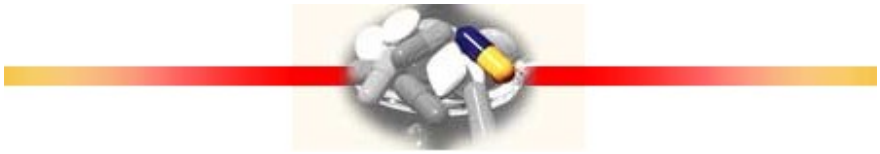
NATIONAL PLACEBO INITIATIVE



FINAL REPORT
OF
THE NATIONAL PLACEBO WORKING COMMITTEE
ON THE APPROPRIATE USE OF PLACEBOS IN CLINICAL TRIALS IN CANADA

Submitted to:

Health Canada Santé Canada

Canadian Institutes of Health Research Instituts de recherche en santé du Canada

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Canada

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Acknowledgments

In the fall of 2001, a general invitation call was sent out across Canada by Health Canada and the Canadian Institutes of Health Research (CIHR) for volunteers to form a committee in order to develop a single policy on the appropriate use of placebos in clinical research. Twelve people came together with two ex-officio members from Health Canada and CIHR, representing a variety of specific disciplines, demography and geography. This opportunity to unravel the debate that has challenged many of us for decades was terrific. The National Placebo Working Committee (NPWC) was formed to tackle the placebo issue and formulate recommendations.

In the Final Report there are areas of complete consensus; however, as in all great debates, there are contentious subjects. We agreed as a committee in the early stages that there would be topics that we must agree to disagree upon; as long as those areas of concern were appropriately represented and tabled. The members have contributed unstintingly and this Final Report represents the expertise, industry and focused work of two years.

I would particularly like to acknowledge the willingness of those Canadians who took the time to share their thoughts. The interest, enthusiasm and generous contribution of all those who prepared for and participated in focus group meetings, the National Stakeholder Conference on the Appropriate Use of Placebos in Clinical Trials, Public and Stakeholder consultations and other events of the National Placebo Initiative gave a larger picture and a greater understanding of issues that had not necessarily been examined previously. Through a unique collaboration involving experts as well as the general public, remarkable work was accomplished in raising awareness regarding the issues surrounding the use of placebos in clinical trials and stimulating constructive discussion.

I am also sincerely appreciative of the opportunity to be part of and to lead the NPWC. A group of very knowledgeable and dedicated people who contributed vigorously to this important undertaking, volunteering tirelessly and graciously in the following particular areas:

Penny Brasher, Stan Shapiro and David Sackett who provided leadership on the scientific subcommittee,

Bernard Keating, Thérèse Leroux, George Webster and Kathleen Glass who were responsible for particular insight into the ethics discussions,

Kathleen Glass and Thérèse Leroux who contributed the legal analysis,

Patricia Huston, Jim Wright and Vratislav Hadrava who worked on the regulatory aspects of this debate,

Phil Upshall and Maureen Smith who were notable for their devotion and commitment to the citizen and patient voices on the committee: as well, Maureen ably steered the Public Involvement Coordinating Committee, charged with running the citizen consultations on the appropriate use of placebos in clinical research project.

And finally my thanks go to John Fisk who allowed me to work with him, bringing the challenges of Research Ethics Boards to the discussions.

I would like to acknowledge the generous contribution of Dr Jennifer Jackman who facilitated the meetings of the NPWC and assisted in preparing the reports, as well as Laura Nash who recorded the proceedings of the NPWC meetings.

I would also like to thank the staff of Health Canada and CIHR who coordinated the initiative and assisted the committee with administrative duties and other matters.

On behalf of the NPWC, I look forward with great anticipation to the acceptance and implementation of this Final Report.

Respectfully submitted,
July 30, 2004
Heather Anne Sampson
Chair, National Placebo Initiative, Working Committee

Executive Summary

In the fall of 2001, Health Canada and the Canadian Institutes of Health Research (CIHR) jointly launched the National Placebo Initiative (NPI) to help determine the appropriate use of placebos in clinical trials in Canada.

Presently, the two main documents that address the use of placebos in clinical trials in Canada -- international regulatory guidance document, *International Conference on Harmonization: Choice of Control Group and Related Issues in Clinical Trials* (ICH E-10), and the Canadian *Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans (TCPS*) (Section 7) -- diverge with regards to what constitutes the appropriate standard. The National Placebo Initiative was undertaken therefore to respond to the nationally recognized need to examine complex issues concerning the appropriate use of placebos in clinical trials and propose a way for clarifying and harmonizing Canada's regulatory framework in this area. This Canadian initiative is particularly timely now when a number of international organizations, such as the World Medical Association and the Council for International Organizations of Medical Sciences (CIOMS) have recently revised their respective guidelines and policies regarding ethical and scientific issues surrounding the use of placebos.

The National Placebo Working Committee (NPWC), an expert group of twelve members representing major Canadian stakeholders, including the general public and patient advocates, was established to examine the issue, develop the report entitled *Report of the National Placebo Working Committee on the Appropriate Use of Placebos In Clinical Trials In Canada* (referred to as the *Report*) and provide concrete recommendations which would inform revision and harmonization of the regulatory framework regarding the appropriate use of placebos in clinical trials in Canada.

In order to achieve its objectives, the NPWC examined the numerous issues regarding the appropriate use of placebos in clinical trials from scientific, ethical, legal, regulatory and REB, as well as citizen and patient perspectives. Accordingly, each section of the Report represents the work of one of six subcommittees formed by the NPWC, in addition to Chapter 8 which includes recommendations and unresolved issues. Within Chapter 8, three situations were possible: (1) all members agree with the wording of the recommendation, then, that recommendation was removed from its original chapter and introduced in Chapter 8 as a **NPWC recommendation.** (2) all members agreed that the questions/issues could not be resolved at this time and require further discussion in a broader community, therefore that recommendation was put in Chapter 8 as an **unresolved policy issue**. Finally, (3) some members of the NPWC disagree on the recommendation as stated, then that recommendation was kept in its original chapter and kept its status of a subcommittee's recommendation.

The NPWC's Report is a reflection of the views of the members of the NPWC on the appropriate use of placebos in clinical trials. The approach and style of each chapter varies since members of each sub-committee were afforded relative independence to describe the issues and offer their own views. The chapters written by the sub-committees facilitated and informed the deliberations of the NPWC. The NPWC achieved significant consensus on many aspects of the

debate which is reflected in its recommendations to Health Canada and CIHR. A number of issues, however, remained unresolved which is not surprising, given the continuing global controversy among experts in this area. Both the areas of consensus and unresolved issues are summarized below.

It should be noted that the Report of the NPWC does not represent the views or policy of Health Canada or the CIHR, nor is it intended to establish a standard for clinical trial design and conduct. It also should not be construed as providing legal advice. This Report is intended to contribute to the ongoing discussion and consensus-building on what constitutes the appropriate use of placebos in clinical trials.

AREAS of CONSENSUS

Policy Recommendations

The NPWC made two policy recommendations reflecting a *consensus* of Committee members. They are as follows:

- The NPWC agreed that as a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic or preventive intervention should receive an established effective therapy.

- The NPWC recommends revision of section 7, Article 7.4 of the *Tri-Council Policy Statement* and recommends its use as the Health Canada Addendum to *ICH-E10* as follows:

  Article 7 should be amended to read:

  "The use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate study design when *established effective therapy or therapies* exist for the population and indication under study." Additionally,

  "A placebo comparator is acceptable in the following situations:

  a) There are no established effective therapies for the population and for the indication under study.
  b) Existing evidence raises substantial doubt regarding the net therapeutic benefit of available therapies,
  c) Patients are refractory to the available therapies by virtue of their past treatment history or known medical history,
  d) The study involves adding a new investigational therapy to established effective therapies, (established effective therapy + new therapy vs. established effective therapy + placebo) ,
  e) Patients have determined that the response to the established effective therapies for their condition is unsatisfactory to them,".

f) Patients have previously refused established effective therapies for their condition."

* For articles (e) and (f) the determinations of response satisfaction and refusal of treatment must take place outside of the context of recruitment for the clinical trial and prior to the offering of trial participation to the potential subject, and be documented in a standardized manner. Under these conditions, study subjects would not necessarily be considered "refractory" to the available therapies since the choice to discontinue available therapies is based on their own opinion and values, not those of the clinicians responsible for their care. As such, regulatory approval of the therapy under investigation would not necessarily be restricted.

Administrative Recommendations

In addition, *consensus* was achieved regarding administrative structures and processes that would improve the consistency and the quality of decision making in approving clinical trials. This consensus is reflected in the following recommendations:

- All research protocols, submitted to Health Canada (for example, as part of the Clinical Trial Application (CTA) process) and/or to a Research Ethics Board should include:
  - justification of the study design (superiority, non-inferiority, equivalence) and the choice of comparator (active control or placebo on both scientific and ethical bases), and
  - systematic reviews of the new investigational therapy and other established effective therapies for the condition under study, sufficient to support the justification of the study design.

  Presently, in many circumstances, it is not possible to conduct a comprehensive systematic review of controlled trial evidence. This is due to the inability to know how many trials have been done, inaccessibility to complete data from published trials and inaccessibility to any data from unpublished trials.

- In order to facilitate the comprehensive systematic review of controlled trial evidence, the policies and regulations of Health Canada should be changed to allow researchers and Research Ethics Boards to have access to all protocols and clinical data from trials that are on file with the government, consistent with the fair information principles for protecting personal data. Health Canada should also assist in obtaining additional trial data from the sponsor or manufacturer, if necessary.

- Health Canada should do everything possible to assist in the development of a comprehensive International Trial Registry, as soon as possible.

- Patients should be made aware, on an active basis, that all information filed with the trial sponsor and available to the Research Ethics Board must be available to them through the primary research investigator. Patients should be informed that they have a right to receive all information that may materially affect decisions to participate in trials.

- The research participant should have available to them, a "participant advocate", free of any conflict of interest with whom they can discuss any aspects of trial participation.

- A safety monitoring function, proportionate to the level of risk and external to both the investigator and sponsor, should be established for all randomized trials including placebo-controlled trials. This function is currently not always being met.

- A national framework governing all Research Ethics Boards should be established to facilitate consistency in the scientific and ethical review of placebo-controlled trials. This governance framework would help ensure that Research Ethics Boards are free of conflict of interest, are constituted with a membership consistent with currently accepted standards of appointment, have resources to support the review process and apply the current national standards when evaluating and approving all clinical trials, including placebo-controlled trials.

- Health Canada should develop and publish a document that clearly identifies the criteria for authorizing the release of a therapeutic product for the purpose of a clinical trial. This includes the particular instance of a placebo-controlled trial when there is an established effective therapy.

- An Educational Guidance Document should be developed by Health Canada and CIHR and distributed to all Research Ethics Boards across the country. The document should identify the key questions that should be posed by the Research Ethics Board in the evaluation of the scientific merit and ethical acceptability of clinical trials. The questions should be constructed so as to account for both national and international standards and policy.

UNRESOLVED POLICY ISSUES

Those issues that remain *unresolved* are listed below. The supporting and opposing views are outlined in detail in the Report.

