution and the community.

[52] National Commission and U.S. regulations, *supra* note 4 and *1987 MRC Guidelines* and TCPS *supra* note 4 and earlier chapters of thesis.

from a presumption of mistrust. This would result in the loss of credibility of the IRB and loss of the informal monitoring system (unsolicited reports by students, nurses and physicians). Levine does not rule out monitoring altogether, but states that monitoring should not be performed by the IRB in most cases. Levine refers to the IRB (U.S.) situation, but his rationale is applicable to the Canadian REB situation. Arthur Caplan asserted that the current system is one which produces paper promises, with a lack of time for enforcement or investigation. He advocates a system of random sampling during initial review of protocols, resulting in more time for enforcement.[53]

I do not agree that monitoring would destroy the atmosphere of congeniality and compromise REB effectiveness. Peer review of scientific validity is universally accepted as a norm. Researchers accept monitoring by pharmaceutical companies and initial review by REBs. What is so different qualitatively with the idea of follow-up of approved research? REB members should be seen as partners and colleagues of investigators in review of ethical research, rather than as adversaries. All health care services are now being followed up on the basis of evidence based results and quality assurance. Should not this aspect of health

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[53] Christakis, *supra* note 4 at 8.
See also: Levine, *supra* note 12 at 348-349. Levine does not oppose all field work by IRB members, but states it should occur when there is "due cause" or when IRB is evaluating its own effectiveness. He prefers operating from a presumption of trust until contrary evidence is presented. Regulations based on presumption of distrust are excessive in detail and inflexible. Levine argues there is no evidence that presumptions of trust are associated with higher frequency of wrongdoing. However, Gray produced evidence that researchers acknowledged not complying with ethical standards or requirements of REB; at 358 where Levine suggested site visits of research institutions using experienced IRB members and staff as site visitors (this is similar to approach of NCBHR site visits-later discussion); Levine acknowledges the necessity for continuing routine inspections and audits of clinical investigators by the FDA; R.R. Faden, C. Lewis & B. Rimer, "Monitoring Informed Consent Procedures: An Exploratory Record Review," (1980) 2 IRB A Review of Human Subjects Research 8 at 9-10; J.M. Cohen, "More on Random Review," (1983) 5 IRB A Review of Human Subjects Research 2 at 10. Cohen disagrees with Caplan that there should be random initial review, as even competent and highly ethical investigators might violate the subjects' welfare.

care involvement (research), also require the same manner of follow up, especially when large sums of public money are used to enhance the health of the community and members of the public are the subjects of research? One must carefully consider how monitoring will affect the overall research environment. However, if the proper approach is taken, I do not believe the reaction will be as negative as Levine predicts. A quality assurance, educational, partnership approach should be taken rather than a punitive, policing approach. Monitoring of approved research should be considered a peer review process.

There appears to be a general consensus in agreement with the principle of informed consent, but there is resistance to the idea of procedures to guarantee it. Monitoring is simply a process to ensure implementation of a principle which most in the research community support.[54]

VI. What Do We Mean by Monitoring by a REB of Specific Approved Research?

Monitoring is intended to ensure that research being done is of the highest standard and that past problems in research are not repeated.[55]

"Monitoring" is a general term that is used to describe IRB/REB functions. Confusion is created, as it is used imprecisely and refers to a range of possible activities, such as continuing review, surveillance and the observation of the consent process. Heath suggests that the term "monitoring" be replaced with four more concrete and precise concepts. The four concepts are 1) **continuing review**; 2) **review of the consent process**; 3) **review for adherence to an approved protocol**; and 4) **review to identify unapproved**

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[54] Gray, *Sociological Study, supra* note 3 at 256.

[55] Freedman & Weijer, "Monitoring REBs," *supra* note 6 at 22.

activities. These four distinct functions do not all have to be performed by the IRB/REB. Other bodies are in a better position to effectively carry out some of these functions.[56]

Continuing review is an IRB/REB's fundamental monitoring activity and is generally accepted. The focus of continuing review should be restricted to assessment of the impact of new developments on the study. The same questions asked in initial review would be repeated, taking new developments into account. As this involves repeating the initial review functions, there should be no argument that the IRB/REB might be extending beyond its competence.[57]

Continuing review activities include: setting a review date at the initial review, interim incident reports and a progress report, (including the number of subjects enrolled, evaluation of the data received to date and an analysis of the risks and benefits based on new information in the field and from the study itself). This responsibility can be shared. These reports could be reviewed by designated members or a subcommittee of the IRB/REB.[58] The department chairs could also be responsible for ensuring these reports are completed. A local/departmental data safety and monitoring committee of experts may be utilized to perform scientific review and ongoing safety monitoring. This may not be feasible in

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[56] E.J. Heath, "The IRB's Monitoring Function: Four Concepts of Monitoring," (1979) 1 IRB A Review of Human Subjects Research 5 at 1. [hereinafter "Four Concepts"].

[57] *Ibid.* at 1 & 2.
See also: Appendix 8 Differing Approaches of HHS and FDA to Compliance Review

[58] Heath, *ibid.* Safety issues include: adverse events, setting up of a safety committee and/or a data safety and monitoring committee and decisions regarding stopping rules.

smaller institutions with fewer colleagues, reducing the likelihood of objective review. A list of other REBs reviewing the protocol would assist with consultation and outside experts.

Regarding the **consent process**, the U.S. National Commission, recommended IRB observation of the consent process, self-report about participation and appointment of a third party to explain the research to proposed subjects.[59] The *TCPS* offers the following as options for researchers and REBs regarding the consent process: a) formal review of the free and informed consent process; b) periodic review by a third party of the documents generated by the study; and c) a random audit of the free and informed consent process[60]

IRBs/REBs spend most of their time in the consent review process, reviewing the consent form. The goal is to design a document that might best arrive at an informed, voluntary consent from the proposed subjects. Factors examined are: simplicity of language, timing of the consent process and distinguishing between research and treatment components.[61] This general IRB/REB review does not consider the specific individual-their fears and capacities (which is the responsibility of the investigator). It is designed for the protection of the average subject, rather than vulnerable populations incapable of autonomous consent. There seems to be agreement that this "monitoring" of the consent

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[59] *Ibid.* at 2.

[60] *TCPS supra* note 4 at 1.10 -1.11.

[61] Heath, "Four Concepts," *supra* note 56 at 2.
See also: Faden, Lewis & Rimer, *supra* note 53 at 9. A nationwide survey found that IRB proposed modifications to consent forms did not enhance either the completeness or readability. The authors recommended against wide implementation of direct observations of the consent process as it could seriously intrude on the research process.

process is a function that should be assumed by the IRB/REB, though the methodology to achieve this has not been agreed upon.[62]

Monitoring adherence to a protocol is not frequently done by the IRB/REB. However, it is a function which does not rest entirely with the IRB/REB. Strategies to achieve institutional monitoring of adherence to protocol include: a) the IRB/REB may designate agents specially trained to perform this function, (comparing documents such as grant applications, human research applications and subjects' files and charts);[63] b) this function could be delegated to a department chair or to a hospital director. Since department chairpersons are generally responsible for departmental initiatives, this is a "simple" extension of their role;[64] c) consent is the area of most concern-- the IRB/REB could collect signed consent forms, ascertain that the correct form is being used and that the number of subjects match the number of consents on file;[65] d) currently, subjects are not asked to participate in audit of research, for which they are subjects. Subjects could help by checking that all the procedures proposed were carried out, (they would require a copy of the information sheet and consent form to check against);[66] e) IRBs/REBs could encourage compliance through educating investigators about their potential liability for actions

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[62] Heath, *ibid.* at 2.
See also: *TCPS*, *supra* note 4 at 1.11 which suggests that beyond scrutinizing reports, the REB itself should not normally carry out the continuing ethics review, except in specific cases where the REB believes that it is best suited to intervene.

[63] Heath, *ibid.* at 2-3.

[64] *Ibid.* at 3

[65] *Ibid.*

[66] *Ibid.*

performed outside the scope of an approved study, (i.e., institutions may seek indemnification from an investigator who was not in compliance).[67] Other methods of assessing adherence originate outside the IRB/REB or the institution. The largest single area of research is likely drug studies.[68] Many clinical trials conducted in Canada are multi-centre and are affected by U.S. legislation and regulation, or industry supported international guidelines (ICH-GCP). Canada also has provision for sponsors or the Health Protection Branch (HPB) of Health Canada to monitor protocols.[69]

It has been argued that the costs of instituting an adherence audit program could be high in financial and social terms, as it could threaten the trust between IRBs and investigators. These are accomplished through on-site inspection. IRBs are not well prepared to carry out this function. Heath suggested that compliance audits be done by IRBs/REBs only when there is a demonstrable breach in compliance and the breach is serious enough to justify IRB intervention.[70] This argument is weakened by the acceptance of the investigators, of monitors from the pharmaceutical companies, auditing protocol compliance.

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[67] *Ibid.*

[68] *Ibid.* The pharmaceutical industry sponsors employ monitors/auditors who do site visits to check the validity of data. The FDA and sponsors of studies have the authority under FDA regulation to assign study monitors to specific studies. The primary reason for FDA doing this is to assure validity of data, but it also accomplishes review for adherence.

[69] *Department of Health Act*, C.S.C. 1996, c.8 H-3.2; Health Canada, *Good Clinical Practice: Consolidated Guideline, Therapeutic Products Directorate Guidelines–ICH Harmonized Tripartite Guideline* (Ottawa: Minister of Public Works and Government Services Canada, 1997). [hereinafter Health Canada ICH-GCP]

[70] Heath, *supra* note 56 at 3.

Identification of unapproved research is usually an issue identified within institutions or by local governments or regulatory agencies. In the U.S., the HHS regulations and OPRR assurances specifically assign this responsibility to the institution, as opposed to the IRB, as it is the institutions which must sign the assurance compliance certificate (this does not relate to privately funded or unfunded research).[71] The *TCPS* does not refer to or assign responsibility for identification of unapproved research.

Heath suggests that the institution (not the IRB) has other informal methods to facilitate or assure review of protocols and provides examples. IRB approval is understood by many investigators, to be ethically and legally necessary, and they can influence their colleagues.[72]

By separating out the distinct functions of monitoring and assigning responsibility for each component to different entities, the IRB/REB can determine its unique and overlapping responsibilities in the research process.

Heath suggests that "monitoring" be replaced with reference to the four functions. Then IRBs/REBs can discuss with institutions, legislatures, regulatory agencies and industry, what role each will play in relation to these four areas.[73] A suggestion for the sharing of responsibilities relating to the monitoring functions follows:

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[71] *Ibid.*, at 12.

[72] *Ibid.* These informal methods tend to be less expensive, more varied, and generally more attractive than formal requirements and include: 1) assistance of department chairpersons; 2) newsletters from the IRB stressing their help, speed and availability, encouraging investigators; 3) open meetings which serve as good educational tools and 4) well-informed staff can assist investigators.

[73] *Ibid.*

Monitoring	
Function	**Responsibility**
a) continuing review	-researcher -IRB/REB -department chairs could ensure completion and submission of reports
b) consent process	-researcher -IRB/REB - regarding consent forms in advance and follow-up -IRB/REB agent or IRB/REB--consent process–achieved by subject interviews and questionnaires
c) adherence to protocol	-researcher--report changes & adverse events (AE) to REB -department chair–perform peer review & on-site AE review -IRB/REB or its agent to conduct subject interviews or questionnaires -pharmaceutical company monitors -IRB/REB in demonstrated breach--single staff affiliated with IRB/REB could field complaints and investigate them;(passive system, responding to complaints, as opposed to active review) -independent data safety monitoring board -departmental data safety monitoring committee
d) identification of unapproved research	-researcher -institution; department chairs

In each of the four areas of monitoring, the investigator has the primary responsibility to conduct ethical research and protect their subjects. The REB is an agent of the institution and should direct how the institution can best monitor. The institution has the responsibility to ensure that monitoring takes place. The institution and department have the responsibility for peer review, including initial review and monitoring of ongoing approved research.

The above division of responsibilities works well for research based in an institution. It does not work well for research located elsewhere, such as in a physician's private office, or for research which is privately funded or not funded (as the parties involved are not the

same as those in institutional research). In these situations, other solutions must be found. In the case of unfunded research which is institution based, once the institution takes on the project, it is bound to assure that it meets ethical standards. If the research is private/industry funded and is based in a physician's private office, the solutions could include: the College of Physicians and Surgeons assuming responsibility (as in Alberta-discussion follows), noninstitutional REBs, national groups, such as the College of Family Practice of Canada or national cooperative research groups (such as the National Cancer Institute-NCI). These parties would assume responsibility for research which is conducted by its members or research which it funds.

An argument could be made that monitoring of the consent process is a quality assurance issue, rather than an aspect of the continuing research question. Following through on the delivery of information to obtain a consent, could be treated in a similar manner to the follow through of other medical services in an effort to determine their effectiveness. Perhaps applying a quality assurance approach or continuing quality improvement concept, to analysis of the consent process, would be effective in overcoming opposition to interference with academic freedom of the research process, as there appears to be general acceptance of the quality assurance approach.

With regard to performance of the REB, the quality assurance approach could be used in all four areas of monitoring described by Heath: continuing review, consent process, adherence to protocol and identification of unapproved research. The approach would focus on the institution and the REB and whether they are fulfilling their responsibilities in these areas.

VII. Monitoring in Canada

1. General Issues

The current environment of research in Canada has changed considerably from the time when the system was developed. Initially, most research was proposed by a single researcher and carried out at a single venue, a teaching/research hospital. Today, an increasing volume of research is multi-centre clinical trials, which are situated in various types of locations, including physicians' private offices. In the last several years in Canada, the federal government support for biomedical research has decreased from about 40% to about 25%, (though this may be increasing with the new funding for the Canadian Institutes of Health Research), while the pharmaceutical industry portion has risen from about 30% to 40-50%. Much more of the activity is focussed on clinical trials sponsored by the pharmaceutical companies. It should be noted that much of the MRC funding is directed to basic bench research, rather than into the area of clinical trials.

Although it is useful to compare the situation in Canada to the research scene in other countries, our situation in Canada is unique in having a research guideline which guides research beyond the health care sector. The Tri-Council Policy was drafted to guide researchers in the biomedical and health care sciences, the social sciences and humanities and the natural and engineering sciences. The process to accommodate multiple disciplines in the same document has led to some differences in approach and emphasis regarding monitoring, (i.e. U.S. regulations are more detailed regarding definition of risk).

The regulatory structures in the U.S. and Canada are different, but many of the issues are similar. A review of the status and a critique of the U.S. IRB system, is presented in detail, through summaries of recent studies, in Appendix 17.

Studies in the U.S.[74] and Canada[75] have demonstrated that the limited involvement of IRBs and REBs in continuing review of approved research is a serious national issue as it compromises their ability to protect human subjects. It inhibits their capacity to identify and address situations of: a) emerging unacceptable risks; b) research results which demonstrate the efficacy of one arm of a study, to such an extent, that it is unethical to continue the research study or c) protocols which go beyond approved limits. It also reduces their ability to ensure that subjects comprehend the risks involved in the research process.

There is no indication of widespread abuse in either country. IRBs/REBs have made and continue to make important contributions. The system works because of many conscientious investigators, IRB/REB members and staff, who are committed to protecting human subjects.[76]

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[74] See Appendix 17 for details of U.S. studies. Recommendations of U.S. studies regarding structural changes may not be relevant to Canada.

[75] See Appendix 14 for recommendations relating to monitoring, from the NCBHR site visit study.

[76] DHHS, Office of Inspector General, *IRBs: Their Role in Reviewing Approved Research, supra* note 48 at iii, 4-6 The study discussed the following problems in research: subjects who consent, but do not differentiate research and treatment, do not understand the goals of research; subjects with unrealistic expectations of potential benefits and risks; focus in informed consent is obtaining signatures and not ensuring understanding by potential subjects; the changing research environment-- increase in industry sponsored research shaped by the marketplace; lapses occur in IRB approved research.

The very proliferation of IRBs/REBs raises critical questions about uniform standards and performance. Can "one size fits all" work well?[77]

Currently, there is a system of monitoring and reporting which takes place at various levels and in various organizations. There is no consistency in methods or the degree of compliance with policy requirements and no requirement of co-operation or communication between the various parties.

Part of the existing monitoring system takes the form of annual reports submitted by investigators, and re-approvals by REBs. The contents and comprehensiveness of these reports varies widely. Some REBs do not require annual reports at all.[78] The continuing review by REBs takes many forms from full REB review, to expedited review by a small subgroup of REB members or the chair. In some cases, administrative staff without any research expertise, ensure that all forms are submitted and completed. Another form of reporting is submission by industry to the investigator, of adverse event reports or serious adverse event reports, which in some, (but not all) cases, are forwarded to the REB. A further problem is that industry receives reports from data safety monitoring boards and some of these reports are received by the investigator, but they are not always forwarded by the company to the REB. Therefore the REB may not have the latest safety information when making decisions about approval of ongoing research. Another issue in monitoring is that

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[77] Edgar & Rothman, *supra* note 40 at 489.

[78] NCBHR, "*Special Report: Protecting and Promoting the Human Research Subject: A Review of the Function of Research Ethics Boards in Canadian Faculties of Medicine*," (1995) 6 Communiqué 1 at 12-13; 15; 23-24. [hereinafter *NCBHR Study*]

changes in protocols or new information regarding risks, require changes to consent forms and perhaps informing subjects currently enrolled. This rarely takes place.

Monitoring of the recruitment process and the consent process is rarely, if ever done by REBs. REBs spend much time reviewing the language of proposed consent forms. REBs are preoccupied with disclosure, due to requirements in case law and existing guidelines and regulations. The consent form is just the last step in a complex *process*. Meslin stated that any monitoring more invasive than requiring annual reports, conflicts with principles of academic freedom and with the trust the REB has in investigators to carry out research according to protocol. Both the REB and the investigator, are reluctant to have this function performed.[79]

Gray made the following observations about research experimentation generally, which are applicable to the current status of research in Canada. The primary control mechanism in human research is peer review at the initial REB/IRB review. Fundamental social control mechanisms such as monitoring and sanctions effectively, are absent.[80] Professionals are regulated by licensing at the beginning of their practice. This same emphasis on the entry point occurs in the research review process, with review of proposed projects only.[81]

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[79] E.M. Meslin, "Ethical Issues in the Substantive and Procedural Aspects of Research Ethics Review," (1993) 13 Health Law in Canada 3 at 186.

[80] Gray, *Sociological Study, supra* note 3 at 14. Gray wrote that regulation of human experimentation relies almost entirely on the socialization of investigators in their training and on prior review of proposed research. Since then, there have been increasing regulatory and policy developments relating to research, in the U.S. and Canada, but controls on the investigators have not changed their focus from initial socialization and the emphasis on prospective review.

[81] *Ibid.* at 246-247.

There is no reason for the reliance of formal social control of human experimentation primarily on prior committee review, which does not assure ethical behaviour in clinical investigation, especially in relation to informed consent. A true commitment to ethical research, requires that a mechanism be developed to identify unethical practices and make them visible.[82]

Today, investigators can be fairly confident that their conduct will never be subject to review. If investigators are aware that their actions will be scrutinized, it is expected that they will avoid careless or improper methods of obtaining consent.[83] Higher visibility of ethical performance would result if there was an institutionalized monitoring procedure to interview subjects to determine whether they understood that they were involved in research, whether they understood the risks, benefits and alternatives, and whether they felt free to

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[82] *Ibid.* at 250.

[83] *Ibid.*
See also: T. Smith, E.J.H. Moore, H. Tunstall-Pedoe, "Review by a local medical research ethics committee of the conduct of approved research projects, by examination of patients' case notes, consent forms and research records and by interview," (1997) 314 BMJ at 1588 &1590. The study found that monitoring of medical research by local medical research ethics committees promotes and preserves ethical standards, protects subjects and researchers, discourages fraud and has the support of investigators; study recommended 10% of projects undergo on-site review with others monitored by questionnaire; discussion of educational value of continuing review; P.M. McNeill, C.A. Berglund & I.W. Webster, "Do Australian Researchers Accept Committee Review and Conduct Ethical Research?" (1992) 35 Soc. Sci. Med. 3 at 317. Researchers were supportive of review of research protocols despite review being time consuming and demanding. Very few research ethics committees actively monitor research in progress; P.M. McNeill, C.A. Berglund & I.W. Webster, "Reviewing the reviewers: a survey of institutional ethics committees in Australia." (1990) 152 Med J Aust at 289-296; P.M. McNeill, "Research Ethics Review in Australia, Europe and North America," (1989) 11 IRB A Review of Human Subjects Research 3 at 4-7 [hereinafter "Research Ethics Review"] Article discusses development of review systems in U.S., Canada, U.K. and Australia; C.G. Foster, T.Marshall & P. Moodie, "The annual reports of local research ethics committees," (1995) 21 Journal of medical ethics at 214 Only twenty three per cent of the reports refer to any form of monitoring of the eventual outcome of the research. None of the reports refers to active monitoring of research in progress; P.C.E. Modie and T. Marshall, "Guidelines for local research ethics committees," (1992) 304 BMJ at 1294. Refers to Julia Neuberger's report which emphasizes the need for monitoring and recommends spot checks on research in progress [J. Neuberger, Ethics and Health Care–The Role of Research Ethics in the U.K., Research Report 13, Kings Fund Institute, 1992]

refuse to participate. (Discussion of the McGill case study of the consent process follows). Timing is an issue. Gray suggests interviewing the subject after participation. In the McGill study, the subjects were interviewed after consent, but before participation.[84] Gray's suggestion that the interview take place after the participation, does not result in protection for the subject interviewed; it would only protect future subjects. A monitoring system would complement (not replace) current review procedures. The IRB/REBs' role in assessing the adequacy of the proposed method of obtaining informed consent and the voluntariness of the decision, is important. If IRBs/REBs learned what subjects did or did not understand regarding research, the process could be improved.[85] Informal social control measures such as peer approval are insufficient as peers lack knowledge of each other's practices of informed consent. Primary reliance on prospective review to influence behaviour of researchers is insufficient.[86]

The peer review system has demonstrated that it is effective in monitoring and regulating the research enterprise in some cases, i.e. Dr.Poisson (discussed earlier) whose misconduct was brought to light utilizing the scientific process. The review was directed at the accuracy of his records and compliance to protocol. His noncomplicance with scientific requirements led to the finding of scientific misconduct and unethical conduct. Only a very

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[84] Gray, *Sociological Study, supra* note 3 at 250. If a pattern of subjects being enrolled without understanding is detected, investigators can be instructed about how to avoid future deficiencies, warnings could be given and wilful or persistent violations could result in temporary or permanent suspension in funding or access to facilities.

[85] *Ibid.*, at 251.

[86] *Ibid.*, at 252 & 253. There is an assumption (which is inaccurate), that there is a high degree of consensus on what the standards should be, and that one can control behaviour by making sure that one does not offend peer standards.

small minority of science involves misconduct. Are there processes in Canada to prevent misconduct? Peer review prior to funding, publication and performed by REBs does provide some protection in Canada from misconduct. However, it took 13 years to bring Poisson's misconduct into the public realm. Is this satisfactory oversight and protection?

2. Current Practice

REBs in Canada have acquired the status of a national standard. Their function has been endorsed in modern international ethical guidelines. The *MRC 1987 Guidelines*[87] proposed the establishment of a council to act as a resource for institutions, to assist them with implementing the *MRC 1987 Guidelines*, and the National Council for Bioethics in Human Research (NCBHR) was created.[88]

The model of ethics review in many countries has three parts: a) a requirement for review of medical research involving humans by a local institutional research ethics committee; b) national research ethics guidelines or principles for evaluating individual research proposals and c) broad goals to guide the REBs. The mandate for local institutional ethics review originates from national guidelines or research funding (Canada, England) or from national legislation (U.S., France and Ireland). The administration of research ethics is at the local level in both systems.[89]

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[87] Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects, 1987* (Ottawa: Minister of Supply and Services Canada, 1987). [hereinafter *MRC 1987 Guidelines*]

[88] *NCBHR Study*, *supra* note 78 at 5.

[89] *Ibid.* at 6.

The focus of REBs in North America is both peer review and protection of the research subject, (flowing from the history of abuse of human subjects).[90]

Studies undertaken by NCBHR in 1989 and 1995, indicate that despite direction in the 1978 and 1987 MRC Guidelines, that monitoring take place at the local level, questions continue, such as: the need for monitoring, a questioning of its value, a desire to transfer the obligation to a national level (by NCBHR doing site visits and MRC funding monitoring), an indication that the REB might not be the appropriate body to undertake monitoring (largely due to lack of time and resources) and a general lack of compliance on the part of REBs and institutions to ensure that monitoring takes place.[91] The studies found that: a) the nature of continuing review and monitoring varies; b) there is little consultation between REBs and investigators once protocols are approved and c) untoward incidents are rarely brought to the attention of the REB, which as a result does not always have the most current information regarding risks and benefits.[92]

With the exception of the Canadian Council on Animal Care (CCAC) program, the MRC (until the new *TCPS*), has not verified that the procedures and processes in institutions are in compliance with its policies. It does not appear that the *TCPS* actually established a mechanism for the MRC (or its successor, the Canadian Institutes of Health Research--

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[90] *Ibid.*

[91] J.N. Miller, "Ethics Review in Canada: Highlights from a National Workshop, Part 2," (1990) 23 Annals RCPSC 1 at 31 and "NCBHR Workshop," *supra* note 6 at 5-35.

[92] S.Verdun-Jones & D.N. Weisstub, "The Regulation of Biomedical Research Experimentation in Canada: Developing An Effective Apparatus for the Implementation of Ethical Principles in a Scientific Milieu," (1996-97) 28 Ottawa Law Review 2 at 325.

CIHR) to monitor the REBs and institutions either. The *TCPS* states only that institutions must comply with the Policy in order to receive funding and must assure MRC that they are in compliance. The NCBHR study is the only follow-up regarding compliance with MRC Guidelines[93]

The human REB model in Canada offers a lower level of protection for humans than the system for animals used in experimentation. The CCAC sets standards and conducts site visits to ensure implementation. The suggestion has been made that humans should be entitled to at least the level of protection given to animals, despite increased costs, administration and complexity resulting.[94] The *TCPS* is more prescriptive than the *MRC 1987 Guidelines* regarding membership and operation of REBs, but no central authority for auditing performance of REBs was created.

In 1995, Weijer and Freedman commented that REBs which rely only on annual review are likely not fulfilling the *1987 MRC Guidelines* regarding their monitoring duties,

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[93] *NCBHR Study*, *supra* note 78 at 3-32.
See also: "NCBHR Workshop," *supra* note 6 at 5-35; P. Deschamps, "Ministerial Action Plan on Research Ethics and Scientific Integrity," (1998-99) 9 NCEHR Communiqué 1 at 9-10. In June 1998, the Quebec Minister of Health and Social Services issued a *Ministerial Action Plan on Research Ethics and Scientific Integrity,* which recommends joint action and accountability by everyone involved in research. The Plan sets out requirements for participation in and supervision of research, conduct expected of health-care institutions, boards of directors and REBs; proposes a regulatory framework along with a 3-pronged review of research projects–scientific, ethical and financial; at the time of review, parties must agree with the REB on follow-up mechanism for each project. The Action Plan includes special measures covering only REBs which are subject to the rules of section 21 of the *Civil Code of Quebec*, (which legislates mechanisms by which contract research is performed in hospitals and universities and the setting up of a central committee in the Quebec Ministry of Health for vulnerable populations).

[94] Panel discussion, at "NCBHR Workshop," *supra* note 6 at 11.

especially if this takes the form of investigators' assurances.[95] This has been reinforced by the wording in the current Tri-Council document, which states exactly that.

Monitoring would enable the institution to learn how research is actually carried on inside its walls and to tailor educational programs for researchers, which will improve consent processes. Monitoring enables the REB to fulfill its mandate of protection of the research subject. It would be optimal if the system and its participants recognized that error in medicine and research is common and that error-checking procedures are necessary. Those who discover the error should not be condemned, as they are the ones who keep the research system free from corruption. The issue of enforcement mechanisms was not clear in the *1987 MRC Guidelines* and is not clearly spelled out in the *TCPS* either.[96]

The concern with research issues is a shared responsibility. Research institutions have other bodies which deal with areas such as contract review, financial issues etc. so that REBs are not acting in isolation. The Department Chair usually indicates endorsement of the protocol prior to its review and implementation, and has some responsibility regarding follow-up. In many cases the study design and scientific merit of a protocol is subject to peer review prior to funding. The ICH-GCP Guidelines on monitoring are accepted by the pharmaceutical industry, so industry is also involved in monitoring.

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[95] B.Freedman & C. Weijer , "Monitoring REBs," *supra* note 6 at 22.