- Treatment of "Minor" Conditions: Use of a placebo is acceptable when withholding an established effective intervention for a minor condition would expose subjects to, at most, temporary discomfort or delay in relief of symptoms.

- Early Phase Clinical Trials: Placebo-controlled trials are accepted in early phase II trials in some circumstances beyond those listed above.

- Informed Refusal of Established Effective Therapy: It is acceptable to conduct placebo-controlled trials when patients have provided an informed refusal of established effective therapy in conditions for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.

- Cost Constraints or Limited Supply of Established Effective Therapy: It is acceptable to conduct placebo-controlled trials in situations where established effective therapies are not available to the population under study due to cost constraints or limited supply. This issue is currently addressed in the *Tri-Council Policy Statement* and *CIOMS* but not *ICH E-10*. However, the NPWC did not formulate a view on this issue because it lacked the time to adequately study it.

The Final Report has been formally submitted to the Director General of the Therapeutic Products Directorate at Health Canada, who will use the recommendations to inform a Canadian Appendix to ICH E-10, and to CIHR for reference to the Interagency Advisory Panel on Research Ethics (PRE), which has been charged with making recommendations for updating the Tri-Council Policy Statement. The final Report can be found on the National Placebo Initiative website at: http://www.cihr-irsc.gc.ca/e/services/5466.shtml. Hard copies of the final Report are available upon request.

1. Introduction

The Final Report of the NPWC is structured and crafted in such a way as to highlight the 6 key perspectives surrounding the placebo debate: citizen and patient, scientific, ethical, legal, regulatory and research ethics board. These perspectives are presented in six individual chapters; each chapter includes specific recommendations that do not necessarily reflect the opinion and consensus of the Committee as a whole. Subcommittee members agreed to disagree, if necessary, on the material and recommendations reflected in the subcommittee chapters. However, the NPWC did achieve a degree of consensus on some of the principles that define the foundation of placebo policy in Canada. The areas of consensus were formulated as final recommendations. These recommendations and the remaining unresolved issues are elaborated in chapter 8.

As an advisory body to Health Canada and CIHR, the NPWC has no decision-making authority. Upon review of the information and recommendations of the NPWC, Health Canada and CIHR will independently decide on the appropriate course of action.

The Context of the Placebo Debate

While not pretending to give a comprehensive historic account of placebo use,[1] this section is intended to provide a brief summary of the subject as a background to the discussions contained in this Report.

Placebos have a long and opaque history of intentional and unintentional use by medical professionals and amateurs alike. "Placebo" comes from a Latin root meaning "I shall be pleasing or acceptable". They were used for centuries in clinical medicine when active treatment was either unavailable or ineffective because they were thought to offer some means of relieving pain and at times even reversing disease processes.[2]

In 1930, Sollmann first used the word "placebo" to refer to a control in studies and linked it to a "blind test". It is likely that the first formal placebo-controlled study occurred in 1931. [3]

The use of placebo underwent a dramatic metamorphosis from clinical intervention to a critical methodological feature of clinical trials in the years following World War II as the double blind randomized controlled trial (RCT) developed. Until mid-century, the placebo was considered as a morally acceptable but innocuous clinical management tool without either curative or symptomatic consequences. By the time the double blind randomized controlled trial took form

[1] The history of placebo use has been well documented in various publications, see, for example, Shapiro, A.K. and Shapiro, E., *The Powerful Placebo* (Baltimore: The Johns Hopkins University Press, 1997); Harrington, A., "Seeing" the Placebo Effect : Historical Legacies and Present Opportunities, in *The Science of the Placebo*, Guess, H.A et al, eds (London, BMJ Books, 2002) 35-74

[2] Harrington, *supra.*

[3] Emanuel, E.J. and Miller, F.G. The Ethics of Placebo-Controlled Trials – A Middle Ground, *N Engl J Med*, 2001; 345, (12): 915-919

and began to establish itself around 1955, the placebo was beginning to be viewed as having powerful therapeutic effects and its clinical use was being questioned as paternalistic.[4]

In 1955, Henry Beecher supported the use of placebos in the evaluation of other drugs,[5] and went on to write extensively on this subject in the medical ethics domain.[6] Importantly, he conducted research showing that patients responded positively to placebos. Notwithstanding the debate over the validity of these results, the paper itself marked the introduction of placebos in medical literature, this time in a clinical context.

Shapiro and Shapiro point to the 1960's as the beginning of the debate on the ethics of clinical research,[7] a debate that finds its roots in part in controversial research practices that were taking place over the preceding decades. In the midst of this debate, in 1964, the World Medical Association published its *Declaration of Helsinki*: *Ethical Principles for Medical Research Involving Human Subjects.*[8] The Declaration recognized that research is often conducted in the context of clinical care. The Declaration stated that, "[I]n any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method." While the word "proven" was the cause of some controversy and confusion, this statement has been prominent in the placebo discussion. Some suggest that read literally, the requirement would have prohibited new research since "unproven" therapies could not be tested. Others believe that the intent of the statement is that effective therapy should not be withheld from patients seeking care.

The 1960's and 1970's saw an increase in the quantity of regulation surrounding all aspects of new medical products. In the 1980's, the European Commission (now known as the European Union) took the first steps towards harmonization, an idea that propagated itself through the World Health Organization (WHO) to policy-makers in Japan and the U.S. Nineteen-ninety saw the birth of the *International Conference on Harmonisation (ICH).* This group, including regulatory authorities and industry representatives from the U.S., Japan and Europe, established the documents that currently act as guidelines for Health Canada regulators (E6 – *Good Clinical Practice (GCP)*, implemented by *ICH* 1996 – 1997; *E10 – Choice of Control Group in Clinical Trials*, implemented by *ICH* 2000 – 2001). The *ICH-E10 Guideline* allows placebo controls except in cases where there is proven treatment that is "life-saving or known to prevent irreversible morbidity".

Meanwhile in Canada, on May 28 & 29, 1998, the National Council on Bioethics in Human Research (now the National Council on Ethics in Human Research) sponsored a consensus-seeking roundtable that brought together representatives of universities, funding agencies, government (including Health Canada) and industry to discuss the issue of placebo controlled trials. The report from the roundtable supported the principle of clinical equipoise and

[4] Kaptchuk, Ted. J. Powerful Placebo: the Dark Side of the Randomized Controlled Trial, *The Lancet*, 1998; 351: 75-78
[5] Beecher HK, The powerful placebo, *JAMA*, 1955; 159(17): 1602-1606
[6] Beecher HK. Ethics and clinical research, *N Engl J Med* 1966; 274: 1354-1360
[7] Shapiro and Shapiro. *The Powerful Placebo: From Ancient Priest to Modern Physician*. Johns Hopkins University Press, 1997.
[8] World Medical Assembly, *Declaration of Helinski* (Adopted by the 18th WMA General Assembly, Helinski, Finland, June 1964)

recommended limiting placebo arms to circumstances where clinical equipoise exists. Clinical equipoise is identified as the guiding moral criterion in the *Tri-Council Policy Statement: Ethical conduct of Research Involving Humans*. It was originally defined by Freedman as "an honest professional disagreement in the community of expert practitioners as to the preferred treatment" for the patient population under consideration. There is confusion about the interpretation of this term, and also disagreement about its application as the moral grounding for decision making.[9] **This is further discussed in the subcommittee reports.** The NPWC was operating on the shared understanding that **clinical equipoise relies on the collective wisdom of the expert practitioners and as a concept, applies to the evaluation of the initiation and continuation of a trial, rather than to the decision about entry of an individual patient into a trial. The understanding is also reflected in Article 7.4 of the *Tri-Council Policy Statement* which lists these circumstances.**

In 2001, the *Declaration of Helsinki* was revised in an attempt to settle an ongoing debate about the interpretation of its statement related to the use of control groups in clinical trials. It reflects concerns that placebos were being inappropriately used in studies when existing therapies would have been effective. Article 29 of the *Declaration* was amended to read:

> "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."

The changes followed a round of debate focusing on both domestic and international studies, including controversial research undertaken in Asia and Africa regarding the use of placebos in studies designed to prevent mother-to-child HIV transmission.[10]

This ongoing controversy has precipitated the current round of debate over placebo ethics and regulation. The debate is by no means unfolding only in Canada. Thus, for example, the National Institutes of Health held a conference in 2000 to discuss many of these very issues in the United States.

In 2002, in a controversial move, the World Medical Association added a "Note of Clarification" to Paragraph 29 of the *Declaration of Helsinki*, allowing for the use of placebo controls even if "proven therapy" is available, "where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm".

Health Canada and the Canadian Institutes of Health Research use different criteria for determining when it is ethical to randomize patients seeking treatment to trials that use placebo controls. CIHR applies the *Tri-Council Policy Statement,* i.e. "the use of placebos in clinical

[9] Miller, FG and Brody, H, "A Critique of Clinical Equipoise", Hastings Center Report 33(3), (2003),19-28
[10] Varmas, H. and Satcher, D. Ethical complexities of conducting research in developing countries, *N Engl J Med*, 1997; (1)

trials is generally unacceptable when standard therapies or interventions are available," whereas Health Canada follows *ICH-E10 Guidelines*. Based on Canada's clinical trial regulations and international regulatory guidelines, the task of the National Placebo Working Committee has been to recommend a single "Canadian approach," which hopefully will be acceptable to Canadian regulators, both Health Canada and the federal funding agencies following the *Tri-Council Policy Statement*.

Outline of National Placebo Initiative

In the fall of 2001, Health Canada, represented by its Therapeutic Products Directorate, and Canadian Institutes of Health Research (CIHR), represented by its Ethics Office, launched a joint initiative to address the fundamental difference in the two policies that presently address the subject of placebo use in Canada - *Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans* (*TCPS*) and the *ICH Harmonized Tripartite Guideline: Choice of Control Group and Related Issues in Clinical Trials* (*ICH E-10*) - and to work towards a harmonized national approach regarding the appropriate placebo use in clinical trials.

The National Placebo Initiative included three main phases:

Phase 1: Identification of issues **(December 2001 – March 2002)**

Conduct of Public Focus Groups

In November 2001, in order to inform the National Placebo Initiative, Health Canada's Office of Consumer and Public Involvement pledged its financial support and professional assistance to conduct focus groups to study public attitude toward the use of placebo in clinical trials in Canada.

The focus groups were designed in such a way as to determine the attitude of patients and the general public regarding the use of placebo in clinical trials, both before and after a simple educational intervention that described the use of placebos and explained both sides of the placebo debate.

Seven focus groups were held in Montreal, Winnipeg and Toronto in February of 2002. First Nations' representatives participated in the focus groups in Winnipeg. All groups of participants had a similar composition that included: the public in general; individuals with common physical conditions, such as type 2 diabetes; and individuals with a common mental condition, such as depression or anxiety.

The results of the Focus Groups were presented at the National Conference and can be found on the NPI web-site at http://www.cihr-irsc.gc.ca/e/19328.html.

Establishment of the National Placebo Working Committee

In December 2001, Health Canada and CIHR requested letters of interest from representatives of various stakeholders in the placebo debate to volunteer on a National Placebo Working Committee (NPWC). The twelve individuals who formed this committee brought a wide spectrum of expertise and representation to its deliberations. The combined expertise and perspectives of the committee members included, among others, a citizen representative, a clinical trial nurse, an ethicist, a health lawyer, a patient advocate, an expert in conflict resolution, a pharmaceutical industry representative, a principal investigator, a regulatory/public health representative, an REB member, and a statistician. The membership of the NPWC also included two representatives of the sponsoring agencies, who as ex-officio members did not have voting rights and whose role was to ensure due process, to provide expert knowledge, and to represent their federal affiliation. All other members held equal voting privileges.

In order to examine the subject of the placebo use from the scientific, ethical, legal, regulatory, REB, as well as citizen and patient perspectives, a corresponding number of sub-groups of the NPWC were created.

The NPWC was mandated to develop recommendations to Health Canada and CIHR as to the appropriate use of placebos in clinical trials which would inform the revision and harmonization of the Canadian regulatory framework in this area.

The NPWC had no decision-making authority. Upon review of the information and recommendations of the NPWC, Health Canada and CIHR will independently decide on the appropriate course of action.

For the membership and other information related to the NPWC, please refer to the official NPI web-site at: http://www.cihr-irsc.gc.ca/e/6880.html.

Organization of a National Stakeholder Conference

The National Conference on the Appropriate Use of Placebos in Clinical Trials was held in Ottawa in March 2002. More than 170 people participated in this two-day event. All stakeholders had a chance to provide their input, learn perspectives of others, and work towards building consensus for a harmonized placebo policy in Canada. The proceedings of the conference can be found on the NPI web-site at http://www.cihr-irsc.gc.ca/e/6856.html.

Phase 2: Building a Common Vision **(April 2002 – Summer 2003)**

Development of the Draft Report by the National Placebo Working Committee

The NPWC met face-to-face five times over the period between February 2002 and May 2003 in order to develop its Draft Report. Numerous conference calls were also organized in the interim.

Public Consultation

Public consultations were held in 5 Canadian cities from March to May 2003. Sixty-nine members of the public participated in a full-day deliberative dialogue on the appropriate use of placebos in clinical trials. These sessions offered a way for participants to: build a shared understanding of an issue and its complexities; clarify the assumptions and values underlying different viewpoints; arrive at common ground that can act as the foundation for policy development, and test the common ground against real-life situations. Participants were provided with background information through a dialogue guide, a video, and access to experts at the sessions. Furthermore, 35 people responded to an online consultation based on the dialogue guide developed for the face-to-face consultations. While the role of PCTs for medical research was affirmed, participants felt their use should be selective. In particular, it would appear that the use of PCTs became less appropriate as the perceived seriousness of the condition being treated increased. The NPWC examined the results of both components of the public consultation process and incorporated many of the findings into their final report.

The *Synthesis Report of the 2003 Citizen Consultation,* available on the NPI web-site at http://www.cihr-irsc.gc.ca/e/20572.html, informed the final deliberations of the National Placebo Working Committee.

Phase 3: Proposing a Placebo Policy **(Summer 2003 – Spring 2004)**

Stakeholder Consultation

The Draft Report of the NPWC was posted on the NPI website and circulated for comments to a large number of individuals and organizations representing a wide range of perspectives. Given the complex nature of the material in the Draft Report, as well as the extensive length of the Draft Report and the questionnaire, respondents were given the option of completing only a portion of the questionnaire. The consultation period continued for approximately nine weeks.

The Report of Stakeholders feedback was submitted to NPWC for its review. 525 stakeholders, including individuals and organizations, were directly invited to give their feedback to the draft Report; the document was also available for comments on-line for other potential stakeholders. Thirty two (32) responses were received. The NPWC considered all responses, discussed them at its face-to-face meeting and revised and clarified the draft Report as deemed appropriate. These changes, however, did not lead to the change in the spirit of the report or its main recommendations.

Preparation of the Final Report and its Submission to Health Canada and CIHR

In February 2004, the NPWC met for the last time to discuss its Draft Report and finalise it in light of the outcomes of the public and stakeholder consultations.

The Final Report, based on the committee's deliberations of the key ethical, scientific, regulatory, Research Ethics Board and legal issues, and on consideration of the citizen and stakeholder feedback, was formally submitted to the Director General of the Therapeutic

Products Directorate at Health Canada, who is responsible for policy work supporting the *ICH E-10*, and to the Ethics Office of CIHR for reference to the Interagency Advisory Panel on Research Ethics, which has been charged with making recommendations for updating the *TCPS*. The Final Report is available on the NPI website at http://www.cihr-irsc.gc.ca/e/5466.html and copies are available upon request.

2. The Citizen and Patient Perspectives

Phil Upshall and Maureen Smith

A. Introduction

Much of the ethical discussion surrounding the appropriate use of placebos in clinical trials has taken place among academics and scientists. Notably absent to date has been the voice of the "human subject", i.e. the patient in a clinical trial. In all clinical trials, including placebo-controlled trials (PCTs), the patient agrees to accept a potential risk of harm after being "fully informed" about the need for the particular research as well as the rules governing the conduct of the trial. In a PCT, the patient usually has a 50% chance of receiving the placebo and a 50% chance of receiving the new chemical entity or therapeutic product which means that the patients in the placebo arm would stop receiving the current treatment for the condition for a period of 6 weeks to 3 months, if the patients were in fact currently being treated.

Citizen and patient representation on the National Placebo Working Committee (NPWC) is an important first step in recognizing the need to hear the voice of the human subject when discussing the ethics of clinical trials involving human subjects. Furthermore, public consultations held across Canada and stakeholder feedback on NPWC's draft report provided invaluable information on Canadians' attitudes towards the appropriate use of placebos in clinical trials.

Many of the important ethical questions have been asked and answered in the absence of an adequate citizen and patient voice. Questions such as:

- What is in the best interest of the patient?
- What is the extent of the risk patients may be allowed to assume when agreeing to be enrolled in a placebo-controlled trial?
- In a placebo-controlled trial, what type of additional protection, if any, does a patient with a mental illness require?
- After the trial, what should the patient be entitled to by way of follow-up and what, in reality, happens to the patient?

The answer to these questions is determined by our view of the extent and scope of the patient's right to autonomy. There was a citizen representative and a patient representative on the National Placebo Working Committee and each brought a perspective about patient autonomy, based on their respective community involvements, interactions and personal experiences. Both representatives also seriously considered the outcomes of the public consultations and stakeholder feedback on the draft report. They were unable to agree on certain aspects of a "common placebo policy" and their differing views are presented for consideration.

B. **Citizen Representative, Phil Upshall**

Scientists, ethicists, and academics debating the relative merits of alternative policy options have had no difficulty suggesting ethical standards to "protect" the subject, even though "patient autonomy" is an underlying norm that they insist must be part of the ethical conduct of clinical trials. What is patient autonomy if:

- The governing policy does not allow for the active involvement of the potential trial subject in the development of the policy and in every aspect of the trial's consideration and approval process?
- The potential subject does not have any real opportunity to determine the level of acceptable risk he or she is willing to assume should they be randomized to the placebo arm?
- Members of Research Ethics Boards are frequently overworked so that adequate review of the trial protocols and oversight of the ongoing trial is of concern?

Subjects may be "fully informed" about all aspects of the placebo-controlled trial and may be inclined to take comfort in the responsibilities of the Research Ethics Board that are described in the materials supporting the consent. They must be able to rely on the Research Ethics Board to follow the progress of the trial and ensure that those involved meet the standards of care as dictated by their fiduciary duties and also as set out in the trial protocols.

The following rights and entitlements logically follow from the theories of "patient autonomy", "fully informed consent", and other ethical and legal concepts contained in Canada's *Tri-Council Policy Statement* and in the *International Conference on Harmonization (ICH-E10) guideline*.

Consumer Rights and Entitlements

1. The consumer as human research subject has, by virtue of the concept of "patient autonomy", the right to:

    - Be involved in all aspects and at all levels of the clinical trial process;
    - Expect that persons representative of the subject's point of view will be members of all Research Ethics Boards; and
    - Determine the level of risk or harm to assume in a placebo-controlled trial in the event of assignment of the placebo arm of the trial, subject to certain limiting factors.

2. The subject has the right to expect that members of Research Ethics Boards have received necessary and sufficient training prior to appointment, receive ongoing training and education as necessity dictates, and that the Research Ethics Board receives all necessary funding and staffing to allow it to execute on its duty.

3. The subject is entitled to full and complete written disclosure of all matters which may impact the decision to formally consent to enter into the placebo controlled trial and to accept the associated risk.

4. The subject is entitled to know both the outcome of the trial and whether he or she was enrolled in the placebo arm.

5. The subject in a placebo-controlled trial must be able to rely on the fact that every aspect of the conduct of the trial is legal, including the commencement of the trial. This information should be provided prior to the execution of consent. A trial started illegally should be terminated since the duty owed to the subject has been breached and the consent is void.

6. The subject in a placebo-controlled trial should have an avenue for communication to the Research Ethics Board. If the subject becomes alarmed for any reason concerning the conduct of the trial, the opportunity to raise questions directly with the Research Ethics Board or a representative could permit a quick response to concerns. This would resolve the problem that, currently there is no mechanism by which subjects can rely on the oversight of the trial by the Research Ethics Board as a condition precedent to execution of the consent to engage in a placebo-controlled trial.

7. A common Canadian policy for the use of placebos in human trials should include the concept of a "patient advocate". Human subjects would be reassured, if given the right to consult a patient advocate. The advocate would be available to discuss, in total confidence, concerns of any nature related to the clinical trial. The patient advocate may simply provide information, but should have authority to report and follow up on matters of abuse or improper or illegal conduct to the appropriate authorities.

From the consumer's perspective, questions of "patient autonomy" and "acceptable level of risk or harm" in the placebo arm of the trial, as noted by the *Tri-Council Policy Statement* and *ICH E-10 guideline* are indeed questions of concern. Within limits, the subject should have the right to determine whether to enter into a trial and whether or not to assume the risk of irreversible harm. Such harm may or may not be of significance to the subject, given particular circumstances. The subject living with a mental illness but with the capacity of consent should not receive any greater protections than others in regard to discussions about risk or harm if randomized to the placebo-controlled arm of the trial. To do otherwise would reflect a discriminatory attitude towards those living with a mental illness that should not be reflected in an ethically based policy.

The concept of "withholding treatment" from a patient during a placebo-controlled trial is difficult to understand for many patients. The concept implies that if treatment is not "withheld" it will be provided, even against a patient's will. Only in rare circumstances not relevant to this discussion, does a doctor have such an onerous ethical obligation. With great respect to the other members of the National Placebo Working Committee perhaps the concept should be revisited and a more accurate description of the doctor's ethical obligation to offer treatment be included in any future ethical policies. If this step were to be taken the autonomy of the patient would be recognized at the outset of discussions as it would flow logically that if the doctor offered treatment, the patient could quite properly refuse the treatment and proceed to determine if he/she would agree to participate in a placebo controlled trial.