[96] *Ibid.* at 23 & 24.
See also: R.M.A. Hirschfeld, W. Winslade & T.L. Krause, "Protecting Subjects and Fostering Research, Striking the Proper Balance," (1997) 54 Arch Gen Psychiatry at 121. IRB/REBs should be more thorough in monitoring, especially with vulnerable subjects.

In fact, research involving human subjects is a very regulated process at this stage and ensuring that monitoring takes place, is just a continuum in the process. REBs are part of a team of players, but they have a very specific role and responsibility–protection of the research subject. The result may be protection of the researcher and institution by identifying or preventing unethical research from being conducted, but the prime focus is protection of the subject.

3. NCBHR Study

Currently, active monitoring of on-going research is "glaringly absent"[97] in the REBs in Canada. REBs must realize that governments, granting agencies and the public are increasingly demanding accountability in all aspects of social behaviour, including research.[98]

Sixteen universities with medical faculties were visited by NCBHR and surveyed regarding the operations of the REBs. The study reported that few REBs were found to monitor research projects after they had been approved and undertaken. These findings are similar to those in studies in the U.K. and Australia. The study authors remarked that this would indicate a need for reform of the model in these three countries: a national research ethics process founded on national guidelines which are applied by local research ethics committees.[99] This remark seems to infer that the U.S. model of regulations is more effective

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[97] G. Crelinsten, "'Who reviews the reviewers? Issues in implementing,' Proceedings of the NCEHR Retreat," (1998-99) 9 Communiqué 1 at 28.

[98] *Ibid.* at 28-29.

[99] *NCBHR Study, supra* note 78 at 5. There are over 240 research ethics committees in England and Wales, 140 in Australia, over 100 in Canada and over 5000 in the US.

than a guideline approach. However, the situation in the U.S. regarding monitoring has been questioned in recent reviews. (Appendix 17). Although regulations are on the books, in the U.S., they have not been implemented fully. The FDA uses an administrative rather than substantive approach in monitoring during site visits and NIH responds to crises and employs prospective approval, in the form of assurances. NIH delegates responsibility for monitoring to institutions. (Appendix 8).

The summary of the NCBHR study results relating to monitoring, is as follows: a majority of REBs required annual reports, filing of adverse event reports, review by the REB of adverse event reports and reports of changes in protocol to the REB. A minority required an end of protocol report. In only 2 of 29 who responded, did the REB review patient charts to determine compliance with the protocol and only 8 of 44 stated that ongoing review or audit of research in progress is carried out by the REB. Of those where there was no monitoring of ongoing research, the most common reason was that they did not consider monitoring as part of their mandate and that they did not have the time or resources to do it.[100]

The study reported that REBs were concerned about continuous monitoring (progress and incident reports) and about investigators' infrequent consultation or discussion with REBs after initial approval of the research protocol. Untoward incidents are rarely reported to the REB, so REBs do not have the most current information about risks and benefits. REBs were uncertain about the kinds of monitoring that should be undertaken, but believed

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[100] *Ibid.* at 12.

monitoring was beyond their capacity. They requested NCBHR to help define monitoring and its particular applications–what is minimal monitoring? how should the process occur? what type of studies require monitoring? what kinds and frequency of monitoring and reports should be undertaken?[101]

Regarding continuing review and monitoring, the *MRC 1987 Guidelines* mandate the researcher to inform the REB of new information that might alter the ethical basis for continuing the research. The institution has a duty to assess the initial and ongoing compliance of research with proper and accepted standards and the researcher must provide an annual status report to the REB. The *TCPS* is not as detailed in its requirements.

The NCBHR study found that because of time and resource constraints, 25% of institutions have no monitoring mechanisms.[102] A possible solution is for some institutions to rely on individual departments to review ongoing research.

Summary

The nature of continuing review and monitoring varies across Canada due to a lack of resources and lack of specifics in Guidelines. This lack of detail regarding the definition of monitoring and minimal standards of monitoring is still present in the *TCPS*. Though the Policy does provide examples of forms of monitoring, it does not say who should be responsible for what and in what circumstances different forms of monitoring might be used.

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[101] *Ibid.* at 15.

[102] *Ibid.* at 23.
See also Appendix 13 for comparison of monitoring sections in both *MRC 1987 Guidelines* and *TCPS* and Appendix 14 for summary of *NCBHR Study* recommendations relating to monitoring.

ICH-GCP have recommended monitoring as part of each clinical trial. With clinical research in Canada, monitoring is usually carried out by experts appointed by the pharmaceutical industry. In some U.S. funded studies, monitors from the U.S. have visited Canadian centres to determine the accuracy of the data. This was the process which identified the problem at St.-Luc Hospital in Montreal (Dr. Poisson).[103] A further solution to the REB's lack of current information could be sharing of these results from pharmaceutical monitors with REBs.

The *NCBHR Study* found that although the *MRC 1987 Guidelines* propose continuous review and monitoring, this activity has not been implemented by REBs in Canada or in other jurisdictions.[104]

The NCBHR study recommended that site visits continue because, knowledge of the forthcoming review and the actual review, stimulated self-evaluation and necessary reforms. Voluntary external review is constructive and valuable for REBs, as there is no national auditing or credentialing yet in Canada.[105]

The study concluded that it is necessary that medical research in Canada remain accountable and accessible to society so the public will trust and be confident in the medical research enterprise. National ethical guidelines have sensitized the medical research community about the importance of ethics. The study confirmed unanimity on the

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[103] *NCBHR Study, ibid.*

[104] *Ibid.*

[105] *Ibid.* at 24.
See: Canada Gazette, Part I, January 22, 2000, Food and Drug Regulations, (Schedule No. 1024)--Clinical Trial. Credentialing may be on the horizon soon with these proposed amendments.

importance of ethics in research practice. However, REBs require more institutional and national support, more administrative and financial assistance, policy assistance, general educational support and training in research ethics, and more refined tools to apply to their review of the ethics of proposed medical research studies.[106]

As stated earlier, the ICH-GCP guidelines (dealing with pharmaceutical industry sponsored protocols) have been adopted by Health Canada. Therefore REBs are bound by them, (as are pharmaceutical companies who conduct research in physician's private offices). When universities accept the *TCPS*, its effect will be expanded to cover all research carried out at universities, however funded, as many universities were currently applying the *MRC 1987 Guidelines* to all research conducted at the university. If Health Canada also endorses the *TCPS*, the breadth of its authority will cover private research in general practitioners' offices as HPB/Health Canada has control over drug approval in Canada, and presumably could monitor research carried out in doctors' private offices. Health Canada and its Therapeutic Products Program have delegated, the legal authority to audit/inspect clinical trials and recognizes that other jurisdictions may conduct audit/inspections in Canada.[107]

Current status regarding monitoring in Canada utilizing Heath's conceptual framework:

a) **of REBs** - monitoring of REBs does not occur in Canada, except for the one NCBHR site visit discussed above;

b) **by REBs and institutions**

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[106] *NCBHR Study, ibid.* at 25.

[107] *Department of Health Act*, C.S.C., 1996, c.8, H-3.2; *Food and Drugs Act*, R.S.C., 1985, c.F-27; Health Canada, *ICH-GCPractice, supra* note 69 at i.

i) **continuing review**–currently takes place inconsistently, in the form of annual reports, adverse event reports, usually overseen by the REB, an REB sub-group, the REB chair or the research administrative staff;

ii) **consent process**-does not generally take place in Canada; current focus of the REB in the area of consent, is on the wording of the consent form, rather than on the consent process; an exception is the McGill study and to a more limited extent, the Halifax study (both to be discussed in detail following);

iii) **protocol adherence and collection of data**-for those studies which are industry sponsored (and under ICH-GCP authority) – monitoring is performed by industry. Industry dispatches company monitors or hires a contract research organization to make site visits every 6-10 weeks, to audit the protocol adherence and data integrity. A problem which the industry has generated through the ICH-GCP is reporting *to all sites*, of adverse events occurring in a study, at *any* study *site*. The difficulty is that the information is not put into context or interpreted for the REB, so the REB cannot use the information in a meaningful way. For those studies which are funded by granting councils, institutional grants or funded through foundations, there is no organized monitoring of protocol adherence or data collection.

iv) **identification of unapproved research**-is also generally not being performed on an organized basis by institutions. Institutions do learn of unapproved research taking place through informal networks within the institution.

Generally, the ongoing review of ethical commitments by the researcher is not taking place in Canada, as the annual reports and most other reports rely on the initiative and

disclosure of the researcher. No random audits are being performed in Canada except by the pharmaceutical industry (limited to their area of concern) and in Halifax.

Canada needs to develop methods to both monitor by the REB, protocols which it has approved and monitor the performance of the REB. Canadians are currently well served by committed individuals–researchers, members of REBs and staff of REBs. However, the universal problems of resources and education of REB members and researchers must be addressed. When the *TCPS* is adopted by universities and Health Canada, it will be seen as standard for research in the public and private sectors.

A major issue remains: what is the magnitude and what are the problems inherent in private (noninstitutional) research? Should NCEHR be responsible for oversight of private research and research reviewed by noninstitutional (independent) REBs? If not the NCEHR, who will assume responsibility to protect research subjects involved in studies which do not take place in a research institution? Is the Alberta model (later discussion), a solution for other provinces?

4. Funding Source

The source of funds, in theory, does impact on the responsibility for monitoring. The *TCPS* encompasses all research funded by the three councils and sets out as a condition of funding, that at a minimum, researchers and their institutions, comply with the ethical principles and articles in the policy. So, it would seem at first blush that Article 1.13 relating to Review Procedures for Ongoing Review, only applies to council funded research.[108]

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[108] *TCPS, supra* note 4 at 1.11.

It should be noted that the Tri-Council document refers to "continuing ethics review" of ongoing research, rather than "monitoring." However, the *TCPS* sets out that "continuing review could include the following: formal review of free and informed consent process, establishment of a safety monitoring committee, periodic review by a third party of the documents generated by the study, review of reports of adverse events, review of patients' charts or random audit of the free and informed consent process." Several of these functions go beyond those included in the "continuing review" function as defined by Heath.

Since such a large proportion of research is generated by the pharmaceutical industry (which has accepted the ICH-GCP as their minimum standard) and ICH calls for the IRB/REB to conduct continuing review of ongoing trials (at intervals appropriate to the degree of risk, but at least once per year),[109] industry sponsored research is bound by similar expectations regarding monitoring as council-funded research. Also ICH was adopted by Health Canada in 1997.

The difficulty is how to monitor research which is privately funded (as most council funded research is directed to institutions), which takes place outside the institution. The Alberta College of Physicians and Surgeons have set up their own research ethics committee for this type of research to be sure that it is reviewed. They also have the power to monitor.

5. Current Canadian Policy Governing the Monitoring of Ethical Conduct for Research Involving Humans – *Tri-Council Policy Statement* (*TCPS*)

The Tri-Council document states that the investigator shall propose at the time of initial review by the REB, the method of continuing review and does not say specifically in

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[109] Health Canada, ICH-GCP, *supra* note 69 at 13.

Article 1.13(b), that the REB must agree with the proposal or that if it does not, that the REB may direct the investigator regarding what it determines is appropriate continuing review. There is provision in the discussion after the articles which provides a list of options for the REB to pursue in addition to annual review, but this approach seems to place much of the initiation for these processes on the REB rather than on the investigator. Regarding the contents of an Annual Report, the *MRC 1987 Guidelines* are much more detailed than the *TCPS* (where there is no direction regarding contents of the Annual Report).[110]

The fact that the investigator must propose a monitoring scheme at the initial review stage provides an educational opportunity, but it also creates an issue for investigators: how to predict what will later be needed for monitoring purposes. The policy states that monitoring should also be proportionate, as review is proportionate, to the risk. However risk is evolving as the protocol proceeds or as other studies are conducted and reported.

The fact that the issue of continuing review must be dealt with in the initial review in the Tri-Council document, brings this issue into higher profile and will result in more consideration of monitoring as an issue, by the investigator and the REB. The mechanism of monitoring will depend on the particular protocol, the investigator and the REB. They may range from annual reports with full information, for protocols which are minimal risk, to detailed and extensive review by a variety of groups delegated the task by the REB for higher risk research.

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[110] *TCPS*, *supra* note 4 at 1.10 & 1.11; See Appendix 13.

The *TCPS* focuses more on informing REB of problems in higher risk protocols as opposed to the more general direction to researchers in the *MRC 1987 Guidelines*, to report changes or problems to the REB. There is not specific direction in the *TCPS* to institutions that it is their responsibility to assess ongoing research with regard to compliance with ethical standards (as there was in the 1987 Guidelines). Regarding institutional responsibility, the *TCPS* only refers to providing education to researchers. Compliance with the *TCPS* is a condition of funding.

6. Who Should Monitor?

The investigator is principally responsible, but someone must oversee the performance of the investigator. Monitoring is not just an REB issue, it is an institutional issue.[111]

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
researcher-most important role	-continuing review submission to REB of protocol amendments, adverse event reports with interpretation, annual or final reports; assure themselves that subject has had an opportunity for voluntary, informed consent -adherence to protocol -identification of unapproved research -inform patients and change consent form to reflect significant amendments	most knowledgeable about risks, benefits, current status of research, patient/subject	hasn't been seen as priority up to now; requires institutional support

[111] See also: graph on page 115 for more suggestions regarding what body could perform various monitoring functions–many groups have a role to play in different aspects of monitoring; See also discussion of current models of monitoring in Canada to follow.

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
REB itself	-continuing review (are investigators following REB directions?) -consent process (particularly higher risk) -adherence to protocol (focus generally on non-industry sponsored research) -identification of unapproved research- might occur through informal means; should be institutional responsibility	-multidisciplinary -lay representation (important in research implementation & review) -experienced about research generally & have reviewed protocol initially reviewed	-possible bias in favour of research generally & particular protocol or researcher -time consuming -may lose credibility with researchers if seen as policing
Subgroup of REB or multidisciplinary group such as past REB members	same areas as REB	-may be less biased & defensive regarding specific protocols -less demanding of full REB time	-if subgroup of REB, policing issue remains & is still time consuming for REB members who are part of subgroup
Single individual[112] i)independent of institution or ii) employee of institution, but not REB member (reports to REB);	same areas as REB	-possibly more independent of institution; less time consuming for REB	-loss of breadth of perspective (as not likely multidisciplinary); likely has not been involved in initial review

[112] This position could be described as the quality assurance officer, compliance officer, peer review officer, or clinical trials manager. Using the quality assurance label may be confusing. Compliance officer might indicate policing. If the person filling this position is not an investigator, the individual might not be considered a "peer."

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
Pharmaceutical company monitors (employees of company or contract research organization)	-only focus on protocol adherence and data integrity -especially concerned with multicentre trials -prevention of fraud & falsification	-could benefit REB by sharing their findings; this could reduce requirement for REB to monitor data (although random audits of data by REB may still be necessary, the industry is highly motivated to do a good job on data integrity as they want regulatory approval & could suffer major economic consequences if fraud or negligence was discovered)	-not a broad mandate; focus only on data integrity & protocol compliance; do not consider ethics process -cannot leave monitoring of industry funded research to industry, as they do not monitor everything

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
Patient advocate	likely focus on consent process	-currently part of research process regarding consent forms & process -not part of current system of monitoring; is useful to have unbiased third party as contact for subjects considering or participating in research -may be able to act as patient contact & convey concerns directly to REB, REB chair or department chair -could facilitate the monitoring function if encouraged to participate & given higher profile, so subjects are informed of their functions	-likely a lack of expertise regarding assessment of research issues -science & ethics
Government	-currently, no structure in government which could perform either monitoring of individual protocols (which was delegated by funding councils to local REBs), or monitoring of REB effectiveness	-has a major role in national standards of monitoring & reviewing performance of REBs -may be performed by existing NCEHR which has Health Canada funding or a new body	-should leave monitoring of individual protocols to local REBs who know local conditions

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
Institution	same as REB -has overall responsibility for high level of scientific & ethical research (generally delegated to REB); -REB terms of reference should include: REB responsibility for initial & continuing review; REB relationship to other institutional committees: data safety monitoring (internal & external), hospital clinical care standards, hospital accreditation, scientific review, scholarship, research, medical advisory, (responsible to hospital board for patient safety & professional performance, so have a role in monitoring research and monitoring REB performance), biohazard management, clinical and faculty education committees should be defined to avoid conflict between the REB and other institutional committees; -it is an institutional & departmental responsibility to do peer review of science & ethics (usually department chair sign REB application); the institution is responsible for the competence of investigator and patient/subject issues; is responsible to set up clinical trials and a quality assurance group to monitor the REB and make sure they are fulfilling their functions; institution or department could set up trial groups or monitoring committees which would review adverse events; -may also be a departmental or institutional clinical research monitoring committee or	-has the power to ensure monitoring occurs & REB & other entities have authority & resources to monitor effectively -has expertise in-house to accomplish peer review -knowledge of all entities which could share responsibility	-must make monitoring a priority & demonstrate leadership -must provide resources to monitor effectively -must define roles of parties and facilitate communication

Responsibility for Monitoring of Specific Protocols			
Who	**What**	**Advantages**	**Disadvantages**
Institution cont'd.	departmental data safety monitoring committee whose responsibilities vis-a-vis the REB should be defined; -departmental heads are responsible for patient safety; this accountability seems to shift to REB once patient becomes a subject; -institution also supervises (through peer review) professional ethical standards of researchers and is responsible for effective information and complaints mechanisms for subjects; -institution is responsible to define role of all parties in institutional policies or guidelines;		
Government Regulator	-Health Canada –concerned with review of adverse events & safety -should ensure that industry provides interpretation for adverse events;	-have authority to impose ethical standards through regulation	-inflexibility; increased bureaucracy -no knowledge of local conditions -no personnel to monitor REB performance or audit approved research

The key is to define who has what responsibility and to provide sufficient moral and financial support within the institution to ensure that the system functions properly to fulfil all ethical obligations. It is not only an REB or researcher responsibility, but an institutional responsibility as well.

Monitoring by the REB is a regulatory function. It has long been a responsibility of the REB to follow up on research it has approved. Just because it was not done in the past (partly due to lack of financial and personnel resources) does not mean that it should not be

part of the REB responsibility now. Monitoring by the REB must be implemented fairly, including input from the research community regarding a proper structure and process for monitoring. The system should work well (as in the Halifax example, to follow). The REB currently performs a component of regulatory function–the assessment of risks and benefits and determining whether research is valid and should proceed given the balancing of these concerns. At this point, the power is regulatory but not punitive. If the REB determines that the research is not being carried out ethically, it reports to the institution and the institution has processes in place to deal with scientific misconduct.

Monitoring of the REB

The issue of how REB effectiveness should be monitored and by whom is a very important one, as can be seen by surveys done in Canada by NCBHR and in other countries. There is a wide variation in the way REBs operate, how they meet, how they perform their review, the process utilized to arrive at a decision and whether they are monitoring approved research. The Tri-Council Policy Statement was an attempt to be more prescriptive regarding the minimum standards expected in conducting and reviewing research.

However, we run into the same problem as we encountered with the REB approval process in advance of the performance of research. Setting out expectations regarding REB operation in a policy statement does not ensure that they are being met in practice.(See pages 112-121 for a more detailed discussion of the issue of monitoring REBs).

7. Barriers to Monitoring and possible strategies for resolution

The process of monitoring seems daunting. How will it be coordinated? The absence of a system of monitoring and noncompliance with existing policies (Tri-Council, ICH-GCP)

is glaring.[113] Many factors act as barriers to the process of monitoring including the following concerns:

i) **REBs lack important information.** If the REB receives serious adverse events reports, they are not usually accompanied by interpretive information to give context and meaning to the information for the REB. The REB seldom receives other REBs' decisions in multicentre studies. The REB infrequently receives study progress reports, or reports of outcomes of trials or discontinuance.[114] On the other hand, recently, safety reports (serious adverse event reports), from sponsors are flooding the REBs with documentation.[115] These reports are not restricted to adverse events which are *both* serious *and* unexpected; they are highly complex without clarifying data. Currently, sponsors, data safety monitoring boards, contract research organizations, clinical trial cooperative groups and regulatory bodies (Health Canada-HPB) fail to submit useful and/or required safety information to the REB. A solution is to have agreement on a national basis, that sponsors, data safety monitoring boards and regulatory bodies will routinely pass on safety information to the REBs.[116] There

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[113] Crelinsten, *supra* note 97 at 28.

[114] W. Bohaychuk, G. Ball, G. Lawrence & K. Sotirov, "Ethics Committee and IRB Audit Results," (1998) 7 Applied Clinical Trials 11at 50 & 52; See page 50 for table of ongoing review activities and percentage of noncompliance in the study sites.
See also: M.S. Adams & D.A. Conrad, "Annual Review: Observed Deficiencies and Suggested Corrections,"(1996) 18 IRB A Review of Human Subjects Research 6 at 3-4. The article refers to a situation of failure to modify consent forms to reflect additional side effects and failure to inform IRBs of toxicities in interim analyses; NIH, OPRR Reports, January 10, 1995, No. 95-01 the Dear Colleague letter on the subject of Continuing Review–Institutional and Institutional Review Board Responsibilities, which sets out the minimum requirements of continuing review.

[115] E.D. Prentice & B. Gordon, "IRB Review of Adverse Events in Investigational Drug Studies," (1997) 19 IRB A Review of Human Subjects Research 6 at 1-4.

[116] Bohaychuk, Ball, Lawrence and Sotirov, *supra* note 114 at 47 & 54. As there are no national regulations stating otherwise, REBs could decide that they will only accept reports of serious and unexpected adverse event

is currently a task force of industry/academe attempting to resolve some of these outstanding issues between REBs and industry (such as: adverse events reports, multiple amendment documentation, consent forms generated by U.S. lawyers and pharmaceutical companies, publication clauses restricting publication by researchers, exclusion clauses which are too broad).

Some financial issues are ethical and should be considered by the REB. Other financial issues are concerns between university research offices and associate deans research and pharmaceutical companies, or between companies and researchers, and are not a direct concern of the REB. Some REBs see the entire contract, some do not. Usually the compensation to patients clause is included in the protocol, as it is pertinent to prospective subjects, but the REB may not know how much and on what basis the investigator is being compensated (financial and other, such as enrolment incentives for investigators, finders fees), which may also be an ethical issue.

The significant point is to define which group has which responsibility, to ensure that the safety of the subject is not at risk, as the responsibility has not been assumed by anyone.

The expectation is that this industry/academe working group will develop draft approval letters, standardized consent forms, resolve contractual issues, develop templates of language relating to finders' fees, compensation and fees for service which will be available as models for use across the country. If some standard clauses or model agreements are acceptable to REBs, this will alleviate some of the frustration of the pharmaceutical

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reports and that sponsors are responsible to provide comprehensive, understandable results; the sponsor is in the best position to interpret results, as they see them all; regular safety reports would be more useful than numerous adverse events reports which are uninterpretted.

sponsors at having to prepare new documentation for each REB. It will also reduce the frustration on the part of the REB members at having to deal with issues or terminology which are not applicable to the Canadian health care system. Some standardization would be mutually beneficial.

Renewal applications from investigators could also be standardized by asking for rationale supporting no change in the protocol (which would put more onus on the investigator and assist the REBs).

A consistent system of reporting adverse events should also be established (focussing on serious *and* unexpected serious events) which sets out: to whom should they be reported? by whom? what should the response be? should REBs report to companies who report to the HPB? How do we learn about ethical misconduct and how and to whom are it reported? What is the result, if misconduct occurs? Should there be a compulsory halt to the research if there is a non-reporting of ethical problems? Is the department head monitoring for ethical concerns? Do young investigators receive sufficient direction and supervision regarding their protocols? The issue of whether it is the REB's or investigators' responsibility to uncover new medical information, affecting the safety or ethics of continuing the protocol, remains to be determined. What are the responsibilities of the investigator and REB regarding adverse events reports or end of study reports?

ii) **legal liability of researchers, REBs and institutions**– The issue is the uncovering of negligent medical treatment in a research study, while monitoring the study.[117] Failing to

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[117] See also: D.B. Bush, G.T. Bryan, D. Easterling, H. Leventhal, E.M. Messing & K.B. Cummings, "Follow-Up: Recontacting Subjects in Mutagen Exposure Monitoring Studies," (1988) 10 IRB A Review of Human Subjects Research 5 at 9-11 for discussion of issues concerning disclosure of test results which are suggestive,

monitor does not protect against such liability. The presence of a monitoring program might be preferable to no monitoring at all, as it would provide the institution with an opportunity to correct problems before research subjects are needlessly harmed.[118] As the case of *Weiss* v. *Solomon* demonstrated, the existence of an REB is not an automatic defence. The REB actions will be examined and if negligence is found in the REB conduct, the REB and institution will be held liable. The concern regarding liability can be met by ensuring the performance of research at the highest medical and ethical standards on the part of researchers, REBs and institutions and the absence of negligence. Strategies to achieve high levels of performance of research might include development of institutional policies regarding research and roles and responsibilities, which can be utilized as standards against which to measure performance (COCO-MEM proposal)[119] and through education of

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but not conclusive, including discussion of potential litigation; D.B. Busch, G.T. Bryan, E.M. Messing & K.B. Cummings, ""Recontacting Subjects in Mutagen Exposure Monitoring Studies," (1986) 8 IRB A Review of Human Subjects Research 6 at 1-4.

[118] B. Freedman and C. Weijer, "'REB Continuous Review and Monitoring,' in Proceedings of Workshop '95 on the Ethics of Human Experimentation: REinventing the Research Ethics Board," (1996) 7 NCBHR Communiqué 1 at 25-26.

[119] P. Deschamps, R. Cavaliere & R. Martineau, *COCO/MEM Project, On The Development Of A Management, An Evaluation And A Monitoring Framework In The Field Of Biomedical Research, General Overview*, December 1998. Utilizing the COCO framework developed by the Canadian Institute of Chartered Accountants, the project developed a comprehensive management, evaluation and monitoring framework which integrates the organizational, scientific, clinical, ethical, legal and financial aspects pertaining to biomedical research activities conducted in health care institutions. As the focus was on institutions, the recommendations do not transfer to the private setting very well.
The four main components are: orientation and objectives, commitment and ethics, capability and training and monitoring and learning. The mission and vision are used as a basis for development of strategic objectives and plans. The basis of risk management is risk identification, such as non-compliance with existing law, regulations, directives and policies, injury of research subjects and misappropriation or improper use of funds. Policies provide a management and evaluation framework and form a basis for the development of an appropriate monitoring framework. Policies can be developed in the following areas: conflict of interest, approval of research protocols, content of consent forms, confidentiality and disclosure of research data and results, follow-up activities, accounting and financial reporting.
The authors hope that the COCO/MEM framework becomes the basis of an accreditation system for research

researchers and REB members regarding expectations. Responsibility for consideration of legal issues is shared between the REB and other groups within the institution, such as university contracts office (indemnification/compensation for injury; ownership of data). There must be integration between research offices and REBs so that they know what each is responsible for (as some REBs see the entire contract and some do not).

iii) **resistance by investigators to monitoring**–Investigators resist monitoring as: they do not see REBs as peers; they view REBs as blocking research; many do not think REBs perform serious review; they view the REB as a challenge to the doctor/patient relationship and they assume monitoring implies a lack of trust, without recognizing that researchers are human and that bias enters everyone's actions. Cooperation of investigators with the REB is key to the success of any monitoring program. Education of investigators regarding the goals of a monitoring program is indispensable. Distinguishing between error and culpable error, as suggested by B. Freedman, would assist investigators to understand their monitoring responsibilities. The parallels between research monitoring and other routine institutional quality control measures—including medical audits and quality assurance reviews–ought to be emphasized.[120] Medical audit (which focuses on outcomes of care for patients, where care is to benefit the individual patient), is recognized as essential to improving the quality

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activities. This framework is most directly applicable to the issue of 'monitoring of REBs' rather than 'monitoring by REBs.' It is directed at institutional rather than noninstitutional research settings.
See also: M.E. Evans, "The Legal Background of the Institutional Review Board," in Greenwald, Ryan an Mulvihill, *supra* note 8 at 25-26. Increasing responsibilities for IRB members (such as adding monitoring to review responsibilities), increases the potential legal liability of IRBs members and increases the procedural safeguards which must be offered to investigators.

[120] Freedman & Weijer, *supra* note 118 at 26.

of medical care. Research audit (which relates to all components of research, including the consent process and requires an understanding of ethical issues) should be viewed in the same way vis-a-vis the quality of research. Research audit is broader than data auditing (which is done by pharmaceutical company monitors. Data monitoring could also be done by an institutional research office).[121]

Investigators perceive an adversarial relationship between themselves and the REBs for many reasons.[122] Both the monitoring body and the investigator should view monitoring as a learning opportunity; if the educational approach is adopted. The REB performing monitoring should be seen as performing continuing peer review and the relationship between the REB and investigator should be collegial, not adversarial.