C. Patient Representative, Maureen Smith

Patient Protection Perspective

What do Canadians expect to see in a policy governing placebo-controlled trials? Seeking citizen and patient input to answer this question is challenging by its very nature because citizens are a diverse group. Nevertheless, a great deal depends on one's views on the patient autonomy versus patient protection debate. Autonomy is one of the principles that we ascribe to as a society. Nevertheless Canadians also expect that medical research will be subject to a system of checks and balances. Patients do not wish to assume the total responsibility of estimating what risks are legitimate for a researcher and a drug company to ask them to take. Moreover, protection is warranted because there is a good deal of scholarly debate on whether placebo-controlled trials are necessary and the circumstances under which they provide scientifically sound and clinically relevant results.

Recommendations:

1. The policy must offer a healthy balance between protectionism (sometimes defined as paternalism) and respect for patient autonomy.

    - Patients should never be approached to participate in a placebo-controlled trial if there is a potential for irreversible harm or negative impact on the quality of life. Proponents of patient autonomy would advocate for the right to choose the degree of risk without direction from Research Ethics Boards, and more specifically, ethicists. However, a policy applies to all members of society. What percentage of citizens has the ability or the desire to analyze detailed and often very complex medical information, weighing the pros and cons in support of a decision, especially when ill?
    - Health practitioners should not be relieved of their "duty to care" because it interferes with patient autonomy. There is both an ethical and legal duty to provide the best possible care for a patient, therefore protectionism is mandated.
    - Patients must be protected from placebo-controlled trials that do not benefit them. Trials for "me too" drugs often benefit the pharmaceutical companies who would like a share of the market, and not the patient.
    - Many factors come into play when a patient is considering whether to participate in medical research. Some of these factors, such as state of mind, trust in doctors, and loyalty may interfere with the ability to exercise sound decision making. More studies into the effects of a patient's vulnerability must be conducted before we can truly understand how this affects decision-making ability. The concept of patient autonomy is not always synonymous with respect for individuals if it exposes people to research that they may not be able to fully evaluate for a variety of reasons.

2. Safeguards must be in place to ensure that the theory of informed consent is translated into practice for all potential participants and their caregivers. Some of these safeguards include:

    - The development of a standard definition of placebo;

- A standard description of a placebo-controlled trial, written in language understandable to the average Canadian be included in the informed consent;
- Provisions made for individuals and special population groups who may require support in understanding the standard informed consent through the use of videos, interpreters, patient advocates, etc. Provision of complete information about the potential consequences of withdrawing treatment while receiving placebo; and
- Adequate reflection time should be mandatory for consent in non-emergency situations.

3. The policy recommendations must acknowledge that placebo-controlled trials offer a specific challenge to Research Ethics Boards and provide the necessary tools to allow Research Ethics Boards to effectively act in the best interests of patients. Education of REB members is of utmost importance

   - More informed citizen and patient representation on Research Ethics Boards to ensure that the voice of the consumer is heard (Presently one representative is mandated);
   - Ensure that all Research Ethics Board members receive adequate training to deal with specific PCT issues, with special attention to the education of the citizen and patient representative;
   - Guidelines, such as the Guidance document in Chapter 7 (Table 7.1), and pre-set limits are necessary for Research Ethics Boards to evaluate placebo-controlled trials; and
   - More collaboration between Research Ethics Boards and Health Canada so that adverse events recurring during the trial, can be disclosed in more effective and timelier manner.

   Research Ethics Boards play a vital role in our system of checks and balances, yet they are continually overworked and under funded. Placebo-controlled trials pose an even greater challenge: they require an even longer discussion and approval process because of the potential risk of withdrawing standard treatment and may require specific scientific expertise to evaluate the trial design. Because Research Ethics Boards are the final arbiters, they need to understand the basic issues. Guidelines will enable the members who do not have a science background, such as lawyers, ethicists, and community members to better judge the trial design.

4. Patients and their advocates should have access to all information necessary, within a planned framework, for them to make an informed decision once regulatory bodies and the local Research Ethics Board have approved a placebo-controlled trial. This does not imply that all patients be provided with volumes of technical and medical details, however, patients should be made aware that this information is available to them or their advocates.

   - Patient autonomy can be exercised when necessary information is readily available and the participant is treated as a partner in research.

5. Full disclosure of results of placebo-controlled trials must be available to patients at the end of the study. Disclosure must include:

    - Uncomplicated access to relevant scientific findings, summarized in a format and language that is understandable to average Canadians; and
    - Whether the participant was on placebo or the experimental drug. At present, this information is very difficult to obtain and it can be critical to determining a patient's further care.

    Given that study results are often presented some time after the study has closed, mechanisms should be developed to facilitate information transfer to patients who have moved or who are difficult to contact.

In conclusion, this perspective is limited to the particular case of the use of placebos in research. Patients and citizens should be cognizant of the fact that much more needs to be articulated about clinical trials in general. The current dialogue, however, will undoubtedly have positive implications for placebo-controlled trials.

3. Scientific Perspectives

Penny Brasher, Stan Shapiro and David Sackett

A Methodological Appraisal of the Use of Placebos in Humans

A. Guiding Principle

This subcommittee report describes the scientific principles and practice identified by its members as necessary for protecting and improving the health and health care of Canadians through the validation of potential therapeutic advances.

B. Preamble

During the discussions about the scientific issues around placebo-controlled trials (PCTs) it has become apparent that there are two underlying views.

Regulatory agencies appear to us to consider a specific trial of a specific drug in isolation from the clinical and patient-centered context in which the drug would be used. This we will refer to as the "regulatory view". In Canada, this is driven by the *Food and Drugs Act.*[11] A colleague on our committee paraphrased it thus,

> "To meet our obligations under the Food and Drug Regulations, and to meet our mandate to protect and promote the health of Canadians, we require substantial evidence of safety and efficacy under specified conditions of use."

This view is in sharp contrast to considering the drug in the context of its use in providing health care. This latter, "health care view" is reflected in the answer of Sir A. Bradford Hill (who introduced the modern era of clinical trials) to the question, "Is it ethical to use a placebo, or dummy treatment?"

> "The answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proved or accepted value. If there is such an orthodox treatment the question hardly arises, for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing."[12]

These two views can come into conflict when a placebo-controlled trial is proposed in the face of a previously proven established effective therapy. Of course, well-conducted placebo-controlled trials can have high internal validity. However, when established effective therapy exists, their relevance to health care is limited.

[11] *Food and Drugs Act*, SRC, c. F-27
[12] Hill BA. Medical ethics and controlled trials. *BMJ* 1963;i:1043-1049

The central ethical issue being addressed by the National Placebo Working Committee is, when is it permissible to withhold established effective therapy? This report addresses the scientific issues around the choice of the control group when investigating new interventions.

C. **Choice of the control group**

Primary design options for the evaluation of a new therapy when established effective therapy exists (and the new therapy is NOT an add-on) include: active control superiority trial (ACST), active control non-inferiority trial (ACNIT), and placebo-controlled superiority trial (PCT). A brief synopsis of the advantages and disadvantages of the various designs is given below, using the example of a promising new, but untested, treatment X for a condition, where treatment S is already universally recognized as established effective therapy for this condition. Trials may be designed to look at one or a number of issues including efficacy, safety, acceptability, and cost. In the table below we will simply use the term "merit" to designate any one or combination of these endpoints.

Table 3.1: Comparison of study designs

Design Option	Question answered by this design	Advantages	Disadvantages
ACST: Active Control Superiority Trial New treatment (X) vs established effective therapy (S)	Is treatment X better than S?	A head-to-head comparison of alternative treatments which provides information about the comparative merit of the new treatment. Provides immediate help in reducing uncertainty and disturbing clinical equipoise. Potentially larger than the PCT, it will provide more information about safety.	Larger than the PCT, it may expose more patients to the new treatment and its unknown effects.
ACNIT: Active Control Non-Inferiority Trial New treatment (X) vs established effective therapy (S)	Is treatment X about as good as (and no worse than) S?	A head-to-head comparison of alternative treatments which provides information about the comparative merit of the new treatment. Provides immediate help in reducing uncertainty and disturbing clinical equipoise. Larger than the PCT, it will provide more information about safety.	Larger than the PCT, it exposes more patients to the new drug and its unknown effects. Must assume the reproducibility of the effect of treatment S*.
PCT: Placebo Controlled Superiority Trial New treatment (X) vs Placebo	Is treatment X better than a placebo?	As the smallest trial of the 3 options, it is the least expensive and exposes the fewest patients to the new therapy and its unknown effects. This design is often preferred or even demanded by regulatory agencies. In a properly conducted PCT will give an estimate of the absolute effect of the new therapy.	Active therapy is withheld from the placebo group Provides no information about the comparative merit of treatment X. Will not resolve uncertainty or disturb clinical equipoise. If the trial is positive, clinicians and patients still won't know whether to use treatment X instead of treatment S. As the smallest trial of the 3 options, it provides the least information about safety. In addition, the measurement of the effect is subject to greater statistical error than in the larger, active control trials

*Considerable attention has been given to the need to assume the reproducibility of effect in ACNITs. This issue is considered in detail in ICH E-10, *Choice of Control Group in Clinical Trials.* PCTs are often referred to as a gold standard but also have pivotal underlying assumptions. This has received less attention and we consider the presumed assay sensitivity of PCTs here.

A Critical Examination of Assay Sensitivity

ICH E-10 defines assay sensitivity of a clinical trial as "…the ability to distinguish an effective treatment from a less effective or ineffective treatment." The document notes that the absence of assay sensitivity decreases the chances of demonstrating superiority and increases the chance that equivalency or non-inferiority trials will conclude that a new treatment is similar to or no worse than its active treatment comparator. If the new treatment is found to be essentially as efficacious as the existing therapy in a two arm equivalency or non-inferiority trial, it may reflect the fact that both therapies were ineffective in the current trial. In a superiority trial the new treatment needs to be shown superior, so the absence of assay sensitivity works against finding in favor of the new treatment. The claim in ICH E-10 is that showing superiority to a placebo arm provides the necessary calibration, i.e. that a positive trial with a placebo control guarantees that the trial possessed assay sensitivity. However, this claim depends on a crucial assumption that has been under examined: e*ffective* blinding. If blinding of the placebo arm is not effective, protection against expectation effects, biased assessment, contamination, and co-intervention is lost. Superiority of the new treatment to placebo could merely be a consequence of the loss of this control. An ineffective new treatment would spuriously appear to be superior merely because a 'placebo effect' appears only in the experimental drug treatment arm. In the absence of evidence that individuals in the placebo arm remain blinded, we can not be sure that a difference between the experimental and placebo arms is not merely a manifestation of the fact that individuals in one group know they are receiving an inert substance. Of course effective blinding applies to the larger cast of characters including investigators and outcome assessors. Unblinding in those groups can also call trial results into question depending on the type of outcome under investigation.

Thus it is difficult to see how any randomized placebo controlled trial can *a priori* ensure that it will deliver assay sensitivity. In order to do so an investigator must either provide evidence that blinding is unnecessary, which seems strange in the context of a placebo controlled trial, or else provide evidence that blinding will be maintained. Effective blinding can be difficult to achieve and difficult to evaluate. It needs to be demonstrated, not assumed. In an attempt to obtain direct evidence about the success of blinding, Ferguson et al (BMJ 2004) examine a random sample of placebo control trials in leading medical journals. The results of that study showed that less than 2% of the 191 trials examined reported data in support of a claim of successful blinding.