Possible strategies to employ in approaching this problem are: education of researchers regarding expectations and responsibilities; increasing sensitivity on the part of researchers regarding perceptions of subjects, role confusion and conflict of interest; utilizing the quality assurance and education approach, rather than focussing on investigation and sanctions. Perhaps using the term "**research audit**" would be more acceptable to investigators than "monitoring."

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[121] C. Weijer, S. Shapiro, A. Fuks, K. Glass, M. Skrutkowska, "Monitoring Clinical Research: An Obligation Unfulfilled," (1995) 152 Can Med Assoc J 12 at 1975.
See: Statement by the Audit Working Group of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom, "Access to medical records for the purposes of medical audit," (1993) 306 BMJ at 897.

[122] Meslin, *supra* note 79 at 185. Four reasons why investigators view their relationship with IRBs as adversarial are discussed.

iv) **resource limitations**–Onerous workloads and the scarcity of resources (financial and administrative), within academic and health-care institutions are a reality.[123] Cost is a factor to consider. It will be costly to implement a system of monitoring where none exists. Is annual ongoing review too costly? Sufficient resources must be provided from the institutions and sponsors (both public and private). A percentage of budgets of protocols (25%- 40%) is currently collected from commercial sponsors for overhead. A portion of this budget must also be directed to funding REB operations, including monitoring of approved research. Freedman suggested that one way to reduce the cost of monitoring is for REBs to take advantage of existing continuous quality improvement measures within the institution. Some of the REBs' monitoring activities could 'piggy-back' on these existing mechanisms, avoiding duplication of staff within the institution.[124] The difficulty in combining purposes is that the often-blurred distinction between research and clinical care, would become even more indistinct.

Quebec has the requirement that private enterprise make a contribution in the context of contract research. This is an additional contribution of 20% above the research costs (included in the contract)–18% of that amount is used to cover the operating and infrastructure costs of the research centre, or the costs of other 'non-contract' research activities as determined by the scientific director or the research director; 2% covers the costs

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[123] A. Lynch, "Research Ethics Boards–Operational Issues I," (1999) 9 & 10 NCEHR Communiqué 2 & 1 at 13.
See also: DHHS Office of the Inspector General, *IRBs: Their Role in Reviewing Approved Research, supra* note 48 at ii.

[124] Freedman & Weijer, *supra* note 118 at 26. NIH regulations require the institution provide sufficient funding for proper IRB functioning.

of accounting services provided by the hospital. This policy applies only to research contracts, not to grants.[125] This is an effort to have industry pay for overhead, which in the past was 'supported' by the hospitals. In Quebec, research centres do receive budgets from the Ministry of Science and Research for infrastructure, but not for operating costs of contract research.[126]

Perhaps this legislation could be utilized as a model to ensure sufficient income from industry to cover the operation of a research office, with responsibilities for ethics review (including monitoring). Neither this Ministerial policy nor past practice require granting agencies to contribute towards the costs of research ethics. Granting agencies seldom grant the total budgets requested. Investigators would not favour further reduction to cover research operations.

The *TCPS* also calls for institutions to ensure that REBs have the appropriate financial and administrative independence to fulfil their primary duties [127] and requires institutions and researchers to comply with policy as a condition of funding. This requirement in the *TCPS* means that institutions must provide REBs with enough resources to review and monitor appropriately. The ICH-GCP also speaks to the issue of funding.[128]

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[125] Appendix 2 of the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique; Ministry of Health, Appendix 2 to the Minister's Action Plan; Contribution of private enterprise in the context of contract research; First issued April 1, 1992, revised October 1993, March 1, 1995

[126] Private conversation with Dr. Jean-Pierre Tétrault, Departement d'anesthésie, Université de Sherbrooke

[127] *TCPS*, *supra* note 4 at 1.2, text following Article 1.2.

[128] Health Canada, *ICH-GCP*, *supra* note 69 at 12 & 17. Investigator responsibilities (4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely); Institutional review board responsibilities-(3.1.1 An IRB/IEC should safeguard the right, safety and well-being of all trial subjects)

v) **confidentiality of patient/subject information** is an important area to consider in monitoring. Planned or ongoing monitoring activities must be disclosed to the subject, as monitoring the consent process (including patient record review and interviewing of patients), may involve infringing patient confidentiality and requires disclosure and subject consent.[129] Random checks of patient comprehension may be done by way of formal questionnaire or interviews in person or by telephone. The McGill study (to follow) is an example of an REB carrying out direct monitoring of the consent process performed by a delegate of the REB, where the research posed serious risk and the REB made independent review of adequacy of consent a condition of approval of the study.[130]

Many of the above suggestions deal with situations of institutional research. The issue remains: how to deal with research in a physician's private office? In Alberta, the issue has been resolved with the establishment of a research ethics committee by the College of Physicians and Surgeons (detailed discussion will follow). Other provinces do not use this approach.

vi) **heightened workload pressures**–relates to an increase in the number of research protocols and a lack of financial and other resources, i.e. unable to add staff or other resources. Methods must be employed to reduce the workload. Possible solutions could include additional REBs, primary reviewers, more expedited review and perhaps, random

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[129] Freedman & Weijer, *supra* note 118 at 25-26.

[130] M. Skrutkowski, C. Weijer, S. Shapiro, A. Fuks, A. Langleben & B. Freedman, "Monitoring Informed Consent in an Oncology Study Posing Serious Risk to Subjects," (1998) 20 IRB A Review of Human Subjects Research 6 at 1-6.

initial review; consideration of forms of compensation and recognition for members of REBs such as academic recognition;

vii) **limited IRB expertise**--insufficient scientific expertise to conduct review of more sophisticated research, such as genetic engineering, and complex multicentre protocols (where assessment of results may entail sophisticated statistical analysis), which may necessitate bringing in external experts to consult on particular studies;[131]

viii) **limited non-scientific and noninstitutional input**–refers to difficulty in obtaining and maintaining lay representation;[132] Suggestions to increase lay representation my include approaching past subjects, advocacy groups for particular disease groupings and provision of education for all REB members, enhancing the REB experience for lay representatives.[133]

8. Other Issues in Monitoring Which the Research Community Must Address

Some of the specific issues which the research community must address, which may not necessarily be considered barriers to monitoring, are the following:

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[131] D.H. Cowan, "IRB Review of Randomized Clinical Trials, Scientific Design, Ethics and Monitoring," (1980) 2 IRB A Review of Human Subjects Research 9 at 1-4. Research design in nationally funded or cooperative group trials has been analyzed. In clinical trials proposed by individual investigators, which are not externally reviewed, the IRB serves a quasi-peer review role relating to trial design.

[132] DHHS, Office of the Inspector General, *IRBs: Their Role in Reviewing Approved Research, supra* note 48 at ii; This report identified Barriers vi-viii above (among others) as limiting the IRB's capacity to conduct continuing review. These barriers are applicable to Canada as well.

[133] See also: Benson, *supra* note 32 at 5-6. Benson discusses issues relating to the efficiency and efficacy of decision-making by local boards; R.M. Veatch, "Human Experimentation Committees: professional or representative?" (1975) 5 Hastings Center Report at 31-40 for discussion of the most appropriate model for IRBs–the interdisciplinary professional review model or the jury model (a variation is the representative model); G.J. Hayes, S.C. Hayes & T. Dykstra, " A Survey of University Institutional Review Boards: Characteristics, Policies and Procedures," (1995) 17 IRB A Review of Human Subjects Research 3 at 1-6 for discussion of functioning of IRBs; the authors suggest a more careful selection of new members representing a broad range of community values and periodic evaluation of the IRB to maintain quality and objectivity in decisions.

i) **criteria for monitoring** (when to conduct spot checks) must be decided upon which could include situations of: high risk, little experience of investigator, poor understanding of protocols (by investigator in relation to the process; by the subject, due to complex procedure or language problem or education level);[134] when the REB suspects unethical research, they may conduct a quiet inquiry, work with the department chair, delegate to a committee or perform an audit or investigation or appoint an independent monitor; ongoing audits have some merit, but they must be detailed and focussed to detect abnormalities, with great financial and human resource commitment (of highly qualified monitors);[135] in the Poisson case, the NIH stopped funding and sent in a team to audit the study; a Canadian body, NCEHR or another body, possibly a government body independent of the funding councils, could do the same thing with projects which are federally funded. With projects funded from other sources, a university with a policy that all research is subject to REB review and *TCPS* guidelines, could stop the flow of finances if there was non-compliance. How should the need for monitoring be determined? The *TCPS* states that the investigator should propose the method of monitoring at the time of initial review. It is not clear whether the REB can propose the monitoring method if the researcher fails to do so, or that the REB

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[134] Christakis, *supra* note 4 at 9.

[135] Crelinsten, *supra* note 97 at 28.

can overrule the method proposed by the researcher.[136] Criteria which REBs should use to judge 'ethical' is not clearly defined.[137]

ii) **authority of the REB**--REBs should have clearly stated, the authority to impose cessation of research, based on inadequate annual review. Annual reports are mandatory according to the *TCPS*. What should the response of the REB be regarding violations by the researcher of conditions for approval–what should sanctions be and who should enforce them? One possible solution is to set up research safety committee-within departments or for the institution as a whole- which would act like a clinical auditing committee (may be similar to structure in Halifax, but Halifax has lay representative). In multi-centre trials, the authority of the REB to refuse approval and make changes on consent forms should be affirmed, particularly in relation to eligibility criteria (based on the responsibility for subject safety and scientific validity);[138]

iii) **issue of consent**--The REB's narrow focus on the consent form is unlikely to result in meaningful consent by research subjects because: 1) the forms may not provide relevant information in understandable language; 2) a signed consent form does not assure that a subject has given a meaningful and voluntary, informed consent; 3) the structure of the recruitment situation often interferes with meaningful choice (the disparity in knowledge and

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[136] *TCPS*, *supra* note 4 at 1.10-1.11; See also Appendix 13 for comparison of *MRC 1987 Guidelines* and 1998 *Tri-Council Policy Statement* monitoring sections.

[137] E.M. Meslin, J.V. Lavery, H. J. Sutherland & J. E. Till, "Judging the Ethical Merit of Clinical Trials: What Criteria Do Research Ethics Board Members Use?" (1994) 16 IRB A Review of Human Subjects Research 4 at 6-10.

[138] B Freedman, "Multicenter Trials and Subject Eligibility: Should Local IRBs Play a Role?" (1994) 16 IRB A Review of Human Subjects Research 1 & 2 at 1-6; *Weiss* v. *Solomon* case is an example.

power of the physician and the patient/subject, often experiencing serious illness). Physicians may consciously or unconsciously manipulate the decisions of their patients.[139] Spot checks by telephone can be done to determine subject's comprehension (timing of follow-up may affect whether are testing memory or comprehension; are these follow-up results reported? to whom? investigator or REB?) As consent forms get major attention from REBs during the initial review, consent forms should also be given much attention during annual reviews and in random chart review. This would enable the REB to determine whether the changes they directed the investigator to make were in fact made, whether the form signed was that approved and whether the form was understandable for the prospective subject;

Another issue deals with research with communities. Does informed consent need to be obtained from communities, and if so, who should be their representative?[140]

iv) **duration of approvals and IRB review**--for how long should REB approval be given, before full re-review as opposed to annual renewal on the basis of the researchers' statement of 'no significant change'?[141]

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[139] Robertson, *supra* note 1 at 1.
See also: P. S. Appelbaum, "Rethinking the Conduct of Psychiatric Research," (1997) 54 Arch Gen Psychiatry at 117-120 The problem with the IRB's excessive focus on the consent form as their primary mechanism to protect subjects is that it does not deal adequately with the many groups of patient/subjects who are incompetent to consent: geriatric, adolescent, seriously medically ill, mentally disabled and psychiatrically ill; R. J. Bonnie, "Research with Cognitively Impaired Subjects, Unfinished Business in the Regulation of Human Research," (1997) 54 Arch Gen Psychiatry at 105-111. The important ethical issues concerning research with those who are cognitively impaired has not been adequately addressed by policy-making bodies; safeguards are linked to undue influence and coercion rather than impaired decisional capacity; C. Elliott, "Caring About Risks, Are Severely Depressed Patients Competent to Consent to Research?" (1997) 54 Arch Gen Psychiatry at 113-116. We may have to alter our ways of assessing competence.

[140] F. Enquselassie, "Communities' confidentiality should be maintained and community consent sought," (1996) 312 BMJ at 54-55.

[141] See also: R.J. Amdur & E. Bankert, "Continuing IRB Review When Research Activity is Limited to Routine Follow-up Evaluations," (1997) 19 IRB A Review of Human Subjects Research 1 at 7-10 for a

v) **costs of monitoring**--should these be charged to the sponsor, whether private industry or funding councils? Should funding Councils change their past practice and provide a line in application/grant for cost of ethics review and monitoring? In the *TCPS*, the Councils confirm that they are responsible for the research they fund. They have delegated the authority and responsibility to the local REBs without the accompanying funding. Where clinical trial centres are established to conduct research, the costs of ethics review and monitoring conducted in these centres should be paid for by those funding the research. These funds should be deposited with the institution (rather than the REB), to avoid the perception of conflict of interest. Institutions must assess the real costs of review and monitoring (including the costs of education of REB members). A national study of fee structures would be useful for REBs and institutions. NCEHR or whatever national organization assumes responsibility for monitoring REB performance must receive at least as much funding from Councils and government, as the CCAC does (responsible for animal safety).[142]

vi) **industry** – does their own monitoring of data. They do not monitor for scientific integrity and validity (the overall validity of doing the research in the first place). Assessing the validity is dealt with in part, if the company has a group of investigators from outside the company who develop the protocol, or at least act as an independent safety monitoring board.

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discussion of situations when IRB review should be continued.

[142] See also: J. Cohen, "The Costs of IRB Review," in Greenwald, Ryan and Mulvihill, eds., *supra* note 51 at 39; S.E. Lind, "Dilemmas in Paying for Clinical Research: The View from the IRB," (1987) 9 IRB A Review of Human Subjects Research 2 at 1-5 for a discussion of the dependence of clinical research on third party coverage of health care costs; the study is often simply a tool to deliver the latest in medical care to the patient; this may be more of an issue for the U.S., but there are still many hidden costs in clinical research in Canada.

Industry does consent monitoring by checking that forms are signed. They do not monitor the consent process. The pharmaceutical industry in Canada, generally monitors its own research in-house (with their own employees). In Canada we do not have many independent data safety and monitoring committees. REBs should continue to monitor industry-sponsored protocols (including data), as industry is concerned with data integrity, not ethics.[143] Drug research sponsored by drug manufacturers does not have the same type of peer review associated with federal research grants and it unlikely to be scrutinized by anyone other than the sponsor and the regulatory agency. To fill this void, FDA adopted audit procedures in the late 1970s, but FDA is limited by its budget and its audit focuses on administrative, rather than substantive review.[144]

vii) the REB should be concerned with the **risk/benefit ratio for particular patients**. The difficulty is that the benefits are to a group of future patients and can be dealt with on a study basis only. However, the risk is incurred by individual subjects and the REB is not in a position to assess the risks to a particular subject. Assessment of risk to the specific subject is left to the researcher and the subject.[145]

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[143] See also: R.F. Schwarz Jr., "Maintaining Integrity and Credibility in Industry-Sponsored Clinical Research," (1991) 12 Controlled Clinical Trials at 753-760. Schwarz discusses the factors affecting the credibility of industry-sponsored research and presents solutions and safeguards.

[144] M.F. Shapiro & R.P. Charrow, "The Role of Data Audits in Detecting Scientific Misconduct." (1989) 261 JAMA 17 at 2509. FDA does not audit the majority of studies submitted by sponsors. Data audit of drug studies requires less technical knowledge than audits of basic research on the cutting edge of a discipline; M.F. Shapiro & R.P. Charrow, "Scientific Misconduct in Investigational Drug Trials," (1984) 312 NEJM 11 at 736. FDA does not randomly audit all investigators. It audits systematically those studies which appear to be important enough to use for drug certification. FDA takes action against those who have engaged in scientific misconduct.

[145] Heath, *supra* note 56 at 2.

viii) With regard to **interim analysis**, the focus is on safety and whether there is a trend that would dictate that the protocol should be stopped due to adverse events or a trend that one arm is far superior to the other. The issues are whether to perform interim analysis in the first place, who should perform it, who should the results be reported to, how the REB deals with the results –should they stop a protocol even though it has not met the criteria for stopping which was established by an independent committee prior to the protocol beginning?

ix) the **MRC should be monitoring its studies**. The *MRC 1987 Guidelines* direct MRC to monitor and the *TCPS* also calls for accountability. The *TCPS* sets up the highest ethical standards and there must be compliance with the *TCPS* in order to receive Council funding, but the Councils have not set up a mechanism to ensure that this takes place.

x) **non-institutional research** which is funded privately-- this research does not fit under the umbrella of standards set out by the *TCPS* and does not require ethical review and monitoring, unless it is a study of a drug and the company sponsor is bound to comply with the ICH-GCP guidelines.[146] Many institutional REBs refuse to review research protocols over which they have no control (the investigator is not an employee, has no hospital privileges, has no university affiliation). Noninstitutional research can also refer to research

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[146] See also: E. Heath, "The Noninstitutional Review Board: What Distinguishes Us From Them?" (1998) 20 IRB A Review of Human Subjects Research 5 at 8-11. Noninstitutional review boards (NIRBs) are known by many names. Ten distinguishing features are discussed and comparisons are made with IRBs regarding these 10 features. NIRBs also exist within a parent institution; none are free-standing. Their parent is usually a corporation; T. Lemmens & A. Thompson, "For-hire Research Ethics Boards and Institutional Review Boards: How do they function? What Do They Do?" (Publication pending in IRB A Review of Human Subjects Research); K.C. Glass & T. Lemmens, "Conflict of Interest and Commercialization of Biomedical Research: What is the Role of Research Ethics Review?" in T.A. Caulfield & B. Williams-Jones, *The Commercialization of Genetic Research, Ethical, Legal and Policy Issues*, (New York: Kluwer Academic/Plenum Press, 1999).

occurring in noninstitutional settings which do not have REB review, i.e. occupational health.[147] One model developed by the Alberta College of Physicians & Surgeons provides a venue for this research to be reviewed and monitored. (discussion to follow).

There are currently about five to ten private REBs operating for profit in Canada and at least fifteen, possibly more in the U.S.[148] These noninstitutional REBs come with their own sets of issues, the foremost being conflict of interest, as the sponsor requesting the review is the one paying for the review. In the U.S., private IRBs are increasing. The FDA allows commercial IRBs for certain protocols.[149] Private physicians are interested in accessing some of the $900 million invested by pharmaceutical manufacturing industry (PMAC) in research, which is directed to Phase IV studies (marketing), which they can perform in their offices. Perhaps it would be helpful if NCEHR, the Royal College of Physicians & Surgeons of Canada and/or the College of Family Physicians of Canada considered the issue of Phase IV studies and made recommendations regarding how they are

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[147] R. Bayer, "Biological Monitoring in the Workplace: Ethical Issues," (1986) 28 Journal of Occupational Medicine 10 at 935-939. Occupational health research in occupational health settings often does not offer participants the same protections of IRB review as hospital research. There is a profound asymmetry in the power relations in the workplace setting.
See also: D. Cantor, "Monitoring of Outside Research," (1983) 5 IRB A Review of Human Subjects Research 2 at 10 for a discussion of issues relating to IRB review of noninstitutional research.

[148] Lemmens & Thompson, *supra* note 146.

[149] S.S. Herman, "A Noninstitutional Review Board Comes of Age," (1989) 11 IRB A Review of Human Subjects Research 2 at 1-6. FDA does not require registration of noninstitutional IRBs, so there is no way of knowing how many there are. The article discusses the Philadelphia noninstitutional review board. With increasing numbers of Phase IV studies (post-marketing), and increasing numbers of private practitioners performing research, an increased role for the noninstitutional review board is likely.
See also: Department of Health & Human Services, USA, Office of Inspector General, *Institutional Review Boards: The Emergence of Independent Boards*, June 1998, OEI-01-97-00192 [hereinafter *IRBs: Independent Boards*]

to be carried out and by whom. What type of qualifications one should have in order to be entitled to conduct this type of research?

Non-institutional research could be reviewed by:

a) an institutional REB–how many institutional REBs take this on? Many institutional REBs perform review of external research as they think someone should review. This review raises issues of legal liability and conflict of interest (payment for doing review for third parties). Review of non-institutional research raises clear questions about monitoring duties and authority over such research. Besides the initial review, the REB considers incident reports and general monitoring of research conduct. Institutional REBs who do review non-institutional research, may wish to insist on a duty to monitor (as they may be held legally responsible for doing so);

b) a bona fide REB which is established by the College of Physicians and Surgeons;

c) national specialty societies such as the College of Family Physicians of Canada or the Royal College (as their focus is on specialty licensing, they may be unwilling to expand their mandate);

d) governmental or non-governmental provincial or regional health authorities or

e) Pharmaceutical Manufacturers' Association of Canada. These REBs could be financed by a blind trust created by pharmaceutical companies to conduct review as they have been operating in the U.S. (in Philadelphia[150]), and would be required to operate at arm's length from its founders.

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[150] Herman, *ibid.* at 1-6.
See also: B. Alberts & K. Shine, "Scientists and the Integrity of Research," (1994) 266 Science at 1660-61, for a discussion of issues which damage the integrity of science, but are not considered 'misconduct.'

What mechanisms, processes, structures and resources ought to be created to ensure that non-institutional research receives coherent ethics scrutiny?[151] Should ethics committees which are supposed to be unbiased and independent, operate for profit? Will marketplace pressures result in investigators seeking approval from the least rigorous or least expensive IRB?[152] There is also the situation of independent research institutes, and/or contract research organizations conducting research and coordinating/conducting/monitoring research for multi centre trials.[153]

Several other issues deserve mention. The first two have received extensive public press coverage and are a matter of broad-based interest and concern. The latter two do not appear to have engendered as much public comment, largely due to the lack of general information about these issues. They are: 1) **academic freedom and restriction of information**–who has control over publication of results? e.g. Dr. Nancy Olivieri was threatened with legal action by Apotex, the research sponsor, if she went public with negative results in her study;[154] 2) **pressure by industry on the regulatory system to**

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[151] *NCBHR Study, supra* note 78 at 25.

[152] Bohaychuk, Bell, Lawrence and Sotirov, *supra* note 114 at 54.

[153] Private conversation with Dr. Mark Poznansky, Director of the Robarts Research Institute, Ontario.

[154] K. Foss & P. Taylor, "Researchers at Sick Kids Threaten to Leave," *The Globe and Mail* (28 August 1998) at A.3
See: *TCPS, supra* note 4 at i.8 in reference to academic freedoms the Policy states.... "These freedoms include freedom of inquiry and the right to disseminate the results thereof...freedom from censorship...."
See also: M. Valpy, "Salvage group tackles Sick Kids' image disaster,"*The Globe and Mail* (2 November 1998) A1 There was international damage done to the hospital's reputation by failure to censure the drug company and fully support its own researchers; P. Arab, "'Harassment' alleged in drug research feud,"*The Canadian Press*, reprinted in *The Edmonton Journal* (18 December 1998) A.14 The University of Toronto Faculty Association filed grievances against the university accusing administrators of failing to give legal or moral support to Olivieri. An external review blamed lax hospital policies and a systematic breakdown for causing the battle to get out of hand; W. Roush, "Publishing Sensitive Data, Who Calls the Shots?" (1997)

approve drugs;[155] 3) **research for hire**–the development of the pharmaceutical industry sponsored clinical drug trial situated in private physicians' offices has created many new concerns regarding conflict of interest, quality of research, protection of patient/subjects, monitoring responsibility (many of these concerns were discussed earlier);

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276 Science at 523-24, which refers to the tension between science's tradition of open publication and industry's desire for secrecy; Toronto Star, "Firm Axes Outspoken Scientist's Research," (26 January 1999) A.2, which deals with suppression of negative data; the growing link between industry and academia affects reliability of information; Editorial, "Editors and Ethics," (1997) 2 Nature Medicine 12 at 129-130 for discussion of the role of journal editors; Editorial, "Research Ethics Clouded," *Winnipeg Free Press*, (22 September 1998) A.14 where reference is made to a suggestion by C. Weijer that as most research done for the Health Protection Branch (Health Canada) review is in the private sector, if HPB adopts the *TCPS*, it would extend the Policy to the private sector; J. Weiner, "Could the U of A have an 'Olivieri' case of its own?" *U of A Folio*, (15 January 1999) 5. Under the General Faculties Council policy, industry contracts cannot give the sponsor total control of the data. The principal investigator must be able to publish the results after the sponsor has reviewed the contents and can only delay publication for a specified period (not to exceed 18 months) in order to protect intellectual property. Investigators entering into contracts with industry must have the contract reviewed by the University's Contracts Office; J. O'Hara & S. Deziel, "Whistle-Blower," *Maclean's*, (16 November 1998) 64-69. Discussion of the Olivieri case and that of another physician in Montreal. Powerful constituencies with vested financial interests are routinely intimidating investigators who point out the health risks of drugs and medical procedures. The increasing potential conflicts of interest for investigators and research institutions, create a greater need to protect the interests of patients; E. Marshall, "Secretiveness Found Widespread in Life Sciences," (1997) 276 Science 525 discussion of delayed publication and data-hoarding.; G. Vogel, "Long-Suppressed Study Finally Sees Light of Day," (1997) 276 Science 525-526 for discussion of Betty Dong situation, company withdrew paper for publication; issue: suppression of unfavourable results; finally published 8 years later.

[155] J. Ditchburn, "Drug Delays Rile Biotech Firms," *The Canadian Press*, reprinted in *The Edmonton Journal* (8 December 1998). Biotech firms will take business elsewhere if Canada's drug approval process does not become more efficient; these comments were made in relation to desired HPB approval of bovine somatotrophin (BST)
See also: J. Dermont, "Pressure Point, Federal researchers say drug companies push hard for approvals," *Maclean's* (16 November 1998) 70-72. Discussion of the case of five Health Canada scientists from the Health Canada relating to a Senate committee the pressure exerted on them to approve bovine growth hormone, including stolen scientific files, critical data missing, an alleged bribe by a giant multinational drug company; HPB is currently undergoing overhaul; events which Health Canada had some responsibility for are the tainted blood scandal and silicone breast implants; Health Canada scientists faced hounding (threats, harassment and intimidation) from their superiors in Health Canada; due to deficit reduction policies, HPB now receives 70% of its drug review budget from corporate sources; this cost recovery creates potential conflicts of interest; article includes details of HPB's reorganization.

4) **research fraud and misconduct**– have reached the top of the science policy agenda; what is the role of the IRB in relation to discovery, reporting and sanctions relating to fraud and misconduct?[156]

9. Sanctions

Who does the body responsible for monitoring report to? Whose responsibility is it to respond to issues of research integrity and scientific misconduct? What is the role of the department head? There is a need to link monitoring results to disciplinary action. Should disciplinary action be taken by the REB or by the department chair (as an extension of the university administration)? Who should be responsible for discipline– the CEO of institution/hospital, or the Dean or associate dean of research? the MRC (as funder)? What is the role of the independent or industry monitor? Who do they report to and are they involved in imposition of sanctions? Should there be established a national research advisory committee for dealing with these types of problems?

The REB has the authority to stop research if annual review is inadequate, (Article 1.2 in the *TCPS*).[157] Presumably this occurs by the REB referring the matter to the institution, which could presumably cut off funding. The REB has a regulatory function. Perhaps it

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[156] S. Hilgartner, "Research Fraud, Misconduct and the IRB," (1990) 12 IRB A Review of Human Subjects Research 1 at 1-4. The traditional view is that misconduct is a problem of individual pathology and is rare. Since the 1980s, observers have lost confidence that scientific misconduct is rare. The broader range of unacceptable practices, beyond fabrication of data and plagiarism, is discussed. Fraud (never acceptable) and error (inevitable in science) must be distinguished. The article discusses three levels of responsibility regarding misconduct and causes of misconduct. Misconduct becomes an IRB issue only when it relates to it performing its fundamental mission.

[157] *TCPS, supra* note 4 at 1.2. "...the REB is to have authority to approve, reject, propose modifications to or terminate proposed or ongoing research, conducted within or by members of the institution, using the considerations set out in the Policy as the minimum standard."

should not play a punitive role. Punitive powers should continue to reside with the institution, or the REB will lose support of the research community. If the REB assumed punitive responsibilities, it would be seen as "prosecutor/investigator" in relation to the issue of the proper implementation of research and as "judge" imposing penalties. If the REB, in its monitoring role, receives reports or otherwise finds that the actual research in progress is not in compliance with the approved protocol, or that there is a failure on the part of the investigator, should the REB simply refer the matter to the university administration? Universities have mechanisms for dealing with scientific misconduct. Article 1.2 of the *TCPS* provides that the REB has the authority to terminate the research, but the mechanics of this would have to be agreed upon with the institution. This is where the COCO-MEM management project suggestions regarding development of policies within institutions is relevant. Beyond providing direction, once the policies regarding which parties are responsible for which functions are in place, there is also a framework from which to assess the activities of the REB and other parties in the research endeavour.