One could argue that it is only the reporting of blinding that is in question; many trials may have preserved blinding, but chosen not to publish those results. Since such reports would lend strength to a trial's conclusions and investigators would likely be eager to share such findings it is unlikely that is the case.

Of course, the potential for unblinding exists as well in an active control trial. However, there are several aspects that differentiate that problem. Perhaps the most important is that when individuals on an active control become unblinded, they become unblinded to the fact that they are receiving an active agent that is currently in clinical use. This is very different from the situation in a placebo control trial. Second, we would venture that the risk of unblinding is generally less in an active control trial than in a placebo control trial. Although that is a point

that should be amenable to empirical examination, an evaluation must wait until reporting on blinding improves.

It should be noted that a 3-arm design with placebo, active control and the experimental treatment also does not protect against an erroneous claim of success resulting from poor blinding. Such designs are subject to the same weakness as above and to the same weaknesses that critics of non-inferiority trials typically cite.

This report will summarize our position on the important issue of the choice of treatment(s) for control patients in clinical trials when established effective therapy exists, and how we arrived at that position:

1. First we will summarize the positions on placebo use found in 3 relevant documents from a methodological perspective.
2. Then we will describe our operational definition of "established effective therapy".
3. Then we will offer a scientifically valid definition of the "placebo" effect.
4. Then we will consider certain situations in which the withholding of therapy from control patients has been advocated.
5. We will close by proposing rules for the use of placebos in Canadian research.

1. A summary of the positions of three relevant documents

(i) The ICH *E-10* guideline*: Choice of control group and related issues in clinical trials* indicates a general preference for placebo controls except when there "is proven effective treatment [that] is life-saving or known to prevent irreversible morbidity."

Comment: This preference for giving placebos to control patients is, we think, motivated by the fact that the analysis of such trials has been deemed to provide a "clean" estimate of the effects of active therapy, unaffected by any active treatment of control patients. The document states (page 14) "Even when the primary purpose of a trial is a comparison of two active agents or assessment of dose-response, the addition of a placebo provides an internal standard that enhances the inferences that can be drawn from the other comparisons".

(ii) The *Tri-Council Policy Statement* does not specifically address the scientific issues around the selection of the control group in a clinical trial. However, article 7.4 outlines 7 situations where the use of a placebo-controlled trial would be acceptable.

(iii) The "Note of Clarification" concerning the *Declaration of Helsinki* on the use of placebo controls (WMA 2001) states that placebo-controlled trials may be ethically justifiable despite the availability of established effective treatment in two circumstances:

a) "Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method, or
b) Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."

Comments: We will deal with the first exception in Section 4. In the case of a minor medical condition it is likely that no treatment is an acceptable therapeutic option and so condition b) falls within the *Tri-Council Policy Statement* (7.4g).

2. Our operational definition of "established effective therapy"

We define "established effective therapy" for a specific group of individuals in terms of an examination of the totality of evidence derived from:

a) Systematic reviews of randomized trials carried out among those individuals (even though there may be just one trial).
b) "All or none" evidence (when, in a universally fatal condition, the therapy is followed by survival; or when some other adverse outcome is totally eliminated following therapy).

That is that there exists, level 1 evidence of efficacy. It is possible that in some circumstances there could be "established effective therapy" in the absence of level 1 evidence of effectiveness. An example would be the use of the PAP smear in the prevention of cervical cancer.

Table 3.2: Level of evidence

Level of Evidence	Therapy/Prevention, Aetiology/Harm
1a	Systematic review (with homogeneity) of RCTs
1b	Individual RCT (with narrow Confidence Interval)
1c	All or none
2a	Systematic review (with homogeneity) of cohort studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
2c	"Outcomes" Research
3a	Systematic review (with homogeneity) of case-control studies
3b	Individual Case-Control Study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

3. A scientifically valid definition of the "placebo effect/response"

There are at least seven reasons why the health status of patients who participate in a randomized trial can improve during the course of the trial:

The natural history of their illness: They may spontaneously recover, or their symptoms may decrease or disappear in the natural course of their disease *in the absence of any treatment whatsoever*. This regularly occurs even in serious conditions such as multiple sclerosis, severe depression, unstable angina pectoris or threatened stroke.

Thankful patients with positive outlooks: Some patients consciously or unconsciously want to show that they are "good" patients and appreciate the care they have been given, and so may report positively about symptom improvement.

Investigator bias: When outcome measures are subjective their assessment may be influenced by investigator bias. For example, when investigators know (or think they know) that a patient is receiving the treatment they have a "hunch" is the better one (even if it is the placebo), they may consciously or unconsciously over-estimate patients' improvements, symptom relief, and freedom from side-effects.

Regression to the mean: Patients often are entered into trials because they are displaying an extremely high (say, blood pressure) or low (say, blood count) value for some measure of their health. If these measurements are repeated a few days or weeks later, they often have returned to or toward normal values *in the absence of any treatment whatsoever.*

Adjunctive care: Other supportive care that may be offered in the trial such as intensive nursing care, diet modification, etc.

Concomitant medications: Patients/Investigators may use other medications to relieve patient symptoms.

The effect of the active or placebo treatment that they received.

Note: The combined effects of 2 and 5 are often referred to as the "clinical trial effect".

These first six improvements occur in both active treatment and placebo patients, and occur even when patients receive *neither active nor placebo treatment* (the sixth is a problem if it occurs differentially across the arms).

It necessarily follows that the "placebo effect" (or "placebo response") during a trial can only be determined by correcting for the other causes for improvement. This means that the valid determination of the placebo effect is not a comparison of placebo patients at the start and end of a trial (for this "observed response in the placebo arm" is contaminated by the other causes for improvement). The only valid determination of the placebo effect is a comparison of improvements among well blinded placebo patients during a trial with improvements among patients who have received no treatment (active or placebo) during the trial at all. Even this will be an overestimate since conditions 2, 3, 5 and 6 above may not apply to a "no treatment" arm. As it happens, there have been more than 100 such "3-arm" trials in which patients agreed to be randomized to active treatment, placebos, or no treatment at all. A recent systematic review of these trials concluded that the true placebo effect is usually small[13], (although we do not have information about the success of blinding in those trials). We suggest that in our discussions about placebos we carefully distinguish between the "placebo response/effect" and the "observed response in the placebo arm".[14]

A useful resource for finding out more about placebo effects has been created by the US National Institutes of Health: It is available on the web at http://placebo.nih.gov/, and in book form as *The Science of the Placebo*. Edited by HA Guess, A Kleinman, JW Kusek and LW Engel and published in 2002 by BMJ Books (ISBN 0 7279 1594 0).

[13] Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med.* 2001; 344:1594-602.

[14] Some psychiatric publications use (incorrectly we think) the term "placebo response" to describe the "observed response in the placebo arm." E.g., Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression. Variable, substantial, and growing. *JAMA* 2002; 287:1840-7.

4. Four situations in which the withholding of active therapy from control patients has been advocated.

First, withholding active therapy from control patients has been advocated WHEN NO "ESTABLISHED EFFECTIVE THERAPY" EXISTS. When there is *no* established effective therapy for a given disorder, it is advocated that experimental patients receive only general supportive care *plus the new intervention*, and control patients receive only general supportive care *plus placebo.* (By "general supportive care" we mean routine examinations and treatment of other health problems as they arise, but only symptomatic therapy and emotional support for the trial's target disorder.)

Comment: This is scientifically sensible; history teaches us that when we use promising treatments that have never been tested in randomized trials, we can do great harm to patients.[15]

Second, withholding active therapy from control patients has been advocated WHEN "SUBSTANTIAL DOUBT ABOUT THE EFFICACY OF ESTABLISHED EFFECTIVE THERAPY HAS ARISEN". For example, a therapy previously regarded to be Established Effective Therapy may, on post-marketing surveillance, be revealed to cause rare but serious side-effects. As a result, it may be concluded that this therapy does more harm than good. When it constitutes the only treatment for the condition, it is appropriate to test a promising new therapy against placebo.

Third, withholding active therapy from control patients has been advocated WHEN "ESTABLISHED EFFECTIVE THERAPY" EXISTS, BUT THE TARGET CONDITION IS TRIVIAL. When there is established effective therapy for patients with a trivial disorder (the usual example is hay fever), it is advocated that experimental patients receive the *new drug*, and control patients are denied an established effective therapy and receive *placebo*.

Comment: This is neither scientifically (nor clinically) sensible. If previously proven therapy exists, the new intervention would be preferable only if it were:

- more effective and acceptably safe, or
- as effective and safer or cheaper.

Thus, relevant scientific question involves a "head-to-head" comparison in which experimental patients receive the *new intervention,* and control patients receive an established effective therapy.

Fourth, withholding active therapy from control patients has been advocated WHEN "ESTABLISHED EFFECTIVE THERAPY" EXISTS, BUT WITHHOLDING OF TREATMENT WILL NOT CAUSE SERIOUS HARM. For example, some would argue that it

[15]The latest example is the great harm done by prescribing estrogen-plus-progestin to healthy postmenopausal women under the presumption that they will be protected against cardiovascular disease. This treatment, when finally tested in a large randomized trial, was found to increase their risks for coronary events, strokes, blood clots, and breast cancer.

is appropriate to withhold established effective therapy in trials of major depressive disorder, anxiety, schizophrenia, and migraines among others.

Comment: We believe that the withholding of "established effective therapy" is scientifically unsound in this situation. In our opinion the testing of the new intervention versus placebo is not a sensible hypothesis. What is of interest to health care providers is not whether the new intervention is better than nothing but rather whether it is better than or as good as established effective therapy. Thus, scientifically sensible trials of new interventions should take the form of either "head-to-head" comparisons with "established effective therapy" (*new drug* vs. *previously proven drug*) or "add-on" trials of *"established effective therapy" plus the new intervention* vs. *"established effective therapy" plus placebo*.

PROPOSED RULES FOR THE USE OF PLACEBO

Our proposed rules are quite simple, are based on whether there is "established effective therapy" that does more good than harm to patients with the target disorder who are eligible for a trial, and reflect our belief that it is the comparative merit of the new therapy that is the relevant scientific question.

i. When there is NO "established effective therapy" for patients with the target disorder (this includes instances of patient subpopulations, i.e. patients refractory to it, those who have previously refused the therapy, experienced severe adverse reactions to it, or are from subgroups known to be non-responsive to it), the scientifically sound trial is one in which experimental patients receive general supportive care plus the new treatment, and control patients receive general supportive care plus placebo or no treatment.

   Indeed, in the absence of solid evidence regarding "established effective therapy" for patients with the target disorder, we hold that it is scientifically inappropriate NOT to do a randomized trial of promising but untested therapy versus placebo.

ii. When there IS "established effective therapy" for patients with the target disorder and a promising new intervention may provide additional benefit, the scientifically sound trial is one in which patients in the experimental group receive the "established effective therapy" plus the new treatment (or, if they cannot be given simultaneously, the new treatment alone), and patients in the control group receive the "established effective therapy" plus placebo or no treatment.
iii. When there IS "established effective therapy" for patients with the target disorder it is not scientifically/clinically sound to withhold that "established effective therapy" from control patients. Active controlled trials should be conducted. This will provide the best information to inform medical-decision making. (An ACST can always be conducted, however, an ACNIT will only be scientifically acceptable if the reproducibility of the effect of EET can be assumed.)

The NPWC has used the term "Established Effective Therapy". This is a change from the TCPS which uses the term "standard therapy". The term "standard therapy" was considered deficient by the NPWC for two reasons:

1. Investigators have, in the past, interpreted "standard therapy" to mean a single standard therapy. Thus, they have argued in cases where there are many possible current therapies that no "standard therapy" exists and so the use of a placebo is appropriate.

2. The use of "standard therapy" does not promote a culture of rigorous evaluation of new therapies which should be a fundamental principle of the ethical conduct of medical research.

Recently, audits have been carried out in various clinical settings to determine how much of our current "standard treatment" has never been subjected to randomized controlled trials, or does not meet the "all or none" criteria. Viewed from the patient's perspective (what proportion of patients in a particular setting are receiving "established effective therapy"?) the results are surprisingly encouraging, 82% on in-patient medical wards, and closely similar rates on in-patient psychiatry, surgery, and pediatrics, and in primary care[16].

It should be noted that even if "standard treatment" has not satisfied the scientific requirements for "established effective therapy", that shouldn't be misunderstood to mean that it should be withheld from patients, on the one hand, or automatically subjected to randomized trials, on the other. There are three reasons why such conclusions are incorrect. First, the "absence of proof" of effectiveness is not the "proof of absence" of effectiveness. Second, "standard treatments" should not be subjected to randomized trials unless and until the expert clinical community develop a "genuine uncertainty about their value" ("clinical equipoise"). Finally, many "standard treatments" are provided to all groups of patients in randomized trials as part of their routine care.

[16] http://www.shef.ac.uk/scharr/ir/percent.html

4. Ethical Perspective

Bernard Keating, Thérèse Leroux, George Webster and Kathleen Glass

A. Introduction

The ethics subcommittee has taken into consideration as objectively as possible the main arguments that are at the heart of the debate over the ethics of placebo-controlled clinical trials. Every attempt was made to identify the criticisms often levied against the various arguments. The purpose of the work of the subcommittee was to promote a better understanding and appreciation of the nature of the arguments and counter-arguments involved in the ethical debate.

The first part of this section offers some elaboration on the main arguments of the ethical debate as found in codes of ethics and the ethics and clinical literature. There is no standardization of style or format for these arguments. They are essentially approached in a variety of ways by a variety of authors anxious to adequately represent their point of view. The second part of this section proposes a number of recommendations of the subcommittee and the rationale behind them.

B. Main Arguments of the Ethical Debate

Argument 1 from the Literature: The fiduciary obligation of the physician

The physician-investigator has the therapeutic obligation to offer the best available medical care. This argument is supported by:

- The *Tri-Council Policy Statement*
- The *Declaration of Helsinki*
- *CIOMS Guidelines (2002)*[17]
- Freedman, Glass, and Weijer (1996)[18]; Freedman, Weijer, and Glass (1996)[19]
- Waring and Glass (2002)[20]
- Rothman and Michels (1994)[21]; Rothman (2000)[22]
- Weijer (1999)[23]

[17] http://www.cioms.ch/frame_guidelines_nov_2002.htm
[18] Freedman, B., K. C. Glass, and Weijer, C., Placebo orthodoxy in clinical research. II: Ethical, legal, and regulatory myths. *Journal of Law, Medicine and Ethics* 1996; 24(3): 252-9.
[19] Freedman, B., C. Weijer, and Glass, K.C., Placebo orthodoxy in clinical research. I: Empirical and methodological myths. *Journal of Law, Medicine and Ethics* 1996; 24(3): 243-51.
[20] Glass, K. C. and D. Waring, Effective Trial Design Need Not Conflict with Good Patient Care. *American Journal of Bioethics* 2002; 2(2): 25-26
[21] Rothman, K. J. and K. B. Michels, The continuing unethical use of placebo controls. *N Engl J Med* 1994; 331(6): 394-8.
[22] Rothman, K. J., Declaration of Helsinki should be strengthened. *BMJ* 2000; 321(7258): 442-5.
[23] Weijer, C., Placebo-controlled trials in schizophrenia: are they ethical? Are they necessary? *Schizophrenia Research* 1999; 35(3): 211-8; discussion 227-36.

***The Rationale*:** The argument presupposes that physicians/investigators are never relieved of their obligations of care towards their patients. This is one of the cornerstones of the *Declaration of Helsinki*, which affirms, in Article 3, the primacy accorded to the well-being of the patient.

> The *Declaration of Geneva of the World Medical Association (WMA)*[24] binds the physician with the words, "The health of my patient will be my first consideration," and the *International Code of Medical Ethics*[25] 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."

The consequences of this statement from a research perspective are taken from Article 5 of the *Declaration of Helsinki.* "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society."

Those *opposed* to Argument 1 suggest that the advancement of science is dependent on the sacrifice of a few for the benefit of many others. The *proponents* of Argument 1 contradict this, resting on methodological considerations concerning the design of clinical trials. At the heart of these considerations is the concept of clinical equipoise. This concept is *a priori* a methodological concept, defined as follows: "Clinical equipoise means a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial."

While this formalization of the state of knowledge has research implications and justifies the needs of a trial, it nonetheless has considerable ethical importance as well.

It is this initial uncertainty which allows a physician to suggest that a patient enroll in a clinical trial without forsaking his/her fiduciary duty to the patient's well-being. If one did not have good reason to believe that the study treatment could be at least as good, or better, than established effective treatment, one should not engage in a trial. Once the trial question has been answered, the trial must be ended!

Ethical acceptability of the use of placebo therefore depends upon not disadvantaging patients, nor compromising their well-being. The authors of the *Tri-Council Policy Statement*[26] identified a number of situations in which this may indeed be the case:

a. There is no standard treatment;
b. Standard therapy has been shown to be no better than placebo;
c. Evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy;

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[24] World Medical Assembly, *Declaration of Helsinki* (Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. Amended most recently by the 52nd WMA Assembly, Edinburgh, Scotland, October, 2000)
[25] American Medical Association Council on Ethical and Judicial Affairs, *Code of Medical Ethics* On line: http://www.ama.assn.org/ama/pub/category/4301.html
[26] *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa: Public Works and Government Services Canada, 1998)

d. Effective treatment is not available to patients due to cost constraints or short supply. (This may only be applied when background conditions of justice prevail within the health care system in question; for example, a placebo-controlled trial is not permissible when effective but costly treatment is made available to the rich but remains unavailable to the poor or uninsured.);
e. In a population of patients who are refractory to standard treatment and for whom no standard second-line treatment exists;
f. Testing of add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed; or
g. Patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude."

Problems with the use of the concept "clinical equipoise" in the placebo debate

There have been many criticisms addressing Argument 1. These criticisms rest upon ethical, methodological and practical considerations.

From the point of view of ethics, the major criticism is that limiting the use of placebo is "paternalistic" and that by insisting on the fiduciary obligation to the patient, one compromises the patient's autonomy. In other words, if competent patients can refuse care in a clinical context, why can't they do the same in a research protocol? It is also argued that patients may be altruistic. In this instance the reasoning is even more convincing. One can, in effect, consider that the limitation on autonomy compromises not only one's liberty to use one's body, but also the possibility of moral engagement for an altruistic purpose.

From the methodological perspective, some people cast doubt on the validity of the principle of "clinical equipoise". In the first instance, the idea of real uncertainty is problematic according to these critics, especially in Phase II trials, where the chance that the study substance is equal or superior to established effective therapy is very slim. In the second instance, the notions of standard treatment as well as best method available and proven method, (*Declaration of Helsinki,* paragraph 29) raise problems when one attempts to operationalize the notions.

From the practical point of view, some *opponents* underscore that the limits imposed by Argument 1 will slow, and possibly compromise, research progress.

Miller and Brody[27] argue that "the principle of clinical equipoise conflates the ethics of clinical research with the ethics of clinical medicine and provides erroneous guidance on the use of placebo-controlled trials."

Argument 2: A placebo is acceptable if it does not involve a high degree of risk

The evaluation of the level and the nature of risk are the core questions for the ethical evaluation of the acceptability of placebo in research. The argument is supported by:

[27] Miller, F. G. and H. Brody, What Makes Placebo-Controlled Trial Unethical? *American Journal of Bioethics* 2002; 2(2): 3-9.

- *CIOMS Guidelines (2002)*
- *ICH E-10 (2000)*
- Houston and Peterson (2001)[28]
- Temple and Ellenberg (2000)[29]

***The Rationale*:** This argument has different versions according to the degree of risk allowed as might be implied in the table below. The argument is shared by a large number of authors whose interest is clinical or regulatory. Philosophically, it is rooted in utilitarian thought. Thus, according to the ICH E-10 guideline, *Choice of Control Group and Related Issues in Clinical Trials,* foregoing standard treatment with a placebo control is acceptable if there is no risk of death or irreversible morbidity. This position is more permissive than that found in the *Institutional Review Board Guidebook*, a document created for use by members of US Institutional Review Boards (IRB) for their evaluation of protocols. Indeed, it does not authorize placebo use if such use deprives the research participant of medications that relieve severe symptoms or contribute to the improvement of a serious illness. Table 4.1 offers some comparative considerations from three sources regarding research design.

Table 4.1: Comparative considerations regarding research design

Institutional Review Board Guidebook 1993	**ICH 2000**	**CIOMS 2002**
Chapter IV	*E 10*	*Guideline 11*
The use of placebos is generally unacceptable if there is an effective therapy that the subjects could be receiving for relief of severe symptoms or amelioration of a serious condition.	Is the proven effective treatment life saving or known to prevent irreversible morbidity?	When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; When use of an established effective intervention as comparator would not yield scientifically reliable results, and use of placebo would not add any risk of serious or irreversible harm to the subjects.

[28] Huston P, Peterson R., Withholding proven treatment in clinical research, *N Engl J Med*. 2001; 345(12): 912-4.
[29] Temple, R. and S. S. Ellenberg, Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. *Ann Intern Med* 2000; 133(6): 455-63.

Opponents of Argument 2 suggest that the argument frequently ignores the principle of the duty to treat which underpins the *Declaration of Helsinki*. For the *proponents* of this argument, Kahn's conclusion (2000) which notes that the risk of suicide in a control group is no greater than that in a group under active treatment, is evidence of the ethical acceptability of the use of placebos. These proponents ignore other kinds of suffering for participants in such trials.

By ignoring the argument that is anchored in the idea of therapeutic obligation, one completely disregards a moral intuition conveyed in the Hippocratic tradition for millennia.

Argument 3: Scientific reasons may justify the exposure of the subjects to risks

Since scientific rigor is required for ethical acceptability, it is contrary to ethics to lack scientific rigor. The use of placebo may be justified when it is necessary to obtain sound scientific results. In this case, a higher level of risk is ethically acceptable. This argument is supported by:

- *CIOMS Guidelines (2002)*
- *Note of Clarification on paragraph 29 of the WMA Declaration of Helsinki (2001)*
- Fritze J and Moller HJ (2001)[30]

***The Rationale**:* According to this argument scientific validity of a research protocol is a *sine qua non* for ethical validity. Therefore depriving participants of treatments of demonstrated value and submitting them to additional risk of serious or irreversible harm is justified morally if the investigator acts with the greatest rigor possible.