This presumes a situation of institutional research. What is the role of the independent REB or College of Physicians and Surgeons REB which has the responsibility for review and monitoring of research? Who do they report problems to and how do they impose sanctions?

The *TCSP* refers to compliance with the policy by researchers and institutions as a condition of funding or continued funding. It does not say specifically that funding will be cut off from the Councils for non-compliance with the policy (although that is inferred).

Should funding for only the specific project be withdrawn, or funding for all the projects that this investigator is responsible for? In the U.S., when an institution signs an assurance agreement and there is a problem with a researcher or a protocol, all government funding to the institution is cut off for all protocols, until the issue is resolved. Should this be the practice in Canada? If the funding councils determine that a particular investigator is in violation—should the funding only be halted or terminated for that particular project, for that particular investigator or for the institution as a whole?

Other sanctions which could be considered are: disciplinary action by the institution, by the REB, by national bodies such as MRC or NCEHR; journals refusing to publish research (i.e. may refuse to publish if not reviewed by REB or not monitored by REB; it may be possible to have certification of monitoring by REB a condition of publishing); disciplinary action by the College of Physicians and Surgeons or by the national speciality licensing group could also be considered.

Measures which could be employed to regulate misconduct include: certifying the competence of potential investigators; peer review of council funded research; limiting an investigator's level of participation in clinical trails; penalizing manufacturers who fail to detect their investigator's misconduct and permitting Councils or institutions to suspend investigator's research by holding funding prior to a hearing.[158]

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[158] Shapiro & Charrow, *supra* note 144 at 2505.

10. Monitoring: What and How? – Structures, mechanisms and models required for monitoring

In addition to the issue of what is monitoring and who should share the responsibility for performing the monitoring functions, there is also the question of "monitoring what?" The *TCPS* refers to: the rigour of continuing ethics review being in accordance with a proportionate approach to ethics assessment.[159]

The major portion of the REB's attention should be focussed on research involving more than minimal risk. The initial decision whether a study entails more than minimal risk, must be made by the REB.[160]

Drug studies generally involve more than minimal risk and can be divided into four types: a) small "in-house" studies; b) peer reviewed studies funded by MRC/CIHR and other funding bodies; c) commercially sponsored, (often multi centre studies); and d) national cooperative group protocols. The "in-house" studies could be monitored by their department or whatever monitoring mechanism is set up in the institution (REB, REB sub-group, research office staff). The MRC/CIHR funded studies require annual reports, but do not necessarily monitor adverse events. The commercially sponsored studies usually have monitors. The national cooperative groups have monitoring committees.

The REB and institution must ensure that there is a mechanism in place to monitor each of these types of studies, as the subjects in each of them are entitled to be protected

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[159] *TCPS*, *supra* note 4 at 1.10.

[160] See: C. Weijer, "The Analysis of Risks and Potential Benefits in Research," (1999) 9 & 10 NCEHR Communiqué (2) & (1) at 17-19. See article for discussion of risks of therapeutic procedures, risks of non-therapeutic procedures (by definition, these have no benefit for research subjects) and minimal risk.

from harm. Once it is determined what type of study is being presented and what level of risk is involved, the appropriate monitoring mechanism with the appropriate structure (personnel) must be assigned to perform the type of monitoring required.

In many cases the responsibility for oversight is shared and the important issue is to clarify between the parties who is looking after what. If we are considering the portion of monitoring which Heath describes as continuing review, then the logical body to perform this continuation of the initial review is the IRB/REB itself or a subgroup of the IRB/REB, as they have reviewed the initial protocol and can assess the ethics of continuation of the study in relation to risks, adverse events etc.

Suggestions made by Weijer and Freedman regarding mechanisms for monitoring of high risk situations included: research officers or outside specialists maintaining periodic review; data and safety monitoring committees, semi-annual or quarterly reports. Other groups do monitor data, such as pharmaceutical companies who regularly visit sites every 6-10 weeks. Information regarding situations of concern gleaned from these visits should be shared with REBs. This would free up the REBs to focus their attention on in-house research, which would not be subject to external review.[161] Responsibilities for various components of monitoring were suggested earlier (at 116, 137-142) and specific models for monitoring will follow.

Either the REB, a sub-group of the REB, an individual employee of a research office in the institution, a contract research organization or an independent body could

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[161] Freedman & Weijer, "Monitoring REBs," *supra* note 6 at 22.

audit/monitor the research. Should the REB choose not to monitor the research itself, it would have to delegate this responsibility. Regardless of who performs the monitoring, subjects would have to be told that this group would have access to their records (data sheets and medical charts), and may interview them (confidentiality issue). For noninstitutional research, one could consider the Alberta College of Physicians and Surgeons model which has authority to monitor (details to follow).

Some have proposed that IRB review should not be continued when a study has reached a phase where future research activity will be limited to the collection of data from routine follow-up evaluations, (which are not associated with a meaningful increase in risks, discomforts or costs compared to nonresearch practice guidelines).[162]

Monitoring has an educational effect on researchers regarding ethical research. Even the threat of spot checks or auditing of research procedures and consent process does result in increasing ethics and altering behaviour, resulting in better protection for human subjects. Implementing a monitoring process complies with the *TCPS* and the requirement in the Common Rule in the U.S. for NIH and FDA research regulations for monitoring. Monitoring would also be in compliance with the ICH Good Practice Guidelines for Europe and pharmaceutical industry.

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[162] R.A. Amdur & E. Bankert, "Continuing IRB Review When Research Activity is Limited to Routine Follow-up Evaluations," (1997) 19 IRB A Review of Human Subjects Research 1 at 10. With medical treatment studies, IRB review should continue as long as an important medical problem is being managed with an investigational approach. When investigational therapy consists of no therapy, placebo therapy, observation, supportive care or some other form of management that involves withholding standard therapy, it is never appropriate to discontinue IRB review.

Weijer et. al offer three models for the administration of research monitoring.[163] They suggest that the three are not mutually exclusive and can be combined. The first model has an office of research audit set up, which reports to the REB. It is responsible for continuing review and coordination of institutional education programs. This office would be involved with periodic monitoring of consent documents, periodic observation of consent negotiations, testing subjects for comprehension and periodic review of documents to check the adherence to protocol and data-audit for in-house research. This office could perform some tasks by indirect monitoring – by liaising with the investigator to obtain information, or could directly monitor the research project by interviewing research subjects.

A second model proposed, suggests that the REB perform all of the monitoring functions itself. This would be particularly appropriate for novel research which presents serious risk to subjects (an example of this is the McGill model discussed below).

In the third approach, the investigator suggests the appropriate monitoring for the protocol. This is the approach which is the general rule articulated in the *TCPS*. The proposals of the investigator could include third party supervision of some aspects of the procedures, such as assessment of subject competence. This third proposal is consistent with the goal of continuing review: education of investigators to raise the level of ethical conduct in human research.[164]

At the local level, there are two institutional examples in Canada of research monitoring which have been implemented with a fair amount of success. These will be

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[163] Weijer, Shapiro, Fuks, Glass & Skrutkowska, *supra* note 121 at 1978.

[164] *Ibid.* at 1978 & 1979.

discussed as well as the noninstitutional model, the Alberta College of Physicians and Surgeons REB.

a) Models at the Local Level

i) institutional model –Halifax model (this model deals with data integrity, the *formalities of consent* and *compliance with protocol*; it does not deal with the consent process; complies with Heath's view of continuing review being an REB function);

- **McGill model**–this model focusses on the *consent process* in high risk situations (intervention prior to participation using interviews in person, or in low risk, telephone following participation)

ii) non-institutional model– Alberta College of Physicians and Surgeons REB

i) Institutional Model

Halifax–A Successful Model

The IWK Grace Health Centre For Children, Women & Families in Halifax began audits of research protocols in 1992.[165] The health centre is associated with Dalhousie University and serves as one of two teaching hospitals for Dalhousie. The motivation for beginning the process was the ICH-GCP document and not the NCBHR visit which took place in 1994 or any particular incident of major research misconduct. The idea for auditing

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[165] Private conversation with Diann Nicholson, Research Coordinator, Research Services, IWK Grace Health Centre for Children, Women and Families.

research arose at a time of increasing contracts and clinical research. To assess how effectively their REB was meeting its goals of ensuring the rights of subjects were not violated, ensuring ethical research and achievement of high quality research, the Hospital Standards Committee (responsible for quality assurance), asked Research Services to conduct an audit on randomly selected research protocols. The goal of monitoring at the hospital is to educate its research staff.

The Hospital Standards Committee receives reports quarterly and an Annual Report (following the yearly audit) from the Research Coordinator of the Research Services Office. Non funded protocols are sent directly to the REB.

The Research Services Office is responsible for the administration of all research in the health centre–research ethics, management of the funding of programs and allocation of research space is done through this office. The office staff review grant applications and review clinical trials proposals, which are then forwarded to the university research services office for contract negotiations regarding budget, liability and publication clauses. The university office and Research Services sign off on the contract on behalf of the university.

The hospital reviewed about 140 new protocols and 150 renewals in 1998, with an average of 12-14 reviewed per REB meeting. Expedited protocols are assigned to two committee members for thorough review and all REB members receive copies.

The Research Office is staffed by a Chief of Research, (a physician--clinical specialist, who is part time), a full-time coordinator, a finance officer (who deals with contracts, nationally funded projects and research accounts), an information officer (who deals with forms, data bases of protocols and provides administrative support) and a part

time volunteer. Projects such as annual reports, an REB Handbook and a Research Handbook require additional support.

The Audit Committee is currently made up of 7 members: the two co-chairs of the REB, two REB clinical representatives, two REB lay members and an external reviewer. Six to ten protocols are chosen both by random and selective methods each year for review. The Audit Committee meets once per year, over a three day period to allow flexibility for the investigators' attendance. "Selective" sampling is used to include research previously targeted for its educational needs. The targeted reviews are used to determine the success of educational programs or changes to REB operating practices. Random selection is utilized to ensure inclusion of a variety of categories: multi-centre protocols, nationally funded protocols, protocols funded internally, protocols extending longer than one year and protocols developed and carried out within the past year. There is an attempt to focus on those investigators with large research practices and those who are inexperienced. The complexity and risk of the protocol is also taken into account regarding selection of protocols for audit.

The Assessment Criteria utilized by the Audit Committee is:

1. Evidence of good record keeping-investigator has original approval, subsequent correspondence and notifications of renewals;
2. Evidence of good research practice-monitoring of integrity of data and adherence to protocol–by checking that clinical laboratory information is systematically collected; there is a process to validate clinical and laboratory information; adherence to

requirements of research protocol; appropriate storage and maintenance of medication;

3. Monitoring of consent–evidence of adherence to requirements on consent form - signatures, dates, evidence that consent obtained by appropriate individual, evidence that consent had not been modified;
4. Monitoring of adverse events during the research study–evidence that the investigator had developed a system to identify and deal with any adverse events during the protocol-system to record major and minor adverse events, existence of safety committee, notification of major adverse events to national or governmental agencies and REB.

Recruitment, inclusion of certain groups and inclusion/exclusion criteria are issues discussed at the initial review and are not part of the audit process. Follow-up of REB suggestions for modifications at the initial review, is done by the two primary reviewers and the Research Office.

The Audit Committee utilizes a paper review and does not perform an assessment of the consent process or interview subjects or observe enrollment of subjects. Investigators are informed in advance about what documents will be required and how the process will be conducted. During the audit, the researcher and two research service staff (including the research coordinator), are present to answer questions. The research coordinator is a resource to the Audit Committee regarding questions such as budgets etc. and provides continuity regarding questions relating to long term protocols, as REB and Audit Committee

membership changes. It is most effective to have the person occupying the position of Research Coordinator, involved in both ethics review and audit of research.

In only one instance of a complex cancer protocol with very ill children, did members of the REB (following consent from parents) observe the consent interview with the parents. The REB observers found that the investigator provided a good explanation of the procedure. Only once did the parents not understand that the procedure was research; they understood that it was part of clinical treatment. This was later discussed with the investigator.

Researchers are informed at the initial review of protocols, that the studies are subject to random audit. The reason for the audit and the procedures are explained to each researcher.

To ensure a climate of trust, monitoring is done in an interactive manner. The investigator provides all the files arising from the conduct of the study and the REB approval form. Six to ten subject records are randomly selected for detailed review for the protocol which is audited. Clinical and laboratory forms and written comments are reviewed for each of the subjects. The investigator provides information relating to adverse events and the process used to review them. One member of the monitoring review committee assesses the consent forms.

The Audit Committee invites investigators to provide feedback regarding the audit process, the REB operation or the functioning of the Research Office. Suggestions made

during these audit conferences have been incorporated into changes in the operation of the Research Office and the procedures used during the audit.[166]

The Research Office has recently developed a form for reporting of serious adverse events. The report requires that the investigator present a synopsis of the event, a summary of the outcome and interprets the information for the REB members and Director of Research. It is not sufficient to present information received from the national safety committee. The form is to be completed for every serious adverse event, no matter where they occur. The supervisor of the researcher is responsible to sign a form acknowledging their responsibility regarding the research protocol. Although the protocol has received REB approval, enrollment cannot begin until the supervisor has completed their acknowledgement.[167]

Other than the Audit Committee, the other mechanisms utilized for continuing review are:

a) final report following completion of the protocol;

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[166] R. Bortolussi & D. Nicholson, "Monitoring of Clinical Research Performance: In a Children's and Woman's Academic Hospital 1992-1999," December 1, 1999 Draft-unpublished
Results of the monitoring review are tabulated by the staff of the research service office for the members of the monitor review committee, who identify problem areas and develop recommendations. The recommendations are discussed by the entire REB. The results of the monitoring audit and REB recommendations are presented to the Research Advisory Committee of the hospital and the Standards Committee of the Board by the co-chairs of the REB. Members of the research service staff are asked to develop corrective measures and educational programs to improve researcher compliance with REB recommendations.

[167] *Ibid.* All researchers participating in the monitoring process are listed in the report and receive a copy of the results and recommendations. Researchers who have performed poorly are not named in the report or in discussions with the REB or other hospital committees. The details of the major deficiencies are presented anonymously to these senior committees to determine if punitive action is required.

b) a sophisticated data base system to track all matters relating to protocols, including all amendments, REB recommendations for change, financial matters. The data base, set up in 1985, allows the Research Coordinator to report on the status of all protocols at REB meetings;

c) all amendments to protocols are reviewed; major changes go to the whole REB and minor changes are dealt with by the Research Coordinator and the Director of Research or the Chair of the REB; 6-8 weeks prior to the anniversary of the annual review, a renewal form is provided to the investigator.

Generally, there has been good performance by researchers in clinical trials.[168]

With regard to funding of research review and monitoring, the hospital charges 30% overhead–50% of this goes to the health centre, directly to research services; 30% is directed to the investigator's home department and 20% goes to the appropriate university faculty. The 50% which goes back to research services is used to pay for infrastructure–heat and light are paid on a set amount yearly and is not dependent on how much income is received or how much research is done.

The research office depends on receiving 20% of undesignated funds from the IWK Grace Foundation which raises funds from a telethon each year. This translates into about

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[168] *Ibid.* Recommendations from the monitoring committee have been made to prevent future major deficiencies or to correct process issues discussed during the review. Examples of educational measures taken include: revision of guidelines for application to clarify poorly understood issues; seminars on *TCPS*; classroom sessions for all studentship trainees, including model consent forms. Examples of policy recommendations are: development of yearly renewal or termination of REB approval polices and storage of records. Recommendations on policy are: increasing the number of REB members on the monitoring team and changes to make the process less intimidating for the researcher.

$1 million for the internal program of research and supports the staff salaries of those employed in the research office. The income from overhead charges to the pharmaceutical companies for clinical trials brings in sufficient funds to cover the overhead charges. Without the secured income from the Foundation, the research office could not exist at the hospital. The Faculty of Medicine REB reviews only student projects as all protocols which are health centre based must be reviewed by the IWK Grace REB.

The Research Coordinator is responsible to support all of the activities of the REB, including initial review and assisting with grant applications so it is difficult to determine how much time is devoted to audit responsibilities. Time and resources to conduct the monitoring audit are significant.[169]

The IWK Grace REB does review protocols conducted in doctors' offices. They also review research if the physician has an appointment at the health centre. In the latter case, the review will be a full review, with follow-up and a certificate of REB approval. In the former, where there is no association with IWK Grace, the review and suggestions are made, but no certificate of REB approval is given and the cost is $500.00 per review.

When asked how the system works and what type of educational and experiential background would be ideal for the position of research coordinator, Diann Nicholson, the current Research Coordinator at IWK Grace indicated that the system is working well and

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[169] *Ibid.* From 70-150 hours are spent by research services and 5-7 monitoring committee members during the interviews with the investigators and at REB meetings. The monitoring committee members require one to two hours preparation for each research protocol. The REB chairs have additional responsibility regarding drafting of recommendations and presentation to senior committees. The research service staff have a major role in the monitoring process, including: notifications, scheduling of meetings, tabulation of results, design of educational or other tools to correct deficiencies. Estimates are between 15-30 hours for review of 10 protocols, for preparation, scheduling and tabulation of results by the research service staff.

is accepted by the research community. Although there was some hesitation in the first few years on the part of researchers, the audit process is now generally viewed by the researcher, the REB, and the Research Office as a learning process to raise the level of protection for research subjects and increase the level of understanding and awareness of ethical issues in research on the part of the researcher. In terms of experience to bring to the position of Research Coordinator, Ms. Nicholson suggested that university preparation and considerable experience in research, particularly with REB ethics, would be ideal. Courses in ethics and a background in research would be valuable.[170]

With regard to the make-up of the Audit Committee, the IWK Grace experience demonstrates that a committee with membership similar to the REB is advantageous, as research expertise, as well as the lay perspective are required. It would be difficult for a single individual to perform the audit, as it is unlikely that they would be able to offer all the perspectives which make the auditing process an effective one.

Having undertaken an informal survey by contacting members of REBs across the country and in discussions with Diann Nicholson about her conversations with members of the national administrators of research across Canada, it appears that IWK Grace is the only institution at this time which has a formal audit process in place. Other groups and

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[170] *Ibid.* and private conversation with Diann Nicholson. The monitoring audit process developed at the IWK Grace Health Centre has evolved over the past 7 years and 5 audits, into an important component of the responsibilities of the REB. The monitoring process is viewed as successful, as it has assisted in identifying weakness in the research ethics process and developing corrective measures. IWK Grace has avoided the "police work" approach and utilized the process as an opportunity for dialogue between researchers and members of the monitoring committee. The REB has benefited. The process has resulted in more knowledgeable researchers submitting better applications for REB review. Identification of recurring problems involving deficiencies in protocols submitted by researchers with little experience in clinical trial methodology and protocols involving trainees have led to specific educational programs targeted to students and supervisors.

institutions have asked for advice and assistance from IWK Grace in setting up a monitoring system, but none is functioning at this point.

The Queen Elizabeth II Hospital in Halifax also has a Centre for Clinical Research with an educator/auditor. One pilot audit has been done with an investigator who volunteered to have his protocol reviewed. The Centre is in the process of developing selection criteria to determine which protocols to audit. The audit will be done by the educator/auditor, who will present a report to the audit committee (made up of members of the ethics committee-the chair, one-two physicians and a lay member). The function has been primarily educational to date-informing the research community of guidelines and regulations. The focus will be on consent process and forms, not data audit (unless dealing with non-funded research). Problems identified to date with the protocols: subject signing wrong version of consent form; incorrect dates on forms; no final report sent to REB; department chair who signed the letter of support was the investigator.[171]

The Hospital for Sick Children is proposing to develop a general schema regarding categories of research, which the researcher and REBs would use to grade the research to

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[171] Private conversation with Kellie Campbell, Educator/Auditor, Queen Elizabeth II Hospital, Halifax. Information presented at MRC workshops indicated that other institutions are fulfilling different parts of the monitoring mandate: 1) Queens–the REB classifies risk at initial review and when there is a high risk protocol, asks for a summary of adverse events every 6 months; 2) McGill-has a data and safety monitoring board which monitors oncology trials only, and reports to the REB; (in the U.S.-generally, only multi centre oncology and AIDS trials have data safety committees);3) McMaster-have the authority to monitor; monitoring is done at the departmental level, to avoid the adversarial relationship with the REB; in general: REBs require some assistance in assessing risk.
See also: B.Gordon & E. Prentice, "Continuing Review of Research Involving Human Subjects: Approach to the Problem and Remaining Areas of Concern," (1997) 19 IRB A Review of Human Subjects Research 2 for a discussion of the continuing review process in place at the University of Nebraska Medical Center, which relies on data submitted by the investigators, rather than the review of the research records by a representative of the IRB

determine the level of continuing review required. The REB may require establishment of a data/safety monitoring committee by the "clinical trials secretariat," if such a committee is not already in place. This proposal relates to monitoring *of* the REBs, rather than monitoring by the REBs of protocols they have approved.. The proposal also includes establishing routine post-approval monitoring of research by a former research coordinator or a former quality assurance monitor. Monitoring would be proportionate to the risk and risk/benefit ratios. Continuing education of researchers is important.

One of the components missing with the Halifax model is the monitoring of the consent process by soliciting feedback (through interviews or questionnaires), from the subjects. A portion of the consent process is reviewed in Halifax, by reviewing the charts for signatures on consent forms, but the voluntariness and comprehension is not apparent in a paper review. This missing component could be easily added to the Halifax process by development of a questionnaire and carrying on of interviews of subjects or administering the questionnaire by members of the research office or audit committee members.

McGill Model - Consent Process

This study involved direct monitoring of the informed consent process to ensure that subjects were adequately informed and that the decision to participate was voluntary. The study involved a phase II regimen for women with advanced breast cancer who were ineligible for hormonal therapy. The protocol combined a variety of aggressive and investigational treatments, including high dose chemotherapy in combination with an

experimental cardio-protective drug.[172] Results from a pilot study of nine patients, were presented to the IRB at the time of review. There were no treatment associated deaths and no clinical heart damage; five patients experienced a complete remission. The REB weighed factors for and against approval of the protocol.[173]

The IRB concluded that the study could proceed but required the Faculty of Medicine Data and Safety Monitoring Board to regularly review study results and the IRB to directly monitor the informed consent process. There literature offered little guidance regarding monitoring of informed consent (other than the situations of Dr. Barney Clark-artificial heart and Baby Fae-transplant of baboon heart to human).

The informed consent monitoring occurred after the patients' discussion with the physician was complete, but before the patient signed the consent form. The IRB was reluctant to intrude on private and confidential discussions between patient and physician, which took place during a number of sessions.

The format of the monitoring was a semi-structured interview, 30-60 minutes in length to assess the subject's knowledge of the disease, study and alternatives to participation, as well as voluntariness. A question guide was designed for the interview with

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[172] M. Strutkowski, C. Weijer, S. Shapiro, A. Fuks, A. Langleben & B. Freedman, *supra* note 130 at 1-6. After 6 cycles of induction chemotherapy, and two sequential autologous bone marrow transplants, if there was no evidence of tumour on biopsies, the patients received irradiation and tamoxifen for up to 5 years. The entire regimen took 10 months to complete, of which 110 days were in hospital and the anticipated treatment mortality rate was 10%-15%.

[173] *Ibid.* Factors against approval were: some of the interventions had little evidence to support their safety or efficacy; a combination of risky and untested interventions; complexity and unusual severity and nature of risks were difficult for subjects to comprehend and lack of other curative or life-prolonging options for subjects might interfere with the voluntariness of consent.
Factors favouring approval were: an investigator, well respected for his skill in administering very high dose chemotherapy and his frankness with patients; results of the pilot study were promising.

open-ended questions and specific questions about knowledge of incremental risks of research participation, the uncertainty, monitoring procedures, potential for irreversible harm and whether consent was voluntary.

An oncology nurse-clinician experienced in interviewing cancer patients conducted the interviews and reported to the IRB chair. The physician was then notified whether the enrollment of the patient could proceed, would be postponed or disallowed.

Ten women were interviewed. Nine received immediate REB approval to enter the treatment protocol. One woman was uncertain. One week later she was interviewed again and received approval to enter the protocol.

The subjects had a great depth of knowledge regarding the disease and treatment protocol. They were informed over a 2-4 week period and no evidence of undue inducement was found. All patients felt that this was their only "real" alternative. After reviewing the results of consent monitoring of the first 10 patients, the IRB decided to allow the study to enrol further patients without such monitoring.

Enrollment of the first ten patients in this study took about a year and a half. For this period, the IRB chair and consent monitor had to be available at relatively short notice. Given resource constraints, direct monitoring should only be utilized rarely. This study involved novel and serious risk to potentially vulnerable subjects. The IRB felt they could not responsibly approve the protocol without such monitoring. The results obtained from the consent monitoring reassured IRB members.

The monitoring process itself may influence the behaviour of both the clinical investigator and patients, which is called the Hawthorne effect. The investigator may be

more thorough regarding the explanation of the protocol and ensure the subjects' complete understanding. The subject, knowing that their comprehension will be tested, and that access to potentially life-saving treatment may be affected, may exert more effort to understand the complex information. While acknowledging the results of the Hawthorne effect on consent monitoring, one could question why the IRB decided to terminate monitoring after the first ten cases. Monitoring of all patients would be ideal, but the resources are not available.

Caplan suggested using a system of random sampling by IRBs for initial review of minimal risk protocols, which would free up time for the IRB to do monitoring. The authors suggest using the same approach to monitoring--having the IRB monitor the first few cases to ensure the adequacy of the consent process and when satisfied, randomly interviewing a proportion of subsequent subjects to ensure the behaviour of the investigator and subject have not altered.

McGill's experience indicated that direct monitoring of informed consent is feasible and an important component of the IRB's approach to high risk protocols. This monitoring is a burden for the IRB, so alternative approaches such as random monitoring should be explored[174]

Most studies require no consent monitoring. IRBs may have assistance from the institution's quality assurance measures to ensure that a policy regarding informed consent in the research context, is in place and that measures are implemented to ensure that informed consent does occur. Quality assurance measures could include: periodic review of

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[174] *Ibid.*

consent documents, periodic post hoc interview of subjects or even periodic assessment of consent negotiations. If the institution includes these mechanisms under its quality assurance program, then all that remains is to determine who should perform this function. If a research office does exist, perhaps this function could be performed by that staff, with reporting responsibilities to the REB. The REB would not implement all aspects of review and monitoring of research, but would be ultimately responsible to ensure that subjects are protected.

A format for review is suggested by Wollman and Ryan as follows: a review team consisting of a physician, a lay member and the staff member to the REB, (all having participated in the original review process) would meet with the researcher. All reviewers' findings of problems or noncompliance are presented to the full IRB for action. The full REB may recommend continued approval, changes in the consent form, changes in the experimental design, or suspension or termination of the study based on its findings.[175]

Most reviews show that investigators have followed REB directives. Some problems ranging from minor irregularities to more serious violations have been uncovered through the audit process.[176]

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[175] Wollman & Ryan, *supra* note 6 at 134 & 135. See article for suggested issues to be included in continuing review.

[176] *Ibid.* For discussion of common situations of noncompliance. Common situations of noncompliance are: different titles of the protocol on various documents relating to the protocol; modifications in methodology, recruitment procedures or consent form without IRB approval; improper witnesses to consent forms such as investigators, which may be a conflict of interest; consent forms which are incomplete (date of signing is evidence that enrollment took place after IRB approval)

ii. Non-institutional model

Alberta College of Physicians and Surgeons Research Ethics Committee

In response to the need for a body to oversee and review the ethics of research taking place in venues other than large, teaching hospitals with personnel that have university or hospital affiliation and the reluctance of the REBs of these institutions to take the responsibility, (moral, ethical and legal) of supervising research over which they had no control, the College of Physicians and Surgeons of Alberta agreed to provide a vehicle for ethics review for research taking place outside of traditional locations.

The College saw research occurring in physicians' offices as within its purview as the College is responsible for practising physicians. A provincial committee was needed to deal with physicians and to protect patients/subjects participating in research. As the College is the licensing body, there was no formal challenge to the College's initiative in taking on this responsibility. The College has the authority to supervise standards of practice and ensure safety of the public for medical care and treatment (including enrolling the public in research projects), provided by its members.

In 1998, the College established it own Research Ethics Review Committee to perform this task. It is a Standing Committee appointed by the Council of the College.[177]

The Committee was formed to develop and administer a program for ethics reviews of research projects involving human participants conducted by registered practitioners who

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[177] Research Ethics Review Committee, Effective January 1, 1998, CPSA Bylaw, Part B, January 12, 1998 Issue.

are not eligible for such review by the three regional institutional research ethics review boards in the province.[178]

A registered medical practitioner must obtain written approval of one of the three regional REBs or this committee prior to embarking on research involving human subjects.[179]

The Committee has the authority to (among other things), determine the scientific validity of research proposals, facilitate ethical research, review researchers' qualifications and develop a process of ethics review consistent with that taken by the TCPS. Section 6, provides that the Committee may collaborate with existing REBs in Alberta to develop and/or provide a uniform standard of ethics review including an audit process of reviews, completed or continuing, performed by the Committee and REBs..[180]

The Committee may approve, refuse to approve or require modification of any research proposal submitted to it. Members, both voting and non-voting, consultants and advisors retained by them, receive a fee for attendance at meetings, (the per diem for sitting on this committee is the same as that for all other Council committees). All expenses incurred by the Council for operation of the Committee shall be recovered through a levy to be paid by each applicant or the sponsor of each applicant for approval of a research protocol [181](the College charges $1,500 for each review).

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[178] *Ibid.*, s. 50 (2). Health Research Ethics Advisory Board of the Capital Health Authority, University of Alberta and Caritas Health Group; the Cojoint Health Research Ethics Board of the Faculty of Medicine, University of Calgary or the Alberta Cancer Board.

[179] *Ibid.*, s. 50 (3).

[180] *Ibid.*, ss. 50 (4), (5) & (6).

[181] *Ibid.*, s. 8 (e), (f) & (g).

Section 11 provides that (a) all research protocols approved by the Committee continuing for more than one year, must be reviewed on an annual basis; (b) this review includes any changes which have occurred regarding ethical or scientific validity, the design of the research study and the progress achieved in the study; (c) the Committee has sole discretion to require any additional monitoring procedures including, but not restricted to–continuing consent monitoring, monitoring of adherence to protocol; (d) the principal researcher is responsible for providing written notice to the Committee of all changes to an approved protocol before such changes are implemented, and, in lengthy studies, providing annual reports to the Committee describing the progress of the research study and providing to the Committee an end of project report detailing the research conducted and the results obtained; (e) if the Committee finds, as a result of monitoring, that the study lacks ethical and/or scientific validity, or is no longer being followed as approved, the Committee gives written notice of recission of approval to the principal researcher and advises Council.[182]

In conversation with current College REC Chair, Dr. Peter Venner, the following comments were made regarding the issues currently being dealt with by the committee:

i) although the Committee has authority to review researcher qualifications, beyond requiring a curriculum vitae, it does not do so;

ii) there are currently no guidelines or rules regarding what is an appropriate level of remuneration for physicians conducting trials; the Committee tries to assure that the amount received is not high enough to create an undue inducement for the physician or patient to

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[182] *Ibid.*, s. 11

participate; fees are set out in the budget which is presented in full to the Committee; the physicians are generally paid on the basis of each individual enrolled; some studies are more involved and time consuming than others; research is a source of income for physicians; some physicians in Canada who are making their living performing research; they do not practice medicine or bill the health care insurance plan for their services;

iii) there is a question regarding what is the proper disposition of unexpended funds; when the budget provides certain amounts for procedures and those procedures cost less, what happens to the surplus which is paid by the pharmaceutical company? The university has a policy regarding funds which are unexpended from a trial. In private practice, this surplus goes to the investigator as part of the investigator's fee. Another issue is that there is currently no way of knowing what tests are being done for research and which are performed for patient care and who is paying for these services. The trend is for a central laboratory to be used by pharmaceutical companies for analysis of all samples;

iv) at present there is no monitoring of research approved by this committee (this is no different from the situation in institutions across the country and around the world); this is due to lack of financial resources and time; no system has been set up to monitor research, though monitoring is performed by external bodies-funders and regulators. This monitoring is retrospective and focuses on documentation, rather than interaction with subjects.

v) the *TCPS* is not binding on these physicians as they are not receiving government funding. Their funding is from the pharmaceutical industry. However, the College does state in their bylaws that they will follow the *TCPS*; Noninstitutional REBs (like the College REC) are also not being monitored and they do not come under the *TCPS* either;

vi) recovery costs for investigations–the investigator may receive $200 U.S. for performing a history and physical examination and would only be paid $50 for these procedures under Alberta Health;

vii) paying for injury to subjects–the sponsors like to restrict their responsibility to injuries that are "directly" related to participation in the research;

The physician (not the company), presents the study to the College Committee for review, as the College only has authority over its members. Confidentiality and privacy are major issues. Many of these protocols are leading edge and the pharmaceutical companies are concerned about competitiveness. Also the investigators do not want others to know what they are doing.

Currently, the committee meets once per month. The investigators do not attend. The documentation is submitted prior to the meeting and is reviewed by primary reviewers and the whole committee. The primary reviewers submit their comments or concerns prior to the meeting and these are available to be discussed at the meeting. Generally, the protocols are not approved without some changes being recommended (to the consent form, scientific validity or sample size). If they are minor changes, the Chair may approve them. There is also an appeal process set out in the bylaw.

The committee is multidisciplinary–two lay individuals, legal and ethical representatives, research physicians, general practitioners and a statistician. The committee is made up of about twelve individuals, appointed by the Council of the College to rotating 2 or 3 year terms.

There are currently few physicians conducting research in their offices. One physician may act as the principal investigator for a group of physicians involved in the study.

The norm in the field is that "healthy volunteers" do get paid for their time and inconvenience. However, it is seen as coercive or an inducement to offer to pay patient/subjects and they may also be receiving a therapeutic benefit. Patient/subjects' involvement in the research may be very demanding, with extra visits and extra tests, extra strain. Is it fair not to pay patient/subjects except for out of pocket expenses? They are the ones submitting to the risk and everyone else in the system gets paid. (This concern expressed by Dr. Venner is applicable to all subjects in all research, not just research reviewed by the College Committee).

According to Dr. Venner, the system is working better now than it was initially. Practitioners who present their protocols as investigators are generally pleased with the work of the Committee. The main concern for the investigators is time delays and the Committee is very conscious of this and turns things around quickly. The issues raised by the primary and secondary reviewers are usually the same ones as other board members have concerns about. The area where there is much discussion is that of budgets of protocols ie. what is a reasonable reimbursement for conducting a history or physical examination. There is currently no guidance regarding what is reasonable in this area and the Committee is looking to an MRC committee which is to be discussing this topic to come back with suggestions.

In summary, Venner stated that the patient/subject is well served by this process. The problem is that it is not certain that all medical practitioners who are conducting research, are submitting their protocols for review. The system may only catch them if something

goes wrong. These physicians may also be conducting research, ignorant of the requirement for review. Prior to this Committee, a pharmaceutical company wishing to perform research, could set up its own REB, which would review the research and meet the requirements of the ICH-GCP guidelines of requiring research review. The ethical pharmaceutical companies now know that there is a local REB in Alberta for physicians performing research outside of an institution. The College Committee was established to regulate physicians (not companies) and to protect the public. As the licensing body, it has all the regulatory sanctions to discipline a member who is not complying with ethical standards.

This is a good model for others to consider as it has a wide scope–all practising licensed physicians in the province are subject to its control. It is a problem for the College, as it is a much bigger commitment in human resources than they anticipated. However, it is offering a vital service to the physicians (reviewing their research and providing guidance on the conduct of ethical research) and to the public (in reviewing proposed research to make sure that it meets ethical standards).

Mechanisms must be designed and adequately resourced so that monitoring of approved research can take place. The Alberta College model is worthy of consideration by other provinces considering regulation of noninstitutional research. Some provinces have noninstitutional for-profit review boards, but they come with the associated weaknesses of conflict of interest.

b) National Level

The NCBHR site visit study reported a wide variance in the operations of REBs in Canada. The more prescriptive content and tone of the *TCPS* has gone some way to address

these issues. The questions remains: will more detailed guidelines result in increased compliance with ethical standards? Who will monitor the REBs to be sure they fulfill their responsibilities, on what authority and against what measures?

There is currently no formal mechanism to monitor REBs and verify the validity of process which have been set up.

To what extent would greater uniformity in adherence to national research ethics guidelines provide more effective, consistent and fair review of protocols? Who should perform the assessment of REB effectiveness and do we require legislation, or accreditation of REBs, or is it sufficient for a body responsible for oversight of REBs to act on a more informal basis, with questionnaires and site visits? Should there be random auditing by NCEHR? Should the approach taken for monitoring be similar to hospital clinical care standards which require certification? This would lead to increased regulation of the activities of the REB.[183] The issue of accreditation of REBs will greatly affect their operation–the question is which body will perform this function? Is full accreditation required, or would less formal policies, spot audits and site visits be adequate to provide protection for research subjects by ensuring that REBs are conducting proper review and monitoring of research?[184] Should NCEHR or another national body do random checks? [185]

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[183] Crelinsten, *supra* note 97 at 28-29

[184] L.N. Fortin & T. Leroux, "Reflections on Monitoring Ethics Review of Research with Human Subjects in Canada," (1997) 8 NCBHR Communiqué 1 at 11-20.

[185] See: Canada Gazette, Part I, January 22, 2000, *Food and Drug Regulations*, (Schedule No. 1024)–Clinical Trials; These proposed amendments may answer these questions, as they make reference to inspections and credentialing of REBs.

Verdun-Jones and Weisstub have recommended establishing a statutory basis for the regulation of human research in Canada. In common law Canada there is no statutory framework authorizing REB operations. It is essential that each province and territory enact appropriate legislation. They suggest a province-wide independent body supervise multicentre trials. The legislation should only set general and minimal requirements for experimentation or REBs will be hamstrung and lose their ability to respond to changing conditions.[186]

The difficulty with legislation is that once it is drafted it is difficult to amend and does not lend itself well to the fast pace of scientific development and related ethical issues. An example is the Newfoundland *Advanced Health Care Directives Act*. The original wording was interpretted to prevent Alzheimers patients from participating in research relating to their condition. It took 4 years to achieve an amendment which reinstated the position of the common law and allowed research which benefited the patient/subject group to be undertaken.[187]

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[186] Verdun-Jones & Weisstub, *supra* note 92 at 327 & 329. The problem is that once you set out minimum requirements in legislation (even with expectation that ethics require higher standards), as the law is seen as more authoritative than ethical policies, or standards, the minimal legal standards become the standards of practice)

[187] Nfld. *Advanced Health Care Directives Act*, c. A-4.1 s. 5(3)(a) states: "A consent by a substitute decision maker on behalf of a maker to medical treatment for the primary purpose of research shall have no effect unless the substitute decision maker is expressly authorized in the advance health care directive to give such a consent." This was interpreted as, in the absence of an advance health care directive, persons deemed incompetent could not participate in research projects. As the proportion of the population with advance directives is small, the effect was that most incompetent people were denied access to research relating to their disease or condition. After a failed attempt to amend the legislation in 1996, the legislation was eventually amended to permit this type of research in 1999. *Attorney General Statutes Amendment Act, 1999* (Bill 24) s. 2 " Sec. 5 of the *Advance Health Care Directives Act* is amended by adding immediately after subsection (3) the following: (4) Notwithstanding paragraph 3(a), the common law applies in the conduct of health research where there is no advance health care directive."

Rather than pursuing legislation as a means to enforce compliance with high ethical standards, a determined effort on the part of those involved in research to fully implement existing policy guidelines regarding monitoring and to confirm in deed the importance of ethical conduct, would result in a higher standard of ethical research and increased respect and safety for the subject of research.

There is a need for a body to assess or monitor the performance of local REBs. The NCEHR or another federal committee, perhaps appointed by the Minister of Health could perform this function. Should a provincial or national ethics committee with the mandate of supervising REBs be established? If these national or provincial ethics bodies are formed, should their purpose be advisory only, focussing on interdisciplinary discussion of broad ethical and emerging issues, which the REB is not designed to deal with, (like the U.S. National Bioethics Advisory Committee)? Should the mandate of the national committee include the oversight of or credentialing of REBs?[188] It may not be realistic to think that a national group could set parameters regarding how much monitoring is needed for how much risk, as they would be general and generic guides. A high risk protocol with a very

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[188] *Report of the Review of the Role and Functioning of Institutional Ethics Committees, A Report to the Minister for Health and Family Services*, Australia, March, 1996. Australia has the Australian Health Ethics Committee of the National Health and Medical Research Council (NHMRC) which monitors institutional ethics committee (IECs), which have the responsibility to ensure research projects are acceptable on ethical grounds and must monitor the projects to ensure that they continue to conform to the approved protocols. NHMRC is responsible for auditing the activities of the IECs.(at 11); the report recommended direct responsibility for monitoring remain with the principal investigator (at 28); the report did not support the development of a separate administrative system of monitoring or the introduction of paid public officials as was recommended by Neuberger in the UK. The report recommended that a system of tailored monitoring be implemented. (at 30); this approach recognizes the IEC monitoring is only one aspect of protecting research subjects; peer review, institutional supervision, professional ethical standards of researchers and effective information and complaints mechanisms all contribute to protecting research subjects (at 31); independent audits should not be routinely used and should be a "last choice" option used when there is evidence of misconduct; there was little support for random audits; monitoring of IECs is done by compliance reports and should continue this way (at 54); IECs have not required sanctions; they use voluntary compliance (at 55)

prominent and trusted researcher may not require as much monitoring as a low risk protocol with an inexperienced investigator or a protocol involving a vulnerable populations. If a national ethics policy body is established, the issue of monitoring the performance of REBs remains and it would be preferable that the body monitoring REBs be national (rather than provincial) as so much research is now multicentre. This monitoring responsibility may lead to accreditation of the REBs to ensure minimal standards.[189]

Performance measurements, outcome analysis and the creation of standards are needed. Establishment of performance indicators would serve as guides to monitor, evaluate and improve the quality of ethics review ie. recognizing adverse events promptly and introducing corrective measures. Examples of standards developed by *clinical* ethics boards in hospitals which could be applied to REBs are: a) mission statement and/or written policies; b) policies and operating rules of the REB to ensure fairness and accountability; c) REB to evaluate and review its services; d) REB members to receive education and become knowledgeable members .[190]

The *TCPS* may be seen as peer-created standards, which may serve as a framework to evaluate REB performance. The question remains: who should review the reviewers? REBs should be self-critical and accept peer scrutiny.[191]

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[189] In the U.S., there are regulations governing IRBs, but it is essentially a system based on self regulation. With a system of accreditation, the questions remain: are you accrediting the institution, REB or investigator? Who would enforce sanctions and what form would they take?

[190] Crelinsten, *supra* note 97 at 28-29.

[191] *Ibid.* at 29.

Do we need two national bodies? 1) CIHR or an independent government appointed and funded policy/broader issues/advisory body and 2) NCEHR or an independent government appointed body to review REB performance, perform site visits, establish standards for accreditation and be responsible for interpretation and amendment of the *TCPS*? How does accountability and reporting work with such a diffuse council/organization as CIHR?[192] (Australia–one national body does both; U.S.-national advisory body only, no national committee with responsibility over all IRBs; FDA and NIH only have supervision over studies which they fund). With regard to accountability, members of the public should sit on funding Councils and help set priorities (they currently do). Annual reports of investigators submitted to MRC for grant extensions, could be summarized and available to the public–taking into account freedom of information and intellectual property issues.

One area of continuing controversy concerns the role of IRBs/REBs as a regulatory device. Studies of IRBs/REBs have raised questions about their effectiveness and fairness.

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[192] Regarding structure and general direction for dealing with ethical issues, several groups have made formal presentations, including one based at Dalhousie and another at UBC. The Interim Governing Council of the CIHR, Sub-Committee on Ethics has also presented recommendations to the Interim Governing Council of CIHR including some which deal with the issue of ensuring that public accountability and transparency concerns are met and quality assurance reviews of research ethics operations are carried out: a) establishment of a Committee on Ethics Policy and Procedures to develop and assist with the implementation of internal ethics policies for CIHR and CIHR funded research and b) a forum is needed for constructive interdisciplinary reflection on the ethical, legal, sociocultural and public policy dimensions of health research and health systems. Until such time as a body, independent of CIHR is created to provide such critical reflection, a CIHR Advisory Committee on Ethics should be established to address current and emerging ethical issues and policy changes.
The last suggestion clearly refers to an advisory, policy-making group. It is not clear whether the first endorses a CIHR committee which would monitor REBs' effectiveness. Does 'implementation of internal CIHR ethics policies' refer to monitoring CIHR funded research or is there room for another group, NCEHR or another independent group, to monitor REBs?
Lastly, a committee has been commissioned by the Law Reform Commission of Canada to study the issues of governance of health care research in Canada and their recommendations have not been finalized. This group will also recommend structures and processes for governance of the research process.

Some of the problems relate to IRB/REB decentralization, leading some to propose the creation of a national research review board. The duties of this board might include the promulgation of uniform procedural standards for IRBs/REBs and acting as a formal appeals board. Such a board would increase federal control over local IRBs/REBs, research institutions and investigators.[193]

In contrast, the emergence of AIDS as a major health crisis has acted as the catalyst for a potentially significant relaxation of federal drug regulations. In 1987 the FDA promulgated new regulations allowing for the treatment use of certain investigational drugs prior to the end of their clinical trials.[194]

The adoption of the new FDA regulations was lobbied for and strongly applauded by a variety of patient advocacy groups. Bioethicists and others, expressed concern over the potential abrogation of regulatory protections for human research subjects.[195]

Local review is the basis of our regulatory system, and it should be maintained. However, local REBs should not be asked to do a job for which they are not appropriately constituted or prepared. The fact that local IRBs cannot, and perhaps should not, undertake the task of thinking about the long-term social consequences of research does not mean that no group should. Carol Levine and Arthur Caplan proposed a national research review board which would examine the social and ethical impact of research on a device like the artificial heart. A new class of activities and innovative therapies that present complex technical,

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[193] Benson, *supra* note 32 at 8.

[194] *Ibid.*

[195] *Ibid.*

social, ethical and legal questions should require review by a national research review board.[196]

A possible function for national advisory groups would be the responsibility for assessing independently, the scientific rationale and design of randomized clinical trials and the data they produce (U.K. and Denmark). The opinions of the national advisory groups would not be binding on the local REB. They could serve as a mechanism to monitor the results of trials during their performance and could help with decisions to terminate prematurely. Problems with national advisory groups include: the source and manner of appointment, their financial and staff support requirements, the extent of their authority and responsibilities and the creation of a complex bureaucracy which might not resolve the problems of local REBs.[197]

Another function which could be performed by a national advisory committee is that of assessing the clinical relevance for Canadians of the research, to prioritize studies, as there are a limited number of patient/subjects. Which study would contribute most to the advancement of knowledge and generalizability of results?

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[196] C. Levine & A.L. Caplan, "Beyond Localism: A Proposal for a National Research Review Board," (1986) 8 IRB A Review of Human Subjects Research 2 at 9. The new category of review would be defined in terms of: a) complexity of the social, ethical and legal issues the proposed activity raises; b) scope in terms of the number of subjects whose welfare is affected; c) vulnerability in terms of the ability and capacity of proposed subjects to protect their interests using the standard of informed consent. The new category of review would supplement local review, which is inadequate in some situations. A broader perspective is needed when research is contemplated that does not fit our usual notions of consent, welfare and risks and benefits. This article was written prior to establishment of the National Bioethics Advisory Committee.
See also: Edgar & Rothman, *supra* note 40 at 501-503 for a discussion of how to adapt public policy to the current research environment, including reference to a national ethics committee.

[197] Cowan, *supra* note 131 at 3.
See also: Boyhaychuk, Ball, Lawrence and Sotirov, *supra* note 114 at 46-50, 52-55.

In terms of the Canadian situation, there are constitutional issues of provinces who are responsible for health, interfacing with a national research ethics body, which is not only advisory. Provinces would have to agree to its jurisdiction. It would be desirable to reach some national consistency regarding monitoring i.e. minimum standards.

Currently in Canada, we have the advisory site visit process of NCEHR and the *TCPS* (which did not set out any provision for an REB monitoring mechanism). Fortin and Leroux recommended that the CCAC model should be considered with regard to a mechanism to monitor local REBs. The CCAC approach is in fact the process which was utilized with the NCBHR visits in 1990-93 and the NCEHR group could assume this role on an ongoing basis with more formal authority. The universality of the monitoring of ethics review of research raises important jurisdictional questions, which may be more urgent depending on the extent of the powers of this national ethics body.

The Deschamps Report, a 1994 Committee of Experts on the Evaluation of Control Mechanisms in Clinical Research recommended a permanent structure–an evaluation board or standing committee responsible for accrediting the institution. The report rejected the idea that this evaluation body be dependent on a research granting agency to avoid an appearance of conflict of interest. The Deschamps Report made a number of recommendations regarding the operation and structure of a permanent provincial structure. The Report dealt with clinical research activities in health institutions, but does not discuss the authority of such an evaluation structure in relation to the private sector.[198]

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[198] Fortin and Leroux, *supra* note 184 at 13-20. *Quebec Civil Code*, Article 21, deals with research sponsored by granting agencies and private industry and with individual protocols and specific subjects; there is no formal or universal mechanism for monitoring the decision-making process of ethics committees at the

It is possible that the NCEHR could act as a monitoring and accrediting body, as it is not a grantor. The issue remains: is NCEHR sufficiently arm's length from the Tri-Council grantors, which are its funders? Also, should NCEHR take on an accrediting role, or focus on education and development of vehicles for monitoring? One of the tasks necessary is to develop monitoring tools–which would be done nationally, though the monitoring of specific research would take place locally. These tools could include: definitions of minimal risk; assisting to define responsibilities for all parties (institutions, REBs, researchers, Councils, NCEHR); development of mission statements and objectives to assist REBs in evaluating their performance; specific directions regarding responsibility for and type of sanction; assistance in bringing industry, regulators and academe together to agree on sharing of information and defining responsibilities.

Fortin and Leroux note that ethics review in Canada is governed by the *TCPS* and the Directives from the Drugs Directorate of Health Canada, which do not have the same force as an act or regulation. The Canadian criteria are not precise enough to use in objectively evaluating the performance of an REB. They suggest that Canadian standards do not lend themselves to establishment of an agency that could sanction non-compliance as severely as that of the U.S. If monitoring rules are not legislated, all those involved in the research enterprise, including the pharmaceutical industry, will have to cooperate to ensure implementation by all REBs in the country. [199] This is likely, as the pharmaceutical industry

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provincial level in Quebec.

[199] *Ibid.* at 20. They provide a model for analysing the increasing levels of formality and authority for monitoring the performance of the REBs and provide analysis of strengths and weaknesses of each approach.

itself has agreed to abide by the guidelines of the ICH-GCP, which call for monitoring. This article was written prior to the finalization of the *TCPS*, which could be argued, is more prescriptive regarding standards required of REBs. But the *TCPS* is silent on the mechanism to enforce the standards set out.

Fortin and Leroux presented a graph similar to that below to indicate the strengths and weaknesses of the models they discussed regarding national monitoring of REBs in Canada. The graph has been altered by inserting comments regarding the status of each of the models:

Model	Strengths	Weaknesses
1. **Informal visits** This is the state of monitoring nationally in Canada at present i.e. NCBHR study	-education -flexibility	-no guarantee of universality
2. **Visits in formal framework** This is the model employed by CCAC, which, it has been suggested, should at least be the level of monitoring for humans involved in research in Canada	-more consistent monitoring -atmosphere conducive to information exchange	-no guarantee of universality
3. **Accreditation or Certification** This is the direction we may be moving in Canada with the *TCPS*, setting out more prescriptive standards for REBs. However, there is no national monitoring structure in place and no sanctions in the Policy (other than an implication of withdrawal of funding)[200]	-status is clear	-repercussions of non-compliance are unclear
4. **Investigation** This is the approach of the FDA, utilizing site visits and OPRR withdrawal of funding from research institutions. However, these decisions are based on assurance contracts and more formal requirements in regulation form. Fortin and Leroux indicate that Canada currently does not have sufficient evaluation criteria upon which to base assessments of REB performance.	-compellability -universality	-complex structure -rigorous formalism

The arrival of the new Canadian Institutes of Health Research (CIHR) will certainly impact the implementation and further development of the TCPS. It's presence will also affect the direction of monitoring of health research, particularly at a national level.

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[200] The progress of the proposed amendments to the *Food and Drugs Regulations* should be monitored to determine whether the federal government will be implementing a system of accreditation of REBs and monitoring their performance.

The questions remain: whether an existing group like NCEHR will assume responsibility for monitoring REBs or whether a new group will be established to assume this responsibility and whether either group will assume responsibility for monitoring (and reviewing) research which is noninstitutional, i.e. taking place in physicians' private offices.

The question of approach is also open. To accomplish implementation of the accreditation or investigation model, much additional work will have to be done to set out in greater detail the standards relating to structure and operation of REBs, against which the REBs will be assessed, in order to be accredited or sanctioned. Moving towards an accreditation system will be a gradual process of incremental steps, which can be started by ensuring meaningful annual reports from all investigators.

In conclusion, it is important to keep in mind the balancing of interests in the area of experimentation with human subjects–protection of the subject and medical progress. Hans Jonas has commented that: "... progress is an optional goal, not an unconditional commitment... its tempo has nothing sacred about it... Society would be threatened by the erosion of those moral values whose loss, probably caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having." [201]

Summary

It is surprising that there is not more clamour from the public for accountability regarding funds given to researchers, universities and hospitals in relation to issues such as: 1) side effects and adverse events caused by poor research methodology or poor follow-up

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[201] Gray, *Sociological Study, supra* note 3 at 256.

(which is rarely reported, so it would be difficult for the public to learn about this); 2) that there is not more demand for results in heart disease, stroke and cancer where so much money has been spent on research; 3) lack of publishing of unfavourable results is standard practice; 4) reliance of universities and researchers on private industry to help with overhead costs; (researchers work on projects for industry which pay the bills to keep their labs open and personnel employed and may give less priority to curiosity driven research); 5) much of the research agenda is being dictated by the marketplace and priorities of private industry, which investigates drugs which have the most commercial payback and ignores rare diseases, vaccines or drugs for conditions which affect people in developing countries, who cannot afford to pay high prices for medicines. In large measure, this lack of public concern may be explained by the lack of awareness on the part of the public, regarding what is really going on in the area of research involving human subjects.

The research enterprise is so large. The potential for being distracted from the primary purpose of protecting human subjects from harm and respecting their rights, while pursuing improvement in the treatment of disease, is high. This is due to many conflicting pressures. Further checks and balances have to be put in place to keep the system open and accountable. Pressures will only multiply as genetics research expands the possibilities for treatments and forces consideration of increasingly complex ethical and societal questions. The costs of new medications and procedures will force difficult decision making and priority setting. These must all take place in an atmosphere where ethical considerations are primary.

CONCLUSION

Where have we come from? What have we learned? The Nuremberg Code declared that experiments cannot be justified by a single principle: scientific concerns or subject consent alone are insufficient. Our inheritance from the Doctors Trial is the insight that knowledge is not the ultimate value.[1] Elie Weisel has said that we must never forget, for memory is part of our humanity.[2]

Although codes are necessary, our experience since Nuremberg teaches that they are ineffective in safeguarding human rights in human experimentation. With greater multinational and international participation in human experimentation, Annas and Grodin conclude that the United Nations is the only credible international group capable of establishing an international code of conduct for human experimentation. They advocate establishment of an international tribunal to judge and punish those responsible for unethical experiments. Without a tribunal capable of enforcement, international norms of human experimentation remain ethical, rather than legal norms.[3]

Where are we now? We must acknowledge that a system designed over 25 years ago to protect research subjects is no longer functional given today's changed medical research environment. Though initial review is widely accepted and functioning fairly effectively

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[1] W.K. Mariner, "AIDS Research and the Nuremberg Code," in G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) 296-297.

[2] G.J. Annas & M.A. Grodin, eds. *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation,* (New York: Oxford University Press, 1992) at 314.

[3] G.J. Annas & M.A. Grodin, "Where Do We Go From Here?" in G.J. Annas & M.A. Grodin, eds., *ibid.* at 312-313.

worldwide, there is acknowledgement that the system has failed to provide the continuing review required to ensure protection of research subjects.[4]

The research enterprise must be re-examined and re-tooled to meet the challenges of: pressure from industry for speed, scarcity of resources, increasing complexity, a realization that there are numerous conflicts of interest operating, (relating to industry, institutions, the REBs and investigators) and acknowledgement of the inequitable power relationship of physician/investigators and patient/subjects. The trust that subjects have in the system and their physician must be reinforced by the supporting structures of research.[5]

We must begin the process by defining monitoring and by whom and how it should be done. What do we mean by monitoring, continuing review and auditing? This requires commitment and extensive effort from all sectors of the research community.