The *Note of Clarification on paragraph 29 of the WMA Declaration of Helsinki*, published in October, 2001 in the Bulletin of the World Medical Association and adopted by the General Assembly in 2002, supports this proposition, thus adopting an argument which, to our knowledge, has never been supported by any normative instrument. The argument essentially permits the use of placebo for scientific reasons and without any explicit mention of the level of risk.

The *CIOMS (Council for International Organizations of Medical Sciences) Guidelines* published in August 2002 define two levels of permissibility. The first level elaborates the general rule that a subject can, at most be submitted to temporary discomfort or delay in relief of symptoms. These criteria are more demanding and stricter than the American rules or the *ICH*. On the other hand, the *CIOMS Guidelines* allow a higher level of risk for motives related to the scientific validity of the results. Note that at the time of adoption of the *CIOMS* document, the *Note of Clarification on paragraph 29 of the WMA Declaration of Helsinki* had been published. Paragraph 29 used for the first time in a document of this type, scientific motives to justify submitting a research participant to a higher level of risk or additional discomfort.

[30] Fritze J and Moller HJ, Design of clinical trials of antidepressants: should a placebo arm be included? *CNS Drugs* 2001; 15(10); 755 764.

Note of Clarification on paragraph 29 of the WMA Declaration of Helsinki

The *WMA* hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebos will not be subject to any additional risk of serious or irreversible harm."

All other provisions of the Declaration of Helinski must be adhered to, especially the need for appropriate ethical and scientific review.

This position is clearly distinguished from that adopted by CIOMS which EXPLICITLY limits the level of risk justified by scientific motives to cases in which the use of placebo does not introduce risks of serious or irreversible harm.

Argument 3 is problematic for a number of reasons. This "interpretation" of the *Note of Clarification Declaration of Helsinki* is seen by many as an about-face rather than a "clarification". By establishing criteria more demanding than *ICH E-10* or regulatory bodies, Paragraph 29 of the *Declaration of Helsinki* created problems. However it must be remembered that the strict limitation on placebo use established by Paragraph 29 (perhaps only allowing for use where there is no existing effective treatment) is in complete accord with Articles 3 and 5. Articles 3 and 5 enshrine an absolute duty on physicians with regard to their patients and the prohibition on sacrificing the well-being of patients to the interests of society.

The Note of Clarification on the paragraph 29 of the WMA Declaration of Helsinki attempts to harmonize the *Declaration of Helsinki* with *ICH E-10*, but at the cost of important breaches to the integrity of the document in general. It introduces clearly utilitarian considerations into a document that was drafted with a deontological perspective. (Brennan 1999, La Vaque and Rossiter 2001).[31]

The fundamental argument concerning the necessity for scientific rigor can be characterized as causing confusion between preconditions that are necessary and those that are both necessary and sufficient. Lack of scientific rigor justifies rejection of a protocol from the point of view of ethics, but its scientific merit is only one of many conditions that must be respected for a protocol to conform to all ethical requirements.

[31] Brennan, T. A., Proposed revisions to the Declaration of Helsinki – will they weaken the ethical principles underlying human research? *N Engl J Med* 1999; 341(7): 527-31; La Vaque, V.T. and T. Rossiter, The ethical use of placebo controls in clinical research: The declaration of Helsinki. *Applied Psychophysiology and Biofeedback* 2001; 26(1): 23 – 37.

Argument 4: To limit the use of placebos is to compromise the autonomy of the patient

Respect for the patient's autonomy is one of the main achievements of bioethics. To limit the expansion of autonomy to research ethics is a moral mistake. This argument is supported by:

- Addington (1995)[32]
- Levine (1999)[33]

***The Rationale**:* The development of bioethics over the last thirty years has emphasized recognition of a patient's autonomy. This view recognizes the rights of patients not only to be informed but also to make their own medical decisions. The patient is viewed as having the right to choose between treatments of which the medical value is not equivalent. Patients may even refuse treatments that are life saving. There is general consensus around the idea that quality of life judgments must be left to patients and that patients can legitimately derogate choices to "those that impose the strict medical logic". In this context, "banning the use of placebos when there is no risk of significant or long-lasting harm would be paternalistic".[34]

The argument has a number of inherent problems. It is ironic that an idea (patient autonomy) that was originally called upon as the result of multiple abuses of research subjects is now invoked to lower standards of patient protection in research.

In the view of its critics, the idea of autonomy as it is currently proposed, is profoundly marked by an individualist vision of the person. Expressions of autonomy of some can be limited when it is necessary for protection of the vulnerable. Furthermore, the fact that 70% of research subjects may suffer from a therapeutic misconception[35] evokes caution about the use of autonomy as an argument for a less stringent protection for research subjects.[36]

Argument 5: The use of a placebo is justified if it doesn't constitute an exploitation of the research participant

The argument is supported by:

- Miller and Brody (2002)[37]

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[32] Addington, D., The use of placebos in clinical trials for acute schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie* 1995; 40(4): 171-6.
[33] Levine, R.J., The need to revise the Declaration of Helsinki. *N Engl J Med* 1999; 341(7): 531-4.
[34] Levine, R.J. The need to revise the Declaration of Helsinki. *N Engl J Med* 1999; 341(7): 531-4.
[35] "The therapeutic misconception is the tendency to view the research context as an extension of the therapeutic, with dangerous consequences for the patient-client. Where interventions are not validated (ie. are experimental), where the primary aim is to ascertain their effectiveness, and where the researcher does not know what the outcome will be, the patient-client is at greater risk than in the customary therapeutic situation." http://www.mcmaster.ca/ors/ethics/tutorial/bioethics2.htm.
[36] Appelbaum, P. S. Clarifying the Ethics of Clinical Research: A Path toward Avoiding the Therapeutic Misconception. 2(2): 22-3.
[37] Miller, F. G. and H. Brody, What Makes Placebo-Controlled Trial Unethical? *American Journal of Bioethics* 2002; 2(2): 3-9.

According to the *proponents* of this argument, "the principle of clinical equipoise conflates the ethics of clinical research with the ethics of clinical medicine and provides erroneous ethical guidance on the use of placebo-controlled trials". It proposes a clear distinction between the ethics of clinical practice and the ethics of research, and therefore the duties of the two are different. If a physician has the obligation to offer "optimal medical care", the physician investigator only has the obligation not to exploit research subjects. They are not exploited if: 1) they are not being exposed to excessive risks for the sake of scientific investigation and 2) they understand that they are volunteering to participate in an experiment rather than receiving personalized medical care directed at their best interests.[38]

This argument is problematic in that it offers a solution to a potential conflict of obligations for many physician-investigators, yet it does so by radically departing from traditional professional ethics. The solution until now has been the strong affirmation of the primacy of the physician's clinical obligation to patients, with a refusal to recognize any dichotomy between treating physician and physician-investigator.

This argument is incompatible with numerous codes of professional ethics, legal principles and standards of research ethics. Accepting it would mean a significant change of paradigm for both research and clinical ethics.

Argument 6: Placebo use is justified because it restricts the number of patient participants who will be exposed to risk.

Minimizing the level of risk is the core concept of research ethics so we must use placebo control trials because it lowers the total number of people exposed to risk. This argument is supported by:

- Addington (1995)[39]
- Leon (2001)[40]
- Levine (1999)[41]
- Miller (2000)[42]
- Young and Annable (1996)[43]

Another type of argument favoring liberalization of the use of placebo invokes the collective good of patients or research subjects. It is argued that the use of placebos prevents the harm that

[38] Miller, F. G. and H. Brody, What Makes Placebo-Controlled Trial Unethical? *American Journal of Bioethics* 2002; 2(2): 3-9.
[39] Addington, D., The use of placebos in clinical trials for acute schizophrenia. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie* 1995; 40(4): 171-6.
[40] Leon, A., Can placebo controls reduce the number of nonresponders in clinical trials? A power-analytic perspective. *Clinical Therapeutics*, 2001; 23(4): 596 - 603.
[41] Levine, R. J., The need to revise the Declaration of Helsinki. *N Engl J Med* 2001; 341(7): 531-4.
[42] Miller, F. G., Placebo-controlled trials in psychiatric research: an ethical perspective. *Biological Psychiatry* 2000; 47(8): 707-16.
[43] Young, S. N. and L. Annable, The use of placebos in psychiatry: a response to the draft document prepared by the Tri-Council Working Group. Canadian College of Neuropsychopharmacology. *Journal of Psychiatry and Neuroscience* 1996; 21(4): 235-8.

the approval of ineffective medications would cause. Interdiction of placebos could compromise the development of new treatments. Use of placebos permits a reduction in the number of persons subjected to the research risks.

A number of the arguments have a common theme: that of relying on group interests - those of subjects or patients needing care. They seem to ignore the requirement of Article 5 of the *Declaration of Helsinki*. This article, as the whole of the Declaration, adopts a clearly deontological perspective when it dismisses the notion that the good of society justifies compromising the protection of individual rights. “In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society”.

On a practical level, this argument ignores the fact that the conduct of placebo-controlled trials when established effective therapy exists does not answer the clinical question “which medication is best for my patient – existing therapy or the new treatment”. Failure to answer this question may also cause harm to future patients.

C. **Ethics Subcommittee Perception of the Debate**

Summarizing the debate in a manner that implies it is a simple matter of choosing “Not to use placebos” versus “Using placebo in occasional, well scrutinized trials” is inaccurate and misleading. This type of summary problematically categorizes the position of the critics of placebos as “absolutism” and asserts that the critics of placebo use “ignore the individuality and complexity of each research question” (Osborn 2001).[44]

A fair examination of the *Tri-Council Policy Statement* leads us to a different conclusion. Paragraph 7.4 identifies seven circumstances in which the offer of participation in a placebo-controlled trial does not compromise the exercise of the duty of care.

It is strongly suggested that the *Tri-Council Policy Statement* position must be subject to an attentive scrutiny before modification is made.

The subcommittee holds that arguments *justifying placebo use exclusively on the basis of scientific grounds are without sound ethical foundation.* This argument depends on an erroneous interpretation of the saying “Bad ethics = Bad science”. Scientific rigor is a necessary but insufficient pre-condition to ethically sound research. If scientific reasons alone were sufficient to legitimize a particular conduct, this would mean that science is not subject to social examination and evaluation.

We must also take into account the fact that there is a strong debate among scientists about what counts as sound scientific evidence. This debate was referenced in the “Scientific Perspective” section[45] of this report. We must be attentive to the fact that “scientific arguments” very often

[44] Osborn, D., Placebos and research ethics: an absolute dilemma? *Current Opinion in Psychiatry* 2001; 14(5): 507 - 511.
[45] See page 17 of this report

incorporate implicit value judgments or explicit value judgments without sufficient argumentation. This is the case with the argument about the duty to minimize risk. This duty is incorporated into Emanuel's synthesis about research ethics as a requirement to assure a "Favorable Risk-Benefit Ratio" in which three conditions are fulfilled:

- the potential risks to individual subjects are minimized,
- the potential benefits to individual subjects are enhanced,
- the potential benefits to individual subjects and society are proportionate to or outweigh the risks (Emanuel, Wendler et al. 2000).[46]

The reference to the individual subjects is common to the three conditions. This is a clear signal that the idea of a "Favorable Risk-Benefit Ratio" must be interpreted in the framework of the duties to individual patients favored by the concept of "fiduciary obligations". To use this idea to justify a lower degree of protection for individual patients for the benefit of the patients in general is out of the scope of this argument. It is possible only if this argument is interpreted as the expression of the adoption of utilitarianism as moral philosophy.