Three broad categories of rationale for monitoring are: protection of subjects, ensuring the continuing validity of the science and appropriate use of funds. Each of these requires a number of players to take responsibility for ensuring that monitoring occurs and that responses to the results of monitoring are appropriate (i.e. that research is halted, that informed consent practice is altered, that generic forms are developed to assist with the monitoring process).

The specific monitoring functions for which the REB is responsible should be defined, vis-a-vis the other players in monitoring, such as the institution, investigators,

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[4] See: references to studies in Australia, U.S., U.K. and Canada in earlier sections.

[5] See generally: E.M. Meslin, "Ethical Issues in the Substantive and Procedural Aspects of Research Ethics Review," (1993) 13 Health Law in Canada 3 at 186-188. Public accountability is limited as the public hears about research after it is complete, through the media.

sponsors and regulators. It is the responsibility of the REB to ensure that monitoring is done, but not necessarily to do it; i.e. the REB should focus on the consent process, conduct annual reviews and leave other issues to others (e.g. scientific fraud is an institutional rather than an REB responsibility).

The *Tri-Council Policy Statement*[6] directs investigators at initial review, to assume primary responsibility for proposing the continuing review process appropriate for the protocol.

Recommendations for division of responsibility relating to various aspects of monitoring were extensively discussed earlier in the thesis. Noninstitutional research requires establishing a mechanism for review and monitoring. Possible solutions include the Alberta College of Physicians and Surgeons Ethics Review Committee (currently performing review, but no monitoring) or a provincial ethics board with authority to review and monitor noninstitutional research.

Monitoring is broader than the issue of researchers' integrity or determining their compliance to protocols. It is an institutional responsibility. Investigators' noncompliance is usually due to error rather than malice. It is most effectively corrected through education. If noncompliance presents risks to subjects, the REB should stop the protocol. In serious cases of noncompliance, the institution could impose sanctions and funding could be stopped. The basic concepts of research ethics review are denied by 'protocol creep'

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[6] Medical Research Council of Canada, 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* (Ottawa: Public Works and Government Services Canada, 1998) [hereinafter *TCPS*].

(extension of implementation of a protocol beyond that approved by ethics review). Clearly articulated consequences of noncompliance with international, national and institutional ethical guidelines are required.

Institutions are responsible for knowing about all the research which is conducted in their institution, that all research meets ethical standards and that grant money is only released upon compliance with the granting agencies' policies and conditions. Institutions and departments have a role in monitoring. Formation of institutional trial groups or monitoring committees may assist with review of adverse event reports. Institutions have the responsibility to ensure that REBs are constituted properly, are functioning effectively and are adequately funded. An office for research audit could deal with day to day audits of research (especially in-house) and report to the REB. This office could develop quality assurance measures to ensure annual reviews are done, to deal with complaints regarding research and to periodically monitor data. They could also be responsible for developing educational programs in the institution. Knowledge on the part of the investigators that there is an audit office should have a deterrent effect regarding noncompliance with protocols or failure to ensure voluntary informed consent.[7]

MRC/CIHR has a responsibility to monitor. Is this being accomplished through NCEHR and site visits conducted by NCEHR?

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[7] K. McGrath & R.J. Briscoe, "The Role of the Subject Advocate in a Community-Based medical Research Facility," (1981) 3 IRB A Review of Human Subjects Research 3 at 6-7; R.J. Levine, *Ethics and Regulation of Clinical Research*, Second Edition (New York: Urban & Schwarzenberg, 1986) 111-112. Levine describes the need for consultation regarding the proposed research with a 'trusted advisor' usually the general practitioner. Specific measures which contribute to monitoring are: development of a standard form for annual review and development of templates or consistent approaches nationally for other issues and establishment of the role of subject advocate.

Medical practice today has many forms of bureaucratic controls and auditing systems in place which are an unquestioned part of daily medical practice. The reasons for nonacceptance of monitoring in research were enumerated earlier. The broad level of respect for peer review has not been achieved by research ethics review. Monitoring should be seen as continuing peer review, as collegial rather than adversarial.

Utilizing the quality assurance vocabulary and approach in relation to continuing review of research creates confusion. It does not address the problem directly. Some research guidelines and policies refer to the exclusion from REB review of studies relating to quality assurance. This might infer that the quality assurance approach to monitoring of research would result in REBs no longer being responsible for monitoring.

The place to refer to quality assurance in review of research is not at the individual protocol stage, but in reviewing the performance of the REB in fulfilling its mandate of protecting research subjects. Criteria must first be formulated upon which to evaluate the effectiveness of REBs. Requirements for accreditation must be developed and set out in the *TCPS* or elsewhere. They must deal with such issues as: a code of conduct assigning responsibilities of investigator, institution and REB for the conduct, review and monitoring of research and sanctions for violations. The system for monitoring of REBs could be based on the CCAC model with regular site visits, or accreditation could be based on submission of documents with only occasional visits (similar to the NIH-OPRR where the focus is on persistent or severe violations).

The stakes are high in medical research: the risks and benefits to the individuals, (including future generations with genetic research), the multi-billion dollar industry, the

trust and confidence invested by the public and the improvement in health and eradication of disease.

Ethical problems can no longer be restricted to the present. Banks of information and frozen tissue have moved us to the future. Today's ethical rules must be strong enough to regulate tomorrow the use of what we collect today.[8]

A system based solely on preliminary review is flawed. That is the reason for continuing review. Seeking input from subjects regarding their understanding of their experience is critical to ensuring that the process is performing as it should to protect their welfare. Monitoring of the consent process can take different forms (some of them less threatening to researchers) such as: record keeping and chart review, meeting with the subjects following their participation or having someone present when consent is elicited.

If it is accepted that monitoring has to/should be done, then the resources necessary will have to be found and will have to be utilized by some body. The issue becomes: which body or structure would be most effective to protect subjects, provide education and preserve the credibility of the system?

REBs provide valuable service to the pharmaceutical industry. Institutions should charge a line item on grant applications and research contracts relating to the cost of REB review and ongoing review. Institutions currently do quality assurance in many areas of their operation, so they cannot argue that there are not sufficient funds to monitor research, which in fact brings in funding to the institution. The *TCPS* also requires institutions to ensure that

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[8] L.E. Böttiger, "Introduction-new horizons for medical ethics," (1995) 238 Journal of Internal Medicine 509.

REBs have the appropriate financial and administrative independence to fulfil their primary duties.[9] Research review and monitoring costs are justifiable expenses for sponsors. Receipt of this income would enable institutions to set up research offices or hire administrative support to implement a program of monitoring research and put in place a computer data-base to keep track of amendments to protocols and remind investigators of annual reviews. Sources of funding for REB operations (initial review and monitoring) include: 1) overhead charges from industry should be used to ensure adequate funding for initial review and monitoring; 2) portion of federal research grants should go to fund review and monitoring of research which they sponsor; 3) the institution/hospital should direct a portion of its operating budget to research review and monitoring (as set out in the *TCPS*) and 4) donations and foundations could provide a portion of the administration of research. If funding of ethics review has been inadequate, perhaps it is reasonable to charge sponsors (all sponsors including Councils) for ethical review and monitoring. In Alberta, the College of Physicians and Surgeons does charge for their services when their ethics review committee reviews protocols being implemented by physicians outside of institutions.

MRC/CIHR must demonstrate leadership within the research industry and show that it is serious about the ethics of research. One way to demonstrate this commitment to the highest ethical standard is to provide funding (not for overhead, but) directed specifically at: a) research ethics initial and continuing review, b) education of all members of REBs (including lay members), and researchers and c) assisting in the establishment of a formal

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[9] *TCPS, supra* note 6 at 1.2.

mechanism (or independent structure), to set standards for REBs and monitor REB compliance to these standards. Anything less than these commitments falls short of being able to say to Canadians that the research enterprise is being stewarded responsibly.

Perhaps the more current term 'continuous quality improvement' rather than 'monitoring' or 'quality assurance' should be utilized to emphasize that the goal is to improve the research process. Perhaps the term should be 'research audit' rather than 'monitoring,' as it connotes 'medical audit,' a term used to refer to the process of ensuring a high standard of medical practice. Referring back to Heath's proposal, the usage of 'continuing review' in reference to issues which form part of the process of annual reviews by the REBs seems to be less problematic than 'monitoring.' Whatever label is attached to the function, the critical issue is that all aspects of research must be overseen in order to ensure subject safety and public trust.

It is important for local REBs to perform well, or industry will take the path of least resistance and pay an independent REB to perform review in order for the sponsor to fulfill its regulatory requirements. At this point, private REBs are not accountable to any authority. With the genomic revolution, research will increase dramatically. REBs should maintain overall responsibility for ethics, but may delegate the function to a separate group (compliance group, which may be independent of the REB, but report to it).

We must also achieve better integration of safety monitoring and risk assessment and better liaison between the Medical Advisory Committee and the REB. Roles of the REB and institution must be articulated. The REB should focus on ethics and the institution on GCP, quality assurance, meaningful data and data monitoring. The institution already has a quality

assurance process in place with regard to patients. This responsibility must be extended to include research subjects. Department heads have a role in ongoing monitoring of research conducted by members of their departments. It is not clear whether this is currently occurring on a broad scale. In many cases, the department chair's involvement is limited to review of the research proposal and endorsement of the validity of the proposal at the initial REB review stage. Health Canada as a regulator receives serious adverse event reports and should communicate necessary safety information to REBs. Questions remain: while industry monitors integrity of data in studies it sponsors, whose responsibility is it to monitor data integrity in Council sponsored research? Who makes decisions about stopping the study and whether an adverse event is serious? Who owns the data and has a right to publish results? The *TCPS* states the researcher has this right. Could Health Canada as the regulator require industry to submit regular summary reports on adverse events to REBs? Or is the industry-academe committee the better approach, to reach agreement between industry and academe on their various roles in providing information to facilitate protection of subjects? It is an institutional responsibility to ensure the validity of an ongoing study, by development of standard checklists for investigators to complete regarding annual reports. Should the checklist be managed by the REB as part of its monitoring of research or by the department chair as part of the institutional responsibility for competence of researchers? REBs should focus on monitoring of the process of gathering data and the ethical process (e.g. informed consent), rather than monitoring of specific data.

A further recommendation is that industry supply regular summary reports on safety issues for REBs. These would put the individual adverse event reports into context (as only

the company may have the full data related to a specific patient or the complete trial data).

Perhaps we should even re-examine the requirement for prior review of all protocols. Levine proposes a different approach to defend against violations: 1) making clear statements that offences will not be tolerated and setting out the punishment for committing them; 2) independent IRBs which provide consultation and guidance; 3) all proposals to be reviewed by some agency that is capable of judging the scientific design and competence of the investigators (through licensing or certification). Prior review would then not be required for all research with competent subjects.[10]

In Canada, we must also answer the questions relating to what kind of a national group should be established or should NCEHR continue to perform some of the broad national responsibilities? On a national basis, should there be one group which is advisory, responsible for education of REB members and investigators and in charge of accreditation and monitoring of the REBs' performance? Should there be two groups or more? Should the responsibilities be national or provincial or should there be a sharing of responsibilities at the federal/provincial level? Should one level provide advisory/educational/accreditation standards while the other focuses on assessment of actual REB performance?[11] Should this body/these bodies report to government rather than the granting councils? The funding of

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[10] R.J. Levine, *Ethics and Regulation of Clinical Research*, Second Edition (Baltimore: Urban & Schwarzenberg, 1986) 361-362; A.L. Caplan, "Random Auditing–A Modest Proposal for Reforming the Regulation of Research," (1983) 31 Clin. Res. 142-143. Caplan agrees. He suggests random audit of initial review allowing resources to be used for monitoring.

[11] S. Verdun-Jones & D.N. Weisstub, "The Regulation of Biomedical Research Experimentation in Canada: Developing An Effective Apparatus for the Implementation of Ethical Principles in a Scientific Milieu," (1996-97) 28 Ottawa Law Review 327-328, 337-340.

this body (whether NCEHR or another) is a federal responsibility as the government is accountable to the public for investment in research and ethical conduct of research (through the granting Councils and *TCPS*).

Models for implementation of monitoring were presented from the management-administrative perspective (COCO/MEM), to the process of consent (McGill), the continuing review and protocol adherence perspective (Halifax-IWK Grace) and that of noninstitutional review/monitoring (Alberta College of Physicians and Surgeons). The McGill study was discussed as an example of monitoring of the consent process in a situation of high risk and vulnerable population. It was included as an example as there are few reported studies demonstrating how the consent process might be monitored. Most studies require no consent monitoring, or not this form of intense oversight, as it is a heavy burden on the REB or its delegate. The Alberta College of Physicians and Surgeons Ethics Review Committee was included as a model for the successful operation of ethics review of noninstitutional research. The bylaw also provides for monitoring of research, but this has not been implemented.

The IWK-Grace model of monitoring of records (REB original approval forms, consent forms), integrity of data and adherence to protocol and adverse events comes the closest to the ideal process. It has proven successful in its acceptance by the research community in the institution. The approach taken is interactive and educational rather than punitive. The membership of the audit committee provides the broad base of expertise required. Follow-up to the process has resulted in improved research, improved REB applications, development of more effective education of research ethics issues and a more effective audit process. The only component which appears to be missing is monitoring of

the consent process which could be easily added as there is a functioning research office with staff who could develop and implement questionnaires to seek input from subjects regarding their understanding of their involvement in research and in a situation of high risk, might be able to carry out the McGill type of monitoring of the consent process. The IWK-Grace model is offered as a possible model for other institutions to consider in developing mechanisms for monitoring of approved research.

Ultimately, it is compliance with the *process* and *procedures* which will ensure the safety of humans who are the subjects of experimentation. Researchers must be reminded of the high ethical conduct expected of them and be given assistance to achieve it (by institutions, those responsible for education and REBs involved with peer review). REBs must be given the same support by their institutions, in the form of financial, moral and administrative encouragement.

All involved in the research enterprise must become sensitive to the trust placed in them by subjects of research to act in their best interests. Researchers must acknowledge the pressures and conflicts in the system and respond appropriately, realizing that the protection of human subjects is the legitimizing basis for research.

In this quickly developing area it often seems that there are more questions than answers. In this thesis, there has been an attempt to canvass a broad spectrum of issues from philosophical to mechanical, some in considerably more detail than others and recommendations have ranged from general to more specific. Where possible, strategies and suggestions for dealing with ethical issues in human experimentation in general and

monitoring in particular have been offered throughout the thesis. There are certainly a variety of acceptable approaches to achieve the same end-protection of the research subject.

REBs, institutions and researchers must hold fast to and champion the procedural protections for human subjects. We are embarking into uncharted waters with the genetics revolution and the boundaries of science seem limitless. We must be sure that appropriate consideration and reflection is given prior to endorsing scientific progress at the expense of recognition of the worth of each individual and respect for the community. We must be assured that individuals have knowingly and voluntarily consented to risk personal harm for the benefit of others or we diminish each other and risk losing the support and cooperation of those we seek to help. Monitoring is needed to ensure that this takes place.

Research is in the service of humanity, not science. The reverse must never be realized. "Science is not the ultimate good, and the pursuit of new scientific knowledge should not be allowed to take precedence over moral values where the two are in conflict."[12]

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[12] M.H. Pappworth, *Human Guinea Pigs, Experimentation in Man* (London: Routledge & Kegan Paul, 1967) 27.

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Appendix 1

THE NUREMBERG CODE

1. The voluntary consent of the human subject is absolutely essential.
This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.
The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability or death to the experimental subject.[1]

The introduction to the 10 principles reads as follows:

Permissible Medical Experiments

The great weight of the evidence before us is to the effect that certain types of medical experiments on human beings, when kept within reasonably well-defined bounds, conform to the ethics of the medical profession generally. The protagonists of the practice of human experimentation justify their views on the basis that such experiments yield results for the good of society that are unprocurable by other methods or means of study. All agree, however, that certain basic principles must be observed in order to satisfy moral, ethical and legal concepts.[2]

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[1] G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation*, (New York: Oxford University Press, 1992) 2.

[2] R.A. Greenwald, M.K. Ryan & J.E. Mulvihill, eds., *Human Subjects Research, A Handbook for Institutional Review Boards*, (New York: Plenum Press, 1982) 229

Appendix 2
Directive of the Prussian Minister of Religious, Educational and Medical Affairs, December 29, 1900

Instructions to the Directors of Clinics, Out-Patient Clinics and Other Medical Facilities

A. I wish to point out to the directors of clinics, polyclinics and similar establishments that medical interventions for purposes other than diagnosis, therapy and immunization are absolutely prohibited, even though all other legal and ethical requirements for performing such interventions are fulfilled if:
   1. The person in questions is a minor or is not fully competent on other grounds;
   2. The person concerned has not declared unequivocally that he consents to the intervention;
   3. The declaration has not been made on the basis of a proper explanation of the adverse consequences that may result from the intervention.

B. In addition, I prescribe that:
   1. Interventions of this nature may be performed only by the director of the institution himself or with his special authorization;
   2. In every intervention of this nature, an entry must be made in the medical case-record book, certifying that the requirements laid down in Items 1-3 of Section I and Item 1 of Section II have been fulfilled, specifying details of the case.

C. This directive shall not apply to medical interventions intended for the purpose of diagnosis, therapy or immunization.[1]

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[1] G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) 127.
This informal translation was prepared by the Health Legislation Unit of the World Health Organization.

Appendix 3
Reich Circular, February 28, 1931
Regulations on New Therapy and Human Experimentation

The Reich Health Council [*Reichsgesundheitsrat*] has set great store on ensuring that all physicians receive information with regard to the following guidelines. The Council has agreed that all physicians in open or closed health care institutions should sign a commitment to these guidelines when entering their employment.

The final draft of the Circular continues with 14 points:

1. In order that medical science may continue to advance, the initiation in appropriate cases of therapy involving new and as yet insufficiently tested means and procedures cannot be avoided. Similarly, scientific experimentation involving human subjects cannot be completely excluded as such, as this would hinder or even prevent progress in the diagnosis, treatment, and prevention of diseases.
   The freedom to be granted to the physician accordingly shall be weighed against his special duty to remain aware at all times of his major responsibility for the life and health of any person on whom he undertakes innovative therapy or perform an experiment.
2. For the purposes of these Guidelines, "innovative therapy" means interventions and treatment methods that involve humans and serve a therapeutic purpose, in other words, that are carried out in a particular, individual case in order to diagnose, treat, or prevent a disease or suffering or to eliminate a physical defect, although their effects and consequences cannot be sufficiently evaluated on the basis of existing experience.
3. For the purposes of these Guidelines, "scientific experimentation" means interventions and treatment methods that involve humans and are undertaken for research purposes without serving a therapeutic purpose in an individual case, and who effects and consequences cannot be sufficiently evaluated on the basis of existing experience.
4. Any innovative therapy must be justified and performed in accordance with the principles of medical ethics and the rules of medical practice and theory.
   In all cases, the question of whether any adverse effects that may occur are proportionate to the anticipated benefits shall be examined and accessed.
   Innovative therapy may be carried out only if it has been tested in advance in animal trials (where these are possible).
5. Innovative therapy may be carried out only after the subject or his legal representative
   has unambiguously consented to the procedure in the light of relevant information provided in advance.

Where consent is refused, innovative therapy may be initiated only if it constitutes an urgent procedure to preserve life or prevent serious damage to health and prior consent could not be obtained under the circumstances.

6. The question of whether to use innovative therapy must be examined with particular care where the subject is a child or a person under 18 years of age.
7. Exploitation of social hardship in order to undertake innovative therapy is incompatible with the principles of medical ethics.
8. Extreme caution shall be exercised in connection with innovative therapy involving live microorganisms, especially live pathogens. Such therapy shall be considered permissible only if the procedure can be assumed to be relatively safe and similar benefits are unlikely to be achieved under the circumstances by any other method.
9. In clinics, polyclinics, hospitals, or other treatment and care establishments, innovative therapy must be carried out only by the physician in charge or by another physician acting in accordance with his express instructions and subject to his complete responsibility.
10. A report shall be made in respect of any innovative therapy, indicating the purpose of the procedure, the justification for it, and the manner in which it is carried out. In particular, the report shall include a statement that the subject or, where appropriate, his legal representative has been provided in advance with relevant information and has given his consent.

    Where therapy has been carried out without consent, under the conditions referred to in the second paragraph of Section 5, the statement shall give full details of these conditions.
11. The results of any innovative therapy may be published only in a manner whereby the patient's dignity and the dictates of humanity are fully respected.
12. Section 4-11 of these Guidelines shall be applicable *mutatis mutandis*, to scientific experimentation (cf. Section 3).

    The following additional requirement shall apply to such experimentation:

    (a) Experimentation shall be prohibited in all cases where consent has not been given;

    (b) Experimentation involving human subjects shall be avoided if it can be replaced by animal studies. Experimentation involving human subjects may be carried out only after all data that can be colleted by means of those biological methods (laboratory testing and animal studies) that are available to medical science for purposes of clarification and confirmation of the validity of the experiment have been obtained. Under these circumstances, motiveless and unplanned experimentation involving human subjects shall obviously be prohibited;

    (c) Experimentation involving children or young persons under 18 years of age shall be prohibited if it in any way endangers the child or young person;

    (d) Experimentation involving dying subjects is incompatible with the principles of medical ethics and shall therefore be prohibited.
13. While physicians and, more particularly, those in charge of hospital establishments may thus be expected to be guided by a strong sense of responsibility toward their

patients, they should at the same time not be denied the satisfying responsibility [*verantwortungsfreudigkeit*] of seeking new ways to protect or treat patients or alleviate or remedy their suffering where they are convinced, in the light of medical experience, that known methods are likely to fail.

14. Academic training courses should take every suitable opportunity to stress the physician's special duties when carrying out a new form of therapy or a scientific experiment, as well as when publishing his results.[1]

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[1] G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation*, (New York: Oxford University Press, 1992) 130-131.

Appendix 4

World Medical Association
Declaration of Helsinki II

Recommendations Guiding Medical Doctors
in
Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly, Helsinki, Finland 1964, and as revised by the 29th World Medical Assembly, Tokyo, Japan, 1975.
The 1975 version is included, as Helsinki I (1964) and Helsinki II (1975) appear to be seminal documents. Subsequent revisions occurred in 1983 (Venice) and 1989 (Hong Kong).

Introduction

It is the mission of the medial doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the doctor with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies *a fortiori* to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every doctor in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interest of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Doctors should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Doctors should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the doctor is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The doctor should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the doctor should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a doctor who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the doctor must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the doctor-patient relationship.

5. If the doctor considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The doctor can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.[1]

World Medical Association
Declaration of Helsinki IV
Recommendations guiding physicians
in biomedical research involving human subjects
48st World Medical Assembly
Somerset West, Republic of South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration,' and the International Code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.'

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[1] G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation*, (New York: Oxford University Press, 1992) 333-336.

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

I. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

II. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

III. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subjects must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

IV. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

V. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

VI. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

VII. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

VIII. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

IX. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

X. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

XI. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

XII. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment, it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient–including those of a control group, if any–should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exits.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic Biomedical Research Involving Human Subjects (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers–either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well being of the subject.[2]

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[2] This is the latest version of the Declaration.

Appendix 5

U.S. Code of Federal Regulations; Title 45, Public Welfare Department of Health and Human Services, National Institutes of Health, Office for Protection From Research Risks, Part 46–Protection of Human Subjects Revised June 18, 1991

Sections dealing with initial and continuing review

Sec. 46.103 Assuring compliance with this policy–research conducted or supported by any Federal Department or Agency

(b) Departments and agencies will conduct or support research covered by this policy only if the institution has an assurance approved as provided in this section, and only if the institution has certified to the Department or Agency head that the research has been reviewed and approved by an IRB provided for in the assurance, and will be subject to continuing review by the IRB. Assurances applicable to federally supported or conducted research shall at a minimum include:

(4) Written procedures which the IRB will follow (i) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution; (ii) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (iii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(5) Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department of Agency head of (i) any unanticipated problems involving risk to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval

(d) The Department or Agency head will evaluate all assurances.....the appropriateness of the proposed initial and continuing review procedures in light of the probable risks and the size and complexity of the institution

(f) ....An institution with an approved assurance shall certify that each application or proposal for research covered by the assurance and by 46.103 of this policy has been reviewed and approved by the IRB. Such certification must be submitted with the application or proposal....

Sec. 46.109 IRB Review of Research

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with Sec. 46.116. The IRB may require that information, in addition to that specifically mentioned in Sec. 46.116, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.
(c) An IRB shall require documentation of informed consent or may waive documentation in accordance with Sec. 46.117.
(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.
(e) An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

Sec. 46.110 provides for expedited review for certain kinds of research involving no more than minimal risk, and for minor changes in approved research

Sec. 46.111 sets out the criteria for IRB approval of research

Sec. 46.115 deals with IRB records and indicates that an IRB shall prepare and maintain adequate documentation of IRB activities, including the following:
(3) Records of continuing review activities.

Sec. 46.116 sets out the general requirements for informed consent.

Sec. 46.205 Additional duties of the IRBs in connection with activities involving fetuses, pregnant women or human in vitro fertilization
(2) (ii) monitoring the progress of the activity and intervening as necessary through such steps as visits to the activity site and continuing evaluation to determine if any unanticipated risks have arisen.

Note: Earlier sections refer to "continuing review"; Later sections referring to protections pertaining to research, development and related activities involving fetuses, pregnant women and human in vitro fertilization and protections for children involved as subjects in research–refer to a "monitoring procedure"

Appendix 6

A Comparison of the Nuremberg Code and the US Federal regulations

A comparison of the Nuremberg Code and the U.S. federal regulations is instructive regarding the different emphasis given to protection of human subjects of research.

Nuremberg Code	NIH & FDA
-directed to researcher	-directed at institutions – drug companies or research institutions; safeguarding the rights and welfare of subjects is primarily the responsibility of the institution, accountable to DHEW for funds awarded;
-prime focus–protection of subject	-view research positively; try to protect subjects, but not at expense of hindering research
-prime vehicle–voluntary, informed consent	-prime vehicles–IRB review and regulations; IRB can waive requirements for consent; -sanction for violation of regulations–loss of funding, or nonacceptance of research data to support a new drug application; not criminal penalties;
-informed consent (provision 1) & right to withdraw (provision 9);	-emphasis–subjects' rights (rather than welfare); include informed consent and right to withdraw;
-voluntary consent–absolutely essential	-permit consent from a "legally authorized representative,"
-governs non-beneficial research	-deals with research that may benefit the subject; includes any novel approach; is broader than Code;
-detailed rules for protection of subjects: -prior animal experimentation -beneficial results improcurable by other methods of means of study; -avoid all unnecessary physical and mental suffering;	-these specific protections are absent; -more enthusiastic for human research than Code; more permissive as: a) regulations were adopted by arm of government that fosters and believes in research; b) applies to therapeutic

Nuremberg Code	NIH & FDA
-prohibits experiments where there is reason to believe death or disabling injury may occur	research which may benefit subject; c) were not written in response to abuses;[1] However, they were drafted in response to Tuskegee, etc -No research activity would be funded by DHEW unless a grant recipient had an IRB review and approval; the IRB must be composed of no fewer than five persons with varying backgrounds & expertise, to facilitate reviews from both scientific and ethical perspectives; the IRB must ascertain that the proposed project complied with institutional commitments and regulations, applicable law, standards of professional conduct and community attitudes; [2]
-The Code is exclusively substantive	-federal regulations contain procedural safeguards (through IRB review and lay representation on IRBs)
-regarding non-therapeutic research- the Code continues to be a vital document; it presents a starting point in discussions of regulation of human research; the enduring value of the Code is not in its detailed provisions, but in its approach to human dignity...scientific progress is important, but the human subject comes first; [3]	

[1] L.H. Glantz, "The Influence of the Nuremberg Code on U.S. Statutes and Regulations," in G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation*, (New York: Oxford University Press, 1992) 198 & 199.

[2] *Ibid.*, 187-189.

[3] *Ibid.*, 199.

Appendix 7

Development of Regulations in the U.S.

1950s-some medical schools performed peer review; [1]

1953-N.I.H. developed a policy called "Group Consideration of Clinical Research Procedures Deviating From Accepted Medical Practice or Involving Unusual Hazard" which dealt with research with volunteers at its clinical centre; it directed that such research must receive approval by a review committee prior to supporting the research; [2]

1962- Federal government involvement in regulation of research–thalidomide led to Kefauver-Harris Amendment to Food, Drug and Cosmetic Act, adding requirement of "efficacy," which is to be determined by well-controlled, double-blind studies; purpose: to keep unsafe or useless drugs off the market; FDA required two studies, informed consent of subject and reporting of adverse reactions;[3] detailed statements by pharmaceutical companies required by FDA, setting out drug testing methods, investigator qualifications and procedures used to secure subjects' informed consent;[4]

1964-Jewish Chronic Disease Hospital

1966-FDA promulgates patient consent regulations; NIH policy–no funding for new or continuing grants unless institution provides prior review of judgment of investigator by committee of institutional associates regarding rights and welfare of subjects,

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[1] R.J. Levine, *Ethics and Regulation of Clinical Research*, Second Edition, (Baltimore: Urban & Schwarzenberg, 1986) 322 & 323. In 1961, Welt reported on a questionnaire he sent to each university department of medicine in the country [Jay Katz, *Experimentation with Human Beings*, (New York: Russell Sage Foundation,1972) 889]; In 1962, a similar survey was conducted by the Law-Medicine Institute at Boston University [WJ Curran: "Government Regulation of the Use of Human Subjects in Medical Research: The Approaches of Two Federal Agencies in Experimentation with Human Subjects," p 402-454, ed. by PA Freund, George Braziller, NY, 1970].

[2] M.E. Evans, "The Legal Background of the Institutional Review Board," in R.A. Greenwald, M.K. Ryan & J.E. Mulvihill, eds., *Human Subjects Research, A Handbook for Institutional Review Boards*, (New York: Plenum Press, 1982) 22.
See also: L.H. Glantz, "The Influence of the Nuremberg Code on U.S. Statutes and Regulations," in G.J. Annas & M.A. Grodin, eds., *The Nazi Doctors and the Nuremberg Code, Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) 185; Subcommittee on Health of the Committee on Labour and Public Welfare, U.S. Senate: Federal Regulation of Human Experimentation, 1975, U.S. Gov't Printing Office, No. 45-273-0, 1975, at 13.

[3] M.K. Ryan, L. Gold & B. Kay, "Research on Investigational New Drugs," in Greenwald, Ryan & Mulvihill, *supra* note 2, at 93 for discussion of drug DES used in pregnancy from 1941-1971, which caused cancer of daughters of those who were on drug; DES highlights the fact that no law calls for surveillance of drug once it is approved for marketing

[4] P.R. Benson, "The Social Control of Human Biomedical Research: An Overview and Review of the Literature," (1989) 29 Soc. Sci. Med.. 1, at 4.
See also: Glantz, *supra* note 2, at 186.

appropriateness of methods to secure informed consent and risks/benefits of investigation; [5] IRBs must assure investigations are in accordance with laws of community and for giving due consideration to pertinent ethical issues;[6] Surgeon General extended prior review requirement to all extramural research funded by Public Health Service (PHS);[7] Surgeon General permitted grantee institutions to file institution-wide assurance and set up standing institutional review boards (IRBs);[8]Beecher article;

1969--1966 NIH policy (part of Department of Health, Education and Welfare DHEW), re-issued in expanded form, called the *Institutional Guide to DHEW Policy on the Protection of Human Subjects*; it required institutional committee review of DHEW funded research; the IRB was charged with establishing continuing review in keeping with initial review; FDA regulations called for review based on degree of risk, but not less than once per year; institutionally sponsored and locally based committee to be responsible for protecting rights and safety of subjects; May 1969--revision--a committee of exclusively biomedical scientists is not adequate for proper review;[9]

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[5] Glantz, *ibid.* at 186 Professor William Curran described the development of regulations at the FDA and NIH in the 1960's.
See also: B.H. Gray, *Human Subjects in Medical Experimentation, A Sociological Study of the Conduct and Regulation of Clinical Research*, (Toronto: John Wiley & Sons, 1975), at 12 outlining effect of Beecher article 1966 in *NEJM*--22 examples of unethical research.

[6] Levine, *supra* note 1, at 323.

[7] Evans, *supra* note 2, at 22.

[8] Glantz, *supra* note 2, at 187.

[9] D.T. Chalkley, "Developing Guidelines," (1973) 21 Clinical Research 4 at 777-780. The 1966 NIH policy was a procedural policy which required grantee institutions to carry out review of projects prior to the involvement of human subjects, but it did not specify what subject rights were involved, nor define informed consent, nor provide any guides for weighing risks and medical benefits. These questions were in theory left to the institutions.
Description of Legislative Process in U.S.
If Congress passes a new law, or if the Executive Branch finds it necessary to reinterpret old law, or to issue new policy, or if a law is changed by judicial interpretation, a "proposed rule making" is issued, which is a draft version of the new regulations. This proposed rule making appears in the Federal Register. Following receipt of comments, the draft is revised. The result is then issued as a final rule, and has the force of law. Regulations published in the Federal Register are binding.
In 1974 the DHEW administrative policy in the field of research on human subjects was replaced by codified regulations. Once issued in this form, the regulations can be amended, altered, or extended by the same procedure--issuance of a proposed rule making, consideration of comments and issuance of a final rule.
Informed consent as a dominant legal doctrine is a product of the 1960s following the decisions in *Salgo* v. *Leland Stanford Jr. University Board of Trustees*, 154 CA 2d 560; 317 P, 1957; *Natanson* v. *Kline*, 186 Kan 393; 350 P 2d 1093, reheard as 187 Kan 186; 354 P 2d 670, 1960; and *Halushka* v. *University of Saskatchewan*, [1965], 53 D.L.R.[2d] 436 (Sask. C.A.).
The 1960s and early '70s was a time of widespread loss of public confidence in the so-called "establishment"

1971-FDA required peer review for all clinical research submitted to it by drug companies; DHHS required all nonmedical research it funded to be peer reviewed;[10]

1974–Department of Health, Education and Welfare (DHEW) administrative policy of 1969 is replaced by codified regulation–45 CFR 46 under Sec. 491 of Public Health Service Act; IRBs rather than investigators responsible for determining whether potential research subjects were "at risk";[11] committee of not fewer than 5 and

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generally. Most medical research centres are located in large cities and originally located in middle-class white districts. They now service predominantly disadvantaged populations. The distribution of research risk was not uniform and is an issue of concern.

See also: Evans, *supra* note 2, at 22; S. Wollman & M.K. Ryan, "Continuing Review of Research," in Greenwald, Ryan & Mulvihill, *supra* note 2 at 125 & 126. In 1978 the National Commission recommended closer monitoring of the conduct of approved research and monitoring of the consent process. The recommendations called for IRBs to "have the authority to conduct continuing review of research involving human subjects and to suspend approval of research that is not being conducted in accordance with the determination of the Board or in which there is unexpected serious harm to subjects;" and "to maintain appropriate records, including copies of proposals reviewed and records of continuing review activities. The federal government included these recommendations in their 1981 regulations regarding review and consent process; J. Brody & A. R. Jonsen, "Evolution of Regulatory Influences on Research with Human Subjects," in Greenwald, Ryan and Mulvihill, *supra* note 2, 6 & 7. The National Commission was conceived as a response to abuses in the research enterprise. The Commission found that research was not, shot through with abuses. In fact, compared to sports, politics and even certain forms of religious practice, the research enterprise, with all its human frailties, can probably be considered quite benign.

A major problem arose in translating technical issues into public policy. Why was biomedical research singled out for this critical scrutiny rather than the more prevalent, but less visible research endeavours with human subjects in engineering, marketing and advertising? One reason is the "boundary problem." It is not always crystal clear to either the patient/subject or to the doctor/researcher, much less to the spectator/public, just where the practice of medicine ends and the conduct of biomedical research begins, as the settings, personnel and manoeuvres that characterize these interacting domains are frequently the same.

[10] B. Barber, J.J. Lally, J.L. Mararushka & D. Sullivan, *Research on Human Subject, Problems of Social Control in Medical Experimentation* (New York: Russell Sage Foundation, 1973) 148.

[11] J. Bell, J. Whiton & S. Connelly (James Bell Associates), *Final Report, Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects*, Prepared for: The Office of Extramural Research, National Institutes of Health, June 15, 1998, online: NIH <www.nih.gov> at 2. [hereinafter *Bell Study*]

include capacity to judge the proposal in terms of community attitudes;[12] resulted from loss of public confidence in the conduct of medical research as part of larger lack of confidence in "establishment;"[13] National Commission for Protection of Human Subjects of Biomedical & Behavioral Research established under National Research Act; the National Commission was charged with studying the nature of research with fetuses, identifying principles underlying research and developing guidelines and recommendations for Secretary of DHEW;[14] Commission recommended local review as local reviewers have knowledge of local circumstances and investigators;[15] the National Research Act required institutions to establish IRBs and established the Office for Protection from Research Risks (OPRR) as part of NIH, to oversee research;[16]

1977–FDA conducts pilot program inspecting IRBs and examined procedures for continuing review;[17]

1978–National Commission recommendations for IRBs; closer monitoring of the conduct of approved research and monitoring the consent process; authority to suspend

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See also: Glantz, *supra* note 2 at 187; Ryan, "IRB Procedures," in Greenwald, Ryan & Mulvihill, *supra* note 2, p. 63

[12] Levine, *supra* note 1, at 323 & 324. The IRB must be composed of sufficient members of varying backgrounds to assure complete and adequate review. The membership should possess not only broad scientific competence to comprehend the nature of the research, but also other competencies necessary in the judgment regarding the acceptability of the research in terms of institutional regulations, relevant law, standards of professional practice, and community acceptance. "The committee must therefore include persons whose primary concerns lie in these areas of legal, professional and community acceptability rather than in the conduct of research, development and service programs of the type supported by HEW.." It is also required that no committee shall consist entirely of employees of the organization where the research will be conducted. No committee should be composed of a single professional or lay group.

[13] Chalkley, *supra* note 9 at 779.

[14] Glantz, *supra* note 2, at 187.

[15] C. Levine & A.L. Caplan, "Beyond Localism: A Proposal for a National Research Review Board," (1986) 8 IRB A Review of Human Subjects Research 2 at 7 & 8. The National Commission stated that rights of subjects should be protected by local review committees due to the advantage of greater familiarity with the actual conditions surrounding the conduct of research. Local review was not intended to and probably should not produce uniformity of outcome of the same research proposal. Federal regulations and institutional assurances of compliance permit flexibility in procedures. Local review is intended to be "institution specific." Local boards use knowledge of the skills, qualifications and trustworthiness of local researchers in their deliberations concerning any given research protocol.

[16] *Bell Study*, *supra* note 11 at 2.

[17] Wollman & Ryan, *supra* note 9 at 125.

approval of research not conducted in accordance with determination of IRB or where there is unexpected serious harm to subjects;[18]

1981–National Commission recommendations [19] and recommendations of the Presidential Commission for the Study of Ethical Problems in Biomedical and Behavioral Research, were included in federal regulations (Department of Health and Human Services, DHHS which is the successor to DHEW), regarding review and consent process; there were major revisions to the rules and regulations for protection of human subjects; these rules apply only to DHHS-funded or conducted research; with general assurances to DHHS, institutions must assure that its responsibilities for protecting the rights and welfare of human subjects conducted at the institution *regardless* of the funding; this provision in the general assurance expands the populations protected by the regulations;[20] the regulations: a) define research; b) set out the elements of informed consent; c) provide that the IRB can waive the requirement for consent;[21] 1981 revisions require review of all FDA regulated research regardless of where it is done (including Phase III drug trials in physician's private offices), resulting in the noninstitutional review board (NRB); [22]

1991–core of DHHS regulations were adopted by 15 other federal departments and agencies as the Federal Policy for the Protection of Human Subjects (56 CFR 28004) known as the "Common Rule" –which supplanted Subpart A of 45CFR46, Title 45 Code of Federal Regulations Part 46;[23]

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[18] *Ibid.*, at 126.

[19] National Commission, Report and Recommendations, DHEW Publications, Nol (OS) 78-0008, Appendix, DHEW Publication No. (OS) 78-0009, Washington, 1978
See also: Levine, *supra* note 1 at 324 & 325; W.J. Curran, "New Ethical Review Policy for Clinical Medical Research," (1981) 304 NEJM 16 at 953. Informed consent requirements are considerably more specific and lengthy than those in the 1974 rules.

[20] Glantz, *supra* note 2 at 190.

[21] *Ibid.*, at 191-194

[22] Curran, *supra* note 19 at 325.
See also: D.F. Phillips, "Institutional Review Boards Under Stress: Will They Explode or Change?" (1996) 276 JAMA 20 at 1623. Before conducting research on human beings, an institution must provide assurances to the funding agencies that it will comply with policy recommendations. These requirements, the Common Rule, were adopted in 1991 by 16 federal agencies (not including the FDA, which has maintained its own regulations) that conduct, support or regulate research using "Assurances of Compliance." The National Institutes of Health (NIH) Office for Protection from Research Risks (OPRR) negotiates and approves these Assurances of Compliance on behalf of the secretary of DHHS. Each is tailored to an institution's needs. An Assurance of Compliance approved by OPRR commits the institution and its personnel to full compliance with the regulations or the policy.

[23] *Bell Study*, *supra* note 11 at 2.
See also: S. Verdun-Jones & D.N. Weisstub, "The Regulation of Biomedical Research Experimentation in

Canada: Developing an Effective Apparatus for the Implementation of Ethical Principles in a Scientific Milieu," (1996-97) 28 Ottawa Law Review 2 at 297-341; J. Porter, "The Federal Policy for the Protection of Human Subjects," (1991) 13 IRB A Review of Human Subjects Research 5 at 8. The 1991 Subpart A differs little from the 1981 Subpart A of the HHS regulations, concluding a decade of effort to extend and standardize human subjects protections.

Appendix 8
Differing approaches of HHS and FDA to compliance review of their regulations

HHS (OPRR)	FDA
-"scout's honour;" believing academic institutions & researchers have too much integrity & too much at stake to violate ethical principles & procedural guidelines in the regulations; an inquiry to the institution is enough to correct shortcomings; -no sanctions against institutions or IRBs; -can withdraw funding and request previous funding to be returned; [3]	-procedural review to determine if IRB is in compliance with federal regulations & operating in accord with own written procedures [1] ie. attendance at meetings, completeness of minutes, review of informed consent document;[2] -have own regulations which are consistent with Common Rule[4]
-assurance process in advance-states the institution's commitment to adhere to Federal requirements;[6]	-on-site inspection; -goal-inspect each IRB every 5 years[5] -200 inspections in 1997;

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[1] M.K. Ryan, "IRB Procedures," in R.A. Greenwald, M.K. Ryan & J.E. Mulvihill, eds., *Human Subjects Research–A Handbook for Institutional Review Boards* (New York: Plenum Press, 1982) 64-65.

[2] Testimony Before the Committee on Government Reform and Oversight, Subcommittee on Human Resources, United States House of Representatives, Statement of George Grob, Deputy Inspector General for Evaluation and Inspections, *Institutional Review Boards: A Time for Reform*, June 11, 1998, Office of Inspector General, Department of Health and Human Services ; online: DHHS <http://www.dhhs.gov/progorg/oig/testimony/irb/irbtest.pdf> at 8- 9. [hereinafter "Testimony"]

[3] M.K.Ryan, *supra* note 1 at 63.

[4] NIH Regulatory Burden v. Human Subjects Protection, Workgroups Report, April 15, 1999, http//www.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm at 4. [hereinafter *NIH Workgroups*]

[5] *Ibid.*

[6] M.K. Ryan, *supra* note 1 at 67-68. Each institution engaged in HHS-funded research must provide the secretary of HHS with an assurance that it will comply with HHS regulations, and HHS-funded research will be reviewed, approved and be subject to continuing review by an IRB. It must also (i)provide a statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects *regardless of the source of funding*, (ii) designate one or more IRBs for which provisions are made for meeting space and sufficient staff to support IRB functions. The assurance must also contain written procedures that the IRB will follow to conduct initial and continuing review of research, to determine which projects require more frequent than an annual review, and ensure prompt reporting to the IRB and HHS of unanticipated problems.

-OPRR goes on-site only in instances of alleged breakdowns in IRB protections; -on-site visits infrequent–only 1 for-cause visit April 1997-May 1998; [7] 1994- OPRR made only 10 site visits;[8]	-focussed on procedural compliance; -little attention to IRB effectiveness;

Differences in Regulations

-require notification to IRBs of any "unanticipated problems;" -sufficient space & staff to support IRB's review & record keeping[10]	-require notification to IRBs of "serious & unexpected" adverse events; -no staff or space requirements[9] -FDA reviewers themselves examine the merits of the protocol & do not leave all decision-making to the IRB, as FDA regulations are stricter than IRB's usual safety concerns[11]
-require IRB to inform researcher, institution and government of reason for suspension or termination of funded research and serious violations of IRB direction by researcher[12] as HHS has an obligation to examine problems	-same requirement of FDA re: IRB informing researcher, institution and government of termination and violations

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The assurance is filed with the Office for Protection from Research Risks, NIH. Final HHS regulations make it clear that federal regulation applies only to HHS-funded research.

[7] "Testimony," *supra* note 2 at 8- 9.

[8] H.Edgar & D. Rothman, "The Institutional Review Board and Beyond: Future Challenges to the Ethics of Human Experimentation," (1995) 73 Millbank Quarterly 4 at 493.

[9] *NIH Workgroups*, *supra* note 4 at 4.

[10] *Ibid.* at 2-3.

[11] Edgar & D. Rothman, *supra* note 8 at 491. FDA procedures provide a degree of national oversight for clinical research, but many experiments do not fall under FDA or NIH review, leaving ethical concerns solely up to the IRB.

[12] *Ibid.*

associated with research supported by public funds.[13] [14]

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[13] *Ibid.*

[14] S. Wollman & M.K. Ryan, "Continuing Review of Research," in Greenwald, Ryan & Mulvihill, *supra* note 1 at 128-129. These regulations create new responsibilities for IRB board members, institutional officers, and researchers which are problematic. An IRB in a routine continuing review procedure (such as reviewing informed consent, discussing progress of the research, and reviewing side effects) is unlikely to uncover serious violations of research ethics. Such violations have been brought to the attention of institutional officials by colleagues, students, nurses and patients. Many feel that it is not the responsibility of the board to report *directly to the government* its decisions to terminate or suspend a study as a result of violations. Such charges carry with them potential liability for the accused, accuser, the institution, and IRB and many IRBs object to being required to trigger institutional review by a federal agency. Up to now, the procedure for dealing with a recalcitrant investigator, unwilling to follow the institution's policy governing research involving human subjects has been to inform the appropriate institutional official. This has been enough to end the violations. Levine remarked that many fear the regulations will make the IRB an enforcement arm of the FDA, which already has the authority to audit any institution under its jurisdiction. The current regulations give the IRB the right to appoint a third party observer of the consent process and could engender a mood of confrontation and distrust, which will not necessarily protect subjects any better than open dialogue between the investigator and the IRB.

Appendix 9

Ethical Considerations in Research Involving Human Subjects, Report No. 6

The Working Group consulted widely, examined existing procedures and guidelines from universities and granting agencies in Canada and abroad and reviewed pertinent literature. Guidelines and legislation from other countries regarding research on human subjects was also consulted. The Report defined human experimentation, discussed the historical context and basic ethical problems and set out ethical requirements to which research involving human subjects should conform, including procedures for implementation of ethical requirements.

The Report stated that the protection of human rights is a responsibility belonging to the public at large and should not be delegated to the medical profession alone. Professional and community input is required in the formulation and adjudication of the ethics of research on human subjects.[1]

The ethics committee (and the investigator), must evaluate the risks and benefits and ensure there are procedures for protecting the subject of research. Direction was given in the Report to both investigators and REBs regarding what questions to consider when weighing the risks and benefits, what factors diminish the ability of the proposed group of subjects to give consent (the group includes prisoners, students, employees, patients), and the extent of information to be disclosed. The Report also referred to the need to monitor an individual's continuing willingness to participate. The Working Group included the direction given by the courts in *Halushka* v. *University of Saskatchewan*, (1965) 53 D.L.R. (2d) 436 (Sask. C.A.)regarding the legal requirements for informed consent in research. Further the Report deals with deception, "debriefing," remuneration and examples of situations of research projects where consent may not be required.[2]

With regard to the issue to research involving individuals incompetent to consent for themselves (children or the mentally incompetent), the Working Group agreed that they would allow experiments of negligible risk (of every day life) on this group. However, there was not unanimity when faced with experiments involving greater than negligible risk and those who cannot consent for themselves, where they would not benefit directly. The majority allowed these experiments to be considered by the REB in relation to risk/benefit analysis. The minority position would instruct the REB to prohibit such research. With regard to consent on behalf of those unable to consent for themselves, the Working Group suggested a proxy consent be given firstly by a parent or legal guardian and secondly, by a subject advocate or ombudsman. Report No 6 also gave specific consideration to the circumstances of pregnant women and fetuses.

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[1] Medical Research Council of Canada, *Ethical Considerations in Research Involving Human Subjects, Report No. 6*, (Ottawa: Minister of Supply and Services Canada, 1978), at 1, 4 & 11

[2] *Ibid.*, at 16-25.

The Report then focussed on the Procedures for Implementation of Ethical Requirements and set out the responsibilities of the various participants in medical research--the investigator, the institution (the ethics review committee REB), the sponsor and the subjects. The primary responsibility of an institution where research on human subjects is carried out, is to foster awareness of the ethical implications of such research among all levels of personnel. The funding agency shares in the ethical responsibilities of the investigator and institution. The volunteer puts himself at risk in order that knowledge of the human body and mind may be obtained. It is possible that the volunteer might derive direct personal benefit.

Besides the investigator and institution, the Medical Research Council examines the ethical considerations as part of its review of each proposal and only funds those that are satisfactory in this regard. This review is carried out by a local institutional committee (REB). The establishment for the requirement of a local REB and its approval of protocols on ethical grounds is a major contribution of this Report. The membership and procedures to be followed by this REB are outlined. The prime responsibility of the Medical Research Council's Grants Committees are to review the scientific aspects of the proposal. However, Council should continue to pay close attention to the ethical aspects of the work proposed in the grant applications it reviews.

The Working Group expressed its intention that all research proposals (regardless of source of funding), involving human subjects should be reviewed by an REB before being allowed to proceed. Prime responsibility for review is at the local institutional level and the document sets out the proposed procedures and responsibilities of the parties in order to accomplish this.[3]

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[3] *Ibid.* at 39-46.

Appendix 10

MRC *Guidelines on Research Involving Human Subjects 1987*
Sections Relating to Monitoring

Introduction to Part 2 - Practice, Implementing Ethical Responsibilities

Responsibility for the proper conduct of human experimentation lies with all who are involved in the research, but most particularly with the researcher and the local REB. The MRC must ensure that public funds are spent only on research that is ethically acceptable.[1]

Chapter VII Responsibilities

A. The Researcher

Researchers have the initial and continuing duty to ensure the ethical conduct of all aspects of their research. The researcher must identify and bring to the attention of the Research Ethics Board (REB) any factors which might raise concerns, both as part of the process of obtaining approval from the REB, and also as the research proceeds. It follows that , in every case, the researcher responsible must be clearly identified and unequivocally take on responsibility for the proper conduct of the entire research team.

B. The Institution

The institution within which the researcher works has the major responsibility to ensure that the research meets the ethical standards of society. Although researchers apply to MRC for grants, the funds are administered through the institution, which acts as trustee. The terms of the trust include not only management of accounts, but also active responsibility for initial and ongoing conformity to proper standards. The Committee reaffirms the role of REBs in undertaking the institution's responsibility for the ethics of research undertaken with MRC support.

C. The Medical Research Council

The MRC has assumed responsibility for providing guidance in research involving human subjects and for ensuring that its funds are used only within acceptable standards. This is achieved through guidelines and by fostering awareness of ethical issues relating to research involving human subjects. The Committee is of the opinion that in discharging its public trust, the MRC must monitor local procedures and practices in ethics review.[2]

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[1] Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects, 1987* (Ottawa: Minister of Supply and Services Canada, 1987) 41.

[2] *Ibid.* at 43.

Chapter VIII Procedures

A. The Institution

The primary responsibility for decisions on the ethics of research, carried out within the institution, or by its staff, should continue to be delegated to Research Ethics Boards (REBs). The Committee has concluded that the REB should be established under the authority of the President of Principal of a university, or a comparable chief executive officer of a non-university institution. This person must give the REB a clear mandate for review of all protocols for research involving human subjects. Also, the REB's relationship to other committees concerned with ethical matters, for example, to professional, teaching or other related bodies, must be defined. The President, Principal or their equivalents, should give the REB full authority for ethics review.[3]

Accountability of the Investigator to the Research Ethics Board

The approval of an REB for a specific protocol is based on the exact and detailed information available to it. The REB may require changes to the protocol as a condition of acceptance. The investigator is then bound to act in accord with the statements made in the submission as approved. If changes are desired in any detail that pertains to the subjects of the experiment, the investigator should seek the further approval of the REB prior to implementing them. The investigator should also immediately report to the REB any apparent risks beyond those predicted and, if necessary, suspend the experiment pending clarification.[4]

The Operation of the Research Ethics Board

An REB need not be supported by an extensive secretariat, but it is important that minutes be kept. These should capture the issues raised and the assessments made, as well as the undertakings given and facts asserted as relevant to the study. The assurances by researchers to the REB may be critical to the assessment that the proposal can be ethically conducted. Since crucial points and undertakings may not be expressed elsewhere, the documentation of the terms and understandings upon which approval was given should include the minutes of the REB. Further, a record of the REB deliberations is valuable for circulation to interested parties, such as other REBs in the same institution or in other centres in a multi-centre trial, government agencies responsible for licencing a drug, or the MRC.[5]

Continuing Review

The Standing Committee believes that the REB and MRC should ensure that the actual implementation and conduct of the project continue to meet the standards of ethics agreed to among the researcher, REB and the MRC.

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[3] *Ibid.* at 45.

[4] *Ibid.* at 48.

[5] *Ibid.* at 48-49.

As part of its initial discussion on ethics, the REB should determine whether audit or review is necessary in each case. If so, the procedures should be set by the REB as one of the conditions of approval. If no ethics audit or review is deemed necessary, the reasons should be given. The plan may provide for inspection of the means by which information is given to prospective subjects, or for an independent assessment of how much those thus informed understand what they have been told.

At a minimum, researchers should be required to provide an annual update on the status of any project for which the REB has given approval. This information should indicate any changes that may have occurred in scientific knowledge or in the design of the study, as well as the progress of the study. For specific protocols, the REB should also be able to require more frequent or rigorous review.[6]

Once REB approval has been given, the researcher must immediately inform the REB of any new information that might alter the ethical basis for continuing the research program.

It is expected, however, that the institution's monitoring will be more active than simply seeking investigators' assurances. Research officers, or members cognizant of ethical concerns, may be required to maintain scrutiny by periodic review of the research and of the factors involved in the ethics approval. The actual form of this monitoring will vary with the specific research protocols. In certain cases, specialists from outside the institution might be asked to act as monitors.

Investigators' applications to REBs should be countersigned by heads of departments or others with senior administrative responsibility. Notification of ethics approval, including minutes of REB meetings and amendments to the original protocols, should be relayed to such officers, thus placing them on notice of commitments made and accepted. Their institutional obligations in the management of their departments and personnel will help ensure compliance with these conditions.

The costs of this monitoring may transcend financial aspects, to include time taken from the monitor's other activities. Monitoring may also strain professional and personal relationships between colleagues or provide increased opportunities for a breach in confidentiality of information about research subjects and premature release of scientific or commercial information.

The Committee believes that researchers and institutions should bear the costs of this day-to-day monitoring, which are largely similar to monitoring practices already well accepted in the health professions and commercially-sponsored research. The human costs of monitoring can often be reduced through mutual understanding of ethical duty and public interest.

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[6] *Ibid.* at 49.

Monitors must be impressed with their own ethical responsibilities in accepting the task, and department heads must recognize their institutional duties to arrange adequate monitoring. Investigators must recognize that monitoring is intended to assist them in meeting commitments they have made in the cause of good science and good ethics.[7]

Finally, it must be stated that the Standing Committee does not believe that appropriate attitudes in research can be ensured by these intensified procedures of monitoring alone. A high standard of ethics results not from policing but from human awareness and personal integrity.[8]

MRC Support of REBs

The Standing Committee is certain that the Medical Research Council must establish mechanisms, perhaps with other agencies, to ensure the effective functioning of the local REBs on which it depends for review of the ethical aspects of research involving human subjects. While these Guidelines place the primary responsibility on the REBs, the Standing Committee is strongly of the opinion that public accountability demands that MRC monitor the functioning of the REBs which review the work that it funds.[9]

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[7] *Ibid.* at 50.

[8] *Ibid.* at 51.

[9] *Ibid.* at 52.

Appendix 11

National Council on Ethics in Human Research (NCEHR)

NCEHR was created in 1989 as the National Council on Bioethics in Human Research (NCBHR). It arose from a request by Dr. Bois, then President of MRC, to the Royal College to form this new organization to support the REBs. Health Canada was invited as a co-sponsor. In 1995, with the development of the Tri-Council Policy Statement, the sponsors (funders) were expanded to include the SSHRC and NSERC; to accommodate this change, NCBHR dropped "Bio" to become NCEHR.

The mission of NCEHR is:

- To advance the protection and promotion of the wellbeing of human participants in research; and
- To foster high ethical standards for the conduct of research involving humans.[1]

Its Terms of Reference are:

The National Council on Ethics in Human Research shall:

- assist Research Ethics Boards (REBs) in interpreting and implementing the Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans (1998);

- assist REBs in resolving contentious issues;

- provide assistance to REBs in establishing and implementing procedures to evaluate and monitor the performance of research involving human subjects;

- foster education, dialogue and understanding in and among institutions, REBs, researchers, organizations that fund research, and the public on the ethical aspects of research involving human subjects and the implementation of appropriate policies or guidelines for such research;

- work with the ethics committees or divisions of the various Research Councils, the Royal College of Physicians and Surgeons of Canada, and Health Canada, to ensure that the Tri-Council Policy Statement meets the needs of research involving human subjects in Canada; and

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[1] NCEHR sponsored by Health Canada, Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, Royal College of Physicians and Surgeons of Canada, Social Sciences and Humanities Research Council of Canada, *National Council on Ethics in Human Research*, Fifth Edition, 1998 at 1.

- assist REBs, institutions and organizations that fund research in assessing the ethical perspectives of research involving human subjects. Such expertise will involve traditional areas of research, those of newer science and technology, and particularly those relating to human cultural diversity in Canada.[2]

[2] *Ibid.* at 2.

Appendix 12

Tri-Council Policy Statement, Ethical Conduct for Research Involving Humans

F. Review Procedures for Ongoing Research

Article 1.13 (a) Ongoing research shall be subject to continuing ethics review. The rigour of the review should be in accordance with a proportionate approach to ethics assessment.

(b) As part of each research proposal submitted for REB review, the researcher shall propose to the REB the continuing review process deemed appropriate for that project.

(c) Normally, continuing review should consist of at least the submission of a succinct annual status report to the REB. The REB shall be promptly notified when the project concludes.[1]

Beyond scrutinizing reports, the REB itself should not normally carry out the continuing ethics review, except in specific cases where the REB believes that it is best suited to intervene. For research posing significant risks, the REB should receive reports on the progress of the research project at intervals to be predetermined. These reports should include an assessment of how closely the researcher and the research team have complied with the ethical safeguards initially proposed.

In accordance with the principle of proportionate review, research that exposes subjects to minimal risk or less requires only a minimal review process. The continuing review of research exceeding the threshold of minimal risk that is referred to in Article 1.13 (b), in addition to annual review (Article 1.13 (c)) might include:

* formal review of the free and informed consent process,
* establishment of a safety monitoring committee,
* periodic review by a third party of the documents generated by the study,
* review of reports of adverse events,
* review of patients' charts, or
* a random audit of the free and informed consent process.

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[1] Medical Research Council of Canada, 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* (Ottawa: Public Works and Government Services Canada, 1998) at 1.10.

Other models of a continuing ethics review may be designed by researchers and REBs to fit particular circumstances.

The process of a continuing ethics review should be understood as a collective responsibility, to be carried out with a common interest in maintaining the highest ethical and scientific standards. Research institutions should strive to educate researchers on the process of a continuing ethics review through workshops, seminars and other educational opportunities.[2]

(reference to Article 1.13 (b) is not helpful in defining minimal risk; discussion of Minimal Risk is on page 1.5; there is no article relating to Minimal Risk

[2] *Ibid.* at 1.11.

Appendix 13

Comparison Between MRC Guidelines 1987 and Tri-Council Policy Statement 1998 Relating to Continuing Review

1987 MRC Guidelines	1998 Tri-Council Policy Statement
-call for REB and MRC to ensure that actual implementation and conduct of research meets ethical standards agreed to among researcher, REB & MRC (explicit reference to monitoring as a REB and MRC responsibility)	-ongoing research shall be subject to continuing review proportionate to risk assessment -REB itself shall not normally carry out the continuing ethics review, except in special cases
-as part of initial review, REB should determine whether audit or review is necessary; procedures set by REB will be one of conditions of approval; if no review is deemed necessary, reasons should be given	-researcher shall propose continuing review process to REB; no reference to requirement for REB agreement, though later reference to REB designating other models
-at a minimum–an annual update, any changes in scientific knowledge, study design, progress of study -expected that monitoring will be more active than simply seeking investigator's assurances -REB may require more frequent or rigorous review -researcher must immediately inform REB of new information which might alter ethical basis for continuing the research	-at least a succinct annual status report to REB and prompt notification of conclusion; (No direction regarding content of status report) -examples of continuing review–formal review of the free & informed consent process; safety monitoring committee; periodic review by third party of documents; review of adverse events; review of patients' charts or random audit of consent process -other models of continuing ethics review may be designated by researcher and REB - minimal risk or less, requires only minimal review process
-applications to REBs should be signed by heads of departments who have institutional obligation to manage their departments	-continuing ethics review is a collective responsibility; institutions should educate researchers

1987 MRC Guidelines	1998 Tri-Council Policy Statement
-researchers and institutions should bear day to day costs of monitoring; is similar to monitoring practices already well accepted in the health professions and by commercially-sponsored research	-no discussion of who to bear costs
-high standard results not from policing but from human awareness and personal integrity	-REB has both educational and review roles; review ethics to determine whether research should start or continue (at 1.1)
-MRC to monitor the functioning of REBs which review the work it funds (due in part to lack of resources, MRC never took on the coordination or monitoring function; instead NCBHR was created in 1988 to furnish advice, consult with REBs and do site visits	-no discussion of who to monitor functioning of REBs
-the aim of the Guidelines is to define the MRC's expectations of the research community in any research involving human subjects funded by the MRC -the MRC must ensure that public funds are spent only on research that is ethically acceptable	-as a condition of funding, the Councils require as a minimum, that researchers and their institutions apply the ethical principles and articles of this policy
	-reference to research in emergency situations

Sources: Medical Research Council of Canada, *Guidelines on Research Involving Human Subjects, 1987*, (Ottawa: Minister of Supply and Services Canada, 1987) Chapter VIII, Procedure, A.5 Continuing Review, at 49-51 and B.2 The Medical Research Council, MRC Support of REBs, at 51-52, xi, 41
Medical Research Council of Canada, 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* (Ottawa: Public Works and Government Services Canada, 1998) Section 1, Ethics Review, F. Review Procedures for Ongoing Research, at i.2, 1.10. 1.11, 2.12

Appendix 14

Recommendations from the NCBHR Study of Site Visits 1995 Protecting and Promoting the Human Research Subject: A Review of the Function of Research Ethics Boards in Canadian Faculties of Medicine

Continuing Review and Monitoring

Recommendation 16

Institutions and REBs should further develop, expand and implement mechanisms for the thorough review and monitoring of human research. These should include at least annual reports on issues such as unexpected events, significant protocol changes and termination reports. These reports should be reviewed by the REB. For sensitive protocols, the REB should require more frequent or rigorous review and may suggest outside monitors.

Recommendation 17

NCBHR and MRC should identify both the mechanisms by which REBs may monitor ongoing research protocols and minimal criteria for adequate monitoring. When sponsoring agencies monitor research within an institution, the monitors for the sponsoring agency should report identified problems to the REB as well as to the sponsoring institution.

With regard to Confidentiality in Monitoring the report suggested that: when entering a protocol, patients should be made aware that the information generated may be seen by monitors who wish to verify the data (is not a recommendation itself, but is included in the text relating to recommendation 18)

Non-compliance with Ethical Guidelines

Recommendation 19

The MRC and NCBHR should provide clear statements or standards about the consequences of noncompliance with national ethical guidelines or the recommendations of an ethics committee. Such standards should encompass the concept that an investigator risks the loss or suspension of the privilege of performing research involving human subjects if misconduct is proven by due process. To complement national standards, processes must also be in place at the university level for curbing, identifying and appropriately sanctioning noncompliance and misconduct.[1]

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[1] NCBHR, *Special Report: Protecting and Promoting the Human Research Subject: A Review of the Function of Research Ethics Boards in Canadian Faculties of Medicine*, (1995) 6 NCBHR Communiqué 1 at 23-24.

Appendix 15

Legislation in Quebec governing medical research

Civil Code of Quebec, S.Q. 1991, c. 64, referred to as (*C.C.Q.*), as amended by Bill 432:

Article 20: A person of full age who is able to give consent may submit to an experiment provided that the risk incurred is not disproportionate to the benefit that can reasonably be anticipated.

(Article 21 is unique in that it is the first time an adult lacking discernment or a minor will be able to become a subject of experimentation; it is also the first time in 1994, that a REB was enshrined in legislation in Canada.)

Article 21. A minor or a person of full age who is incapable of giving consent may not be submitted to an experiment if the experiment involves serious risk to his health, or where he understands the nature and consequences of the experiment, if he objects. Moreover, a minor or a person of full age who is incapable of giving consent may be submitted to an experiment only if, where the person is the only subject of the experiment, it has the potential to produce benefit to the person's health or only if, in the case of an experiment on a group, it has the potential to produce results capable of conferring benefit to other persons in the same age category or having the same disease or handicap. Such an experiment must be part of a research project approved and monitored by an ethics committee. The competent ethics committees are formed by the Minister of Health and Social Services or designated by that Minister among existing research ethics committees; the composition and operating conditions of the committees are determined by the Minister.

Consent to experimentation may be given, in the case of a minor, by the person having parental authority or the tutor and, in the case of a person of full age incapable of giving consent, by the mandatory, tutor or curator. To allow a person of full age having suddenly become incapable of consent to be submitted to an experiment which, insofar as it must be undertaken promptly after the appearance of the condition justifying it, does not permit, for lack of time, the designation of a legal representative, consent may be given by the person authorized to consent, in the absence of a legal representative, to any care the person requires; it is incumbent upon the competent ethics committee to determine, when examining the research project, whether the experiment meets that condition.
Procedures considered by the ethics committee to be innovative care required by the state of health of the person concerned do not constitute experiments.'

Bill 432 amended Article 21 CCQ by eliminating the requirement that all research protocols involving minors and incompetent adults, be approved by the Minister of Health. Now the

ultimate responsibility for approving such protocols rests with research ethics boards formed by the Minister.

In June 1998, the Minister published his Action Plan, setting out the composition, mandate, functions and responsibilities of research ethics boards.

Bill 432 further expands the range of substitute decision-makers in emergency situations to next of kin (from the more restricted--legally appointed mandators, tutors or curators). The section now reads: consent may be given by a person's spouse, or close relative or someone who shows a special interest in the person; the initial decision to be made, regarding whether this clause may be applied is the responsibility of the REB; first they must decide if an emergency exists.
Research in non-emergency situations (ie. protocols with Alzheimers patients) still require authorization of legally appointed mandator, tutor or curator. This effectively excludes a large proportion of incompetent persons who do not have formal legal representatives.
Bill 432 removes the requirement for court authorization in experiments on one person alone.
Article 22 deals with removal of organs, tissues or other substances as part of the care he receives, with his consent or a person qualified to give consent for him, to be used for purposes of research.
There is no mention of anonymized samples of blood or tissue, stored for a number of years, being exempt from the consent requirement.
Bill 432 was adopted June 12, 1998 and came into force June 17, 1998.

Other legislation in Quebec affecting research is:
Charter of Human Rights and Freedoms, (R.S.Q., c. C-12); *Code of Ethics of Physicians*, (R.R.Q., c. M-9, r.4); *An Act Respecting Health and Social Services*, (R.S.Q., c. S-4.2); *An Act Respecting Access to Documents held by Public Bodies and Protection of Personal Information*, (R.S.Q., c. A-2.1); *An Act Respecting Protection of Personal Information in the Private Sector*, (R.S.Q., c. P-39.1).

See also: C.C. Roy, "Revisions of Civil Code of Quebec and Research Involving Children," (1992) 3 NCBHR Communiqué 1 at 6-7, where the hospital interpreted Article 21 as allowing research on minors if the health of the child will benefit directly in the medium or long term; K.C. Glass, "Research Involving Humans," in *Canadian Health Law and Policy*, J. Downie & T. Caulfield, eds., (Toronto: Butterworths, 1999) at 388-389.

Appendix 16

Canadian Council on Animal Care (CCAC)
Mandate

The Canadian Council on Animal Care (CCAC) is the national peer review agency responsible for setting and maintaining standards for the care and use of animals used in research, teaching and testing throughout Canada.

The CCAC was established in 1968. Its mission statement underlines the focus of the CCAC on the ethical principles of animal-based experimentation.

"The purpose of the Canadian Council on Animal Care is to act in the interests of the people of Canada to ensure through programs of education, assessment and persuasion that the use of animals, where necessary, for research, teaching and testing employs optimal physical and psychological care according to acceptable scientific standards, and to promote an increased level of knowledge, awareness and sensitivity to relevant ethical principles."[1]

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[1] CCAC Mandate, online: CCAC <http://www.ccac.ca/english/mandate.htm>

Appendix 17

Current Studies in the U.S. Evaluating the IRB System Their Observations and Recommendations

Statement of George Grob: *Institutional Review Boards: A Time for Reform*

The system of protections is in need of reform, based on the following six main findings: 1) IRBs face major changes in the research environment;[1] 2) IRBs conduct minimal continuing review of approved research; [2] [3] 3) IRBs review too much, too quickly, with too little

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[1] Testimony Before the Committee on Government Reform and Oversight, Subcommittee on Human Resources, United States House of Representatives, Statement of George Grob, Deputy Inspector General for Evaluation and Inspections, *Institutional Review Boards: A Time for Reform*, June 11, 1998, Office of Inspector General, Department of Health and Human Services, online: DHHS <http://www.dhhs.gov/progorg/oig/testimony/irb/irbtest.pdf> at 5 [hereinafter "Testimony"]
When the regulations were established in the 1970s and 1980s, research was most often government funded, carried out by a single investigator, with a small cohort of subjects at a single site, a university teaching hospital. There was a considerable awareness of the risks of participating in research and IRB workloads were more limited and allowed ample time for deliberations over proposals. In the past 20 years, academic medical centres are subject to increasing cost pressures due to the risk of managed care and capitated payments. Proportionately, much more research is funded by commercial sponsors. IRBs feel pressure to accommodate these sponsors, looking for quick turnaround of their research and for whom time is money. Much research is now multi-centre. Each institution has little knowledge of the other sites. Advances such as gene testing and gene therapy raise difficult ethical issues. Patients/consumers now demand access to research trials hoping to receive a benefit or treatment for life-threatening illnesses.

[2] *Ibid.* at 6. An IRBs' monitoring of approved research can provide an important safety net for human subjects. This is especially important now that the 1994 Advisory Committee on Human Radiation (Final Report, 1995) has shown that individuals who consent in writing to participate do not necessarily understand the implications of their decision to participate. Few subjects realized they were participants in research and many did not understand the informed consent forms they signed. Continuing review is a low priority for many IRBs. Where it does occur, continuing review is usually limited to a paper-based review, as there is no time to go beyond perfunctory obligations. IRB members seldom leave the board room to visit the research site. Although many would like to, few IRBs oversee the consent process or solicit feedback from subjects. The IRBs rely on research investigators to provide timely, accurate reports.

[3] *Ibid.* at 7. Continuing review is also limited as the IRBs receive inadequate information from outside sources. There is little communication between the Data Safety Monitoring Boards, (created by research sponsors to oversee many of the large-scale trials), and the IRB. The adverse-event reports that IRBs receive from sponsors, arrive without sufficient contextual information to make them meaningful. FDA warning letters to clinical investigators, usually are not forwarded to the IRB. When a sponsor or investigator submits a protocol, it may not inform the IRB of any prior review of the protocol by another IRB. The IRB may have very little information about how the informed consent process really works and about how well the interests of subjects are being protected during the course of research.
To improve continuing review NIH/OPRR and the FDA have issued interpretations of Federal requirements

expertise;[4] [5] 4) neither IRBs nor DHHS devote much emphasis to evaluating IRB effectiveness; [6] 5) IRBs face conflicts that threaten their independence;[7] and 6) IRBs and their institutions provide little training for investigators and members.[8]

Institutional Review Boards: A Time for Reform, Executive Summary
The recommendations include the following:

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in the forms of Dear Colleague letters and Information Sheets. From the IRB's perspective, some of these have served only to reduce IRB flexibility and add to their burdens.

[4] *Ibid.* There has been an average increase of 42% in initial reviews during the past five years at sites the committee visited. IRBs are also being flooded with adverse-event reports from the multi-centre trials they oversee.

[5] *Ibid.* at 8 This increased workload, combined with decreased resources, causes problems for IRBs and threatens the quality of their reviews. In order to cope, many IRBs are forced to rely on a pre-assigned reviewer to examine and summarize research plans. In some IRBs, unless one of the assigned reviewers raises a questions or concern about the research, the board has little or no discussion at its meeting. Science is becoming more complex and many IRBs lack sufficient scientific expertise on their boards or staffs to adequately assess protocols. Sometimes, IRBs will have consultants fill the gap. This can be costly and can slow down an already overburdened review process.

[6] *Ibid.* at 8 & 9. IRBs do not know how well they are accomplishing their mission of protecting human subjects, as they seldom obtain feedback from human subjects or their families. Nor do they often examine the complaints they receive to learn whether they reflect broader, system problems or inquire as to how well the informed consent process is actually working. Even less common are independent, outside parties conducting such evaluations.

[7] *Ibid.* at 10. IRBs face conflicts that could threaten their objectivity. Clinical research, funded by commercial sponsors, is an important source of revenue and/or prestige for most institutions. Independent IRBs, which review primarily commercial research, are subject to similar pressures, particularly those which are owned by contract research organizations. Others may have equity-owners as board members reviewing protocols. As a important counterbalance to these pressures, the presence of IRB members whose concerns are primarily in nonscientific area or who are not otherwise affiliated with the institution is critical. The study found few such "outside" members on the boards. It was not unusual for an IRB of 15 or 20 or more members to include only one or two noninstitutional members.

[8] *Ibid.* at 11. The review process often involves complex ethical issues and scientific questions. The education of board members, especially "outside" members is important. Often IRBs face the obstacle of the reluctance of investigators to participate in training sessions.

1. Recast Federal IRB requirements so that they grant IRBs greater flexibility and hold them more accountable for results
   a. eliminate or lessen some of the procedural requirements directed to IRBs;
   b. require that IRBs undergo regular performance-focussed evaluations;
2. Strengthen continuing protections for human subjects participating in research
   a. require data safety monitoring boards for some multi-site trials;
   b. provide IRBs with feedback on developments concerning multi-site trials;
   c. routinely provide IRBs with feedback about FDA actions against investigators;
   d. call for increased IRB awareness of on-site research practices;
3. Enact Federal requirements that help ensure that investigators and IRB members are adequately educated about and sensitized to human-subject protections
   a. require that research institutions have a program for educating its investigators on human-subject protections;
   b. require that investigators provide a written attestation of their familiarity with and commitment to human-subject protections;
   c. require that IRBs have an educational program for board members;
4. Help insulate IRBs from conflicts that can compromise their mission in protecting human subjects
   a. require more representation on IRBs of nonscientific and noninstitutional members;
   b. reinforce to IRB institutions the importance of IRBs having sufficient independence;
   c. prohibit IRB equity owners from participating in the IRB review process;
5. Recognize the seriousness of the workload pressures that many IRBs fact and take actions that aim to moderate them
   a. require that IRBs have access to adequate resources
6. Reengineer the Federal oversight process
   a. revamp the NIH/OPRR assurance process
   b. revamp the FDA on-site inspection process
   c. require the registration of IRBs."[9]

Testimony of George Grob: *Institutional Review Boards: A Time for Reform*
Recommendations include:
a) greater flexibility may be achieved by eliminating or decreasing the number of procedural requirements that Federal regulations require of IRBs, such as the current regulation requiring IRBs to conduct full, annual reviews for all research plans regardless of the level of risk to the human subjects. Accountability may be achieved by: all IRBs under

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[9] Department of Health and Human Services, USA, Office of Inspector General, *Institutional Review Board: A Time for Reform*, Executive Summary, June, 1998. OEI-01-97-00183 at iii & iv.

NIH/OPRR and FDA's purview undergoing performance-focussed evaluations to assess their effectiveness in achieving their core mission and more extensive representation on IRBs of nonscientific and non-institutional members;
b) reengineer the federal oversight process–the federal oversight of IRBs is currently not equipped to respond effectively to the issues. Reorienting the NIH/OPRR assurance process to rely on an institutional attestation to conform to the IRB requirements in Federal regulations, would free up scarce OPRR resources now devoted to reviewing and negotiating assurances to instead, conduct periodic performance-based reviews and to provide education. The FDA should revamp its inspections, so they focus less on compliance matters and more on performance issues. FDA and NIH/OPRR are urged to incorporate into their oversight efforts an attempt to determine how well IRBs are actually protecting human subjects by examining matters such as how the processes of recruiting, selecting and gaining informed consent from human subjects actually works;
c) strengthening continuing protections for research subjects; The IRBs need to be more aware of what is actually occurring in research implemented under their jurisdiction. IRBs need to move beyond relying on signed informed consent forms to ensure the integrity of the consent process itself. Currently, IRBs have no way of knowing whether research subjects fully understand that they are involved in research which may entail risks. IRBs must find mechanisms to ensure that the research under their purview is being conducted as planned. Trust is an important element in the system, but IRBs have a vital role in verifying the information presented to them. To conduct meaningful reviews of approved research, IRBs need continuous feedback from the various players involved in overseeing research. The FDA should provide IRBs with feedback on actions it takes against investigators;
d) enhance education for research investigators and IRB board members–the most important protection for human subjects is the presence of well-trained and sensitized investigators, which will minimize the need for regulatory intervention, either by the Federal agencies or by IRBs themselves. The NIH should take a leading role in education. It should require institutions receiving funds under the Public Health Service Act to have a program to educate their investigators about human-subjects protections. Investigators should attest to the commitment to upholding Federal policies relating to protection of human subjects.[10]

James Bell Associates, *Final Report*

The study examined 246 high-volume IRBs which conduct 88 percent of the yearly total of reviews. Multi-centre protocols represented 30 percent of the total submissions for initial review. NIH (25 percent) and industry (25 percent) were the leading sources of funding for protocols reviewed by the IRBs, together accounting for about one-half of protocols that were implemented. Institution funds (11 percent) and pre-existing resources (17 percent), which are both internal sources, and a combination of other external sources,

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[10] "Testimony," *supra* note 1 at 12-16.

including federal, philanthropic and state funds, together supported the remainder of funded protocols (22 percent).

Nearly half (46 percent) of investigators indicated that some subjects (experimental or control) were seeking or receiving clinical care for the mental or physical condition under study. Almost one-half of those investigators said their subjects had very serious conditions; within that group, one in three protocols had subjects with either a terminal condition, medical emergency or attenuated ability to comprehend.[11]

The government and the research community, have as their ultimate goal, the advancement of scientific knowledge. They struggle to balance two sometimes competing objectives--the need to protect research subjects from avoidable harm and the desire to minimize the regulatory burden on research institutions and their individual scientists. The study concludes that the balance seems to have been achieved and most people involved in research believe the current system for protecting human research subjects is working well. In response to concerns about irregularities--for example, wide variations in the quality of IRB reviews, the lack of checks and balances with regard to regulatory compliance, and possible compromises in the independence of IRB reviews due to factors such as close collegial ties between investigators submitting protocols to the IRB, and IRB members, pressures from institution officials to attract and retain government or corporate research funding, and the reluctance to criticize studies conducted by leading scientists, many suggestions for strengthening the oversight of IRBs and researchers were made, including:

-periodically evaluating the entire system, to ensure that the sanctions set out in the Common Rule are functioning adequately;

-extending the scope of human subjects protection to research which is not federally funded;

-increasing the effectiveness of the oversight mechanism to ensure compliance by investigators and IRBs through random samples of protocols from all types of research settings, including interviews with the subjects of the research, and through random site visits to IRBs by federal agencies (may be done by consultants to offset the increase in workload);

-regarding conflict of interest, to include in the IRB process experts from scientific groups outside the institution, especially with high-volume IRBs, and quasi-professionalizing the role of outside members, linking them in groups that could come together to study common issues and perhaps give greater uniformity to concepts like minimum risk;

Suggestions included the following: enlarge OPRR staff and use IRB members from across the country to perform site/project visits and reviews; hold institutions accountable for oversight, monitoring and education; create a mechanism to ensure that all research with human subjects is reported to IRBs. Overall, survey respondents were more concerned with

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[11] J. Bell, J. Whiton & S. Connelly (James Bell Associates), *Final Report, Evaluation of NIH Implementation of Section 491 of the Public Health Service Act, Mandating a Program of Protection for Research Subjects*, June 15, 1998. Prepared for The Office of Extramural Research, National Institutes of Health online: NIH <www.nih.gov>at vii & viii.

revising and clarifying present regulations and practices regarding oversight, than with establishing new regulatory requirements.

In its final 1996 report on the human subjects protections system, GAO declared that finding the balance between that extreme [continuous on-site inspections of every institution and its studies] and a process that relies on paper reviews is the fundamental challenge facing regulators and IRBs in the current HHS oversight system.

An appreciation of the ethical aspects of human subjects research and the value of institutional oversight is required so that the rights and interests of research subjects can be protected. Necessary changes in attitudes will not likely occur by strengthening federal rules and regulations or developing harsher penalties. It is essential that medical colleges and researchers make ethical considerations central to the conduct of research, so that future scientists have a clear understanding of their duties to human subjects, and an expectation that the leaders of their fields value good ethics as much as they value good science. Despite rapid changes in the biomedical environment and an increasing workload, it appears that the IRB system continues to ensure that human subjects are adequately protected from undue risk. [12]

NIH Regulatory Burden v. Human Subjects Protection, Workgroups Report

Off-site adverse events reports–IRBs are being overwhelmed with off-site reports that are not presented in a useful format. Each IRB receives individual reports on every event from every site. This data is neither aggregated nor interpreted and does not provide useful information to the IRB to allow it to make an informed judgment on the appropriate action to be taken, if any; regulations are confusing; FDA calls for reporting of adverse events which are both 'serious and unexpected' and DHHS contains broader requirements for reporting of 'unanticipated problems;' data safety monitoring boards (DSMBs) oversee some clinical trials for the purpose of data and safety monitoring, but these reports are rarely received by IRBs;[13]

Differences in administration of FDA and OPRR result in regulatory burden for IRBs Administrative differences exist in areas such as: operational differences (OPRR performs its oversight function primarily through negotiation of assurances; FDA does not pre-approve IRBs, but relies on inspections of institutions), regulatory and policy differences between FDA and OPRR, and different interpretations of regulations and policies between and within

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[12] *Ibid.* at 83-86.

[13] NIH Regulatory Burden v. Human Subjects Protection, Workgroups Report, April 15, 1999; online NIH < http://www.nih.gov/grants/policy/regulatoryburden/humansubjectsprotection.htm> at 5-9.

agencies; and differences in sponsors' practices and their imposition of these practices on IRBs;[14]

Timing of IRB review of new proposals--Institutions must certify at the time of submission of the application that the IRB has reviewed the proposal. The effect of this policy is that the IRB must undertake its review of the proposal before the funding agency makes a decision on funding. As fewer than 1/3 of the grant applications submitted to NIH are actually funded by NIH, a significant portion of the time spent by IRB members in reviewing grant proposals is wasted.[however, if the project is not fully funded or funded by another source, the IRB still has to review the ethics of the protocol]; [15]

Continuing review of proposals– Regulations governing the timing of continuing review are too rigid. They require that the IRB review the project at intervals commensurate with the level of risk facing the research subject, but not less than once per year. OPRR has interpreted this to require IRB review occur on or before the one-year anniversary date of the previous IRB review. Increased flexibility has the potential to increase efficiency without compromising protections.[16]

Assurance process--At present, the assurance process is exceedingly and needlessly legalistic and complex.[17]

Education programs-undervalued. Minimal training needs have not been developed.[18]

Ensure adequate resources for IRBs–There is concern that resources to support the IRBs are not growing as fast as the workload. The Common Rule requires that adequate staff and meeting room resources be made available to support the IRB's review and record keeping duties; FDA has no such provision. The workload is increasing because of increased numbers of protocols and due to Federal government increasing the IRB responsibilities to require the review of protocols for the inclusion of women, children and minorities as subjects in clinical research.[19]

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[14] *Ibid.* at 6.

[15] *Ibid.* at 7.

[16] *Ibid.*

[17] *Ibid.* at 8.

[18] *Ibid.* at 9.

[19] *Ibid.*