D. State of International Ethical Regulations

The ethics subcommittee agrees with the opinion of Miller and Brody[47] about the *"Note of Clarification on paragraph 29 of the WMA Declaration of Helsinki"* adopted by the World Medical Association. "This statement marks a fundamental departure from the revision of October 2000". It makes clear concessions to supporters of placebo-controlled trials without offering any rationale for the change. This change is a substantial modification of Paragraph 29, giving to the supporter of a broader use of placebo what they have requested. The positive reception of the "*Note of Clarification*" by these supporters is a clear indication that it marks a dramatic change of mind for the WMA. The new Paragraph 29 is out of touch with the ethical framework initiated in Articles 3 and 5. The result of the modification is a breach in the general integrity of a document written from a Hippocratic point of view.

The CIOMS document proposes two levels of risk that are considered acceptable. One could interpret the first as formulating a general rule, and the second as an exception to the rule based on reasons of scientific validity.

The first rule: "When withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms". The **second rule** includes risk appreciably greater, and is justified by motives of scientific methodology. "When use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects".

Note that the CIOMS criteria are appreciably more demanding than those in the *Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki* and in *ICH E-10*. First of all, contrary to the World Medical Association, CIOMS puts a limit on the levels of allowable risk

[46] Emanuel, E. J., D. Wendler, et al., What makes clinical research ethical? *JAMA* 2000; 283(20): 2701-11.
[47] Miller, F.G. and H. Brody What Makes Placebo-Controlled Trial Unethical? *American Journal of Bioethics* 2002; 2(2): 3-9.

justified by scientific merit. The proposed threshold excludes the possibility of the risk of serious or irreversible damage. In the case of *ICH E-10*, the level of acceptable risk is clearly more elevated because it gives a "green light" to placebo use where the subject is not deprived of treatment which is life saving or known to prevent irreversible morbidity.

Even though the CIOMS position is more acceptable in the opinion of the ethics subcommittee, the committee does not endorse it. The work of the scientific subcommittee casts serious doubt on the scientific necessity for which patients are invited to sacrifice a part of the protection that has, in principle, been accorded to research participants over the past several decades.

E. **Conclusions**

While respecting the autonomy of the patient, Canadian policy should recognize the concept of "fiduciary obligations" as fundamental in the ethics of clinical research and the Canadian position on the use of placebos should remain firmly grounded in the fiduciary obligations of physicians towards patients as formulated in Article 3 of the *Declaration of Helsinki.*

The fiduciary duty of the physician is formulated in Article 3 of the *Declaration of Helsinki:* «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." 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".»

The structure of argumentation of the *Tri-Council Policy Statement* document is shaped by the recognition of the fiduciary duty of the clinician. The fiduciary model is challenged today by a more libertarian model in which medical services are seen as "free market transaction". The *Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki* is a substantial event in the erosion of the dominant ethical and legal paradigm of fiduciary relation. Virginia A. Sharpe was perfectly correct when she wrote in 1997 "the fiduciary model will be challenged to address the conditions under which the interests of the patient may be justifiably weighed against the legitimate interests of the others". [48]
Contrary to Miller and Brody[49], the members of the ethics subcommittee believe that the duty of the clinician in clinical research is the same as that of the clinician outside of clinical research. The committee supports this principle as fundamental, rooted not only in traditional medical ethics but also equally in the reflection of tragic recurrent experiences which occur when physicians forget or deny their inalienable obligations to their patients.

The subcommittee calls attention to the potential for the powerlessness/vulnerability of sick persons. Illness can destabilize individuals, changing their rapport with themselves and their families. Patients may find themselves immersed in a complex medical universe. They may be overwhelmed with information that is often difficult to interpret even for a person in good health in a calm situation.

[48] Sharpe, V. A., Why "do no harm"? *Theor Med* 1997; 18(1-2): 197-215.
[49] Miller, F.G. and H. Brody, What Makes Placebo-Controlled Trial Unethical? *American Journal of Bioethics* 2002; 2(2): 3-9.

Recognition of potential vulnerability of sick persons is at the heart of deontological systems of protection[50]. Ethical or legal weakening of this protection in the name of an abstract principle of autonomy ignores reality and at its limit, renounces obligations that society has to protect persons who are vulnerable and sick. Such protection is not a denial of autonomy, but rather a means of restoring persons to a state of autonomy. The subcommittee takes into account the conclusions made by the legal subcommittee about autonomy and the obligations driven by the fiduciary relation. The individual patient cannot, by his own will, weaken obligations driven by the fiduciary relation.

To make clear that clinical equipoise demonstrates the means to achieve the fiduciary obligation, the subcommittee believes that the concept of "clinical equipoise" plays an essential role as a test to substantiate the true possibility of fulfilling the physician-researcher's fiduciary obligation in a specific protocol.

To submit a specific protocol to this test, at a precise moment in the state of development of medical sciences entails recognizing the complexity of the question. The construct of clinical equipoise permits us to determine whether physician-researchers can be involved in clinical research without compromising their fiduciary obligation to the patient.

Consideration of any additional situations (beyond those listed in the *Tri-Council Policy Statement*) in which the use of placebo as the control arm in a clinical trial would be appropriate should those situations meet the test of clinical equipoise.

[50] Sharpe, V. A., Why "do no harm"? *Theor Med* 1997; 18(1-2): 197-215.

5. Legal Perspective

Kathleen Glass and Thérèse Leroux

The choice of treatments for control patients in clinical trials has long been recognized as a methodological and ethical issue. A great deal has been written about the science and the ethics of using placebo controls in clinical trials when established effective intervention or standard therapy is available. However, little consideration has been given to important legal questions following from such trials. In particular, questions of potential legal liability for harm to a research participant occasioned by withholding available treatment in the placebo arm of a trial have not been addressed.

In looking for legal guidance on the placebo issue, there is no legislation or case law directly on point. However, the law does provide basic principles and a number of legal frameworks for examining placebo-controlled trials. Although medical negligence is the most probable cause of action, under some circumstances a separate claim for breach of fiduciary duty might be made. Since some persons do not wish to, or cannot afford to, access the legal system the possibility of lodging a complaint of professional misconduct with those bodies governing the conduct of physicians is also explored. The discussion below is limited to placebo-controlled trials when there is established, effective therapy for the population under study.

A. Liability/Causes of Action

1. Medical Negligence

Regimes of medical negligence apply to all areas of medicine and medical research, whether a trial is testing a new therapy against placebo or active treatment. To establish negligence in a malpractice suit, research participants who are harmed must first prove that the physician/investigator owed them a duty of care. Only then will the alleged negligence be considered. Here the principle of "holding out" will be relevant. Did the physician/investigator hold him/herself out as ready and willing to diagnose, treat or refer the patient/participant? The American Medical Association's *Code of Medical Ethics* assumes this to be the case, stating that in research designed to test the efficacy of treatment, the investigator "must recognize that the physician-patient relationship exists and that professional judgment and skill must be exercised in the best interest of the patient".[51]

Once a doctor-patient relationship has been established, how will the physician/investigator's behavior be judged? To establish negligence, the plaintiff must prove that the defendant failed to meet the established standard of care, that is, failed to act with the skill and care of a reasonable practitioner of the same experience and standing. In the case of placebo-controlled trials, the first question will be, is it standard to offer treatment to patients in the same condition as the prospective research participant?

[51] American Medical Association Council on Ethical and Judicial Affairs, *Code of Medical Ethics* on line: http://www.ama.assn.org/ama/pub/category/4301.html

In determining what constitutes the standard of care, is the standard for a physician/investigator different from that of a physician who does not conduct research? It has been argued by some in the ethics literature that judging clinical research by the same standard as clinical care is inappropriate, because the goal of the former is answering the research question and the latter is providing optimal care to patients.[52] This argument is questionable both legally and ethically. If an individual seeks medical services from a physician, and a doctor-patient relationship is established, by what mechanism would a different (and lower, given it would allow leaving some patients untreated), standard of care be established?

Although research and therapy can be distinguished, they often occur together. While there is no case law dealing with medical malpractice on this point, there is legal commentary to the effect that the standard of care for physician-investigators will be the same as that imposed on physicians in the context of their therapeutic practice.[53] In fact, courts have set a higher standard for researchers than for non-researcher physicians when issues of informed consent are in question. (*Halushka*, 1965[54]; *Cryderman*, 1977[55]; *Coughlin*, 1987[56]; *Weiss*, 1989). A recent decision of the Quebec Court of Appeal (*Gomez*, 2001),[57] while not a medical malpractice case, clearly confirms that research participants can rightly expect that when research activities undertaken in medical centres involve medical procedures, they will meet the standard of care owed to patients.

The World Medical Association's *Declaration of Helsinki* also states that "[i]n medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." The Canadian *Tri-Council Policy Statement* makes clear that the welfare and integrity of the individual remain paramount in human research. Neither in law nor in ethics guidelines are there any provisions for "opting out" of the duty to provide needed clinical care to patients who participate in clinical research.

2. Breach of Fiduciary Duty

A fiduciary is defined by law as a person entrusted with power or property to be used for the benefit of another and is legally held to the highest standard of conduct (Prosser and Keeton, 1984).[58] As fiduciaries, physicians must act in the best interests of their patients and must not allow their own interests to come in conflict with those interests.[59] Breach of fiduciary duty can give rise to a separate cause of action against a doctor. While this cause of action has been given

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[52] Emmanuel, E and Miller, F., The Ethics of Placebo-Controlled Trials: A Middle Ground, *N Engl J Med* 2001; 345: 915-919. Miller, F. and Brody, H. What Makes Placebo-Controlled Trials Unethical? *American Journal of Bioethics* 2002; 2: 3-9.

[53] Geisen, D., Civil Liability for New Methods of Treatment and Experimentation: A Comparative Examination, *Medical Law Review*, 3(1995): 22-25.

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

[55] *Cryderman* v. *Ringrose*, [1977] 3 W.W.R. 481 (Alta. C.A.).

[56] *Coughlin* v. *Kuntz* (1987), 17 B.C.L.R. 365; [1990] 2 W.W.R. 737.

[57] *Gomez* v. *Comité exécutif du Conseil des médecins, dentistes et pharmaciens de l'Hôpital universitaire de Québec*, [2001] J.Q. No. 5544, online : QL (C.A.Qc.)

[58] Prosser, Keeton, *The Law of Torts*, 5th ed, W. Page Keeton, (ed) (St. Paul. Minn.: West Publishing Co, 1984).

[59] Robertson, G., Negligence and Malpractice, in J. Downie, T. Caulfield and C. Flood (eds), *Canadian Health Law and Policy*, 2nd ed. (Markham, Ontario: Butterworths, 2002), 91-109

limited scope by US courts, Canadian courts have begun to refer to the fiduciary aspects of medicine. [60,61, 62]

Breach of fiduciary duty may be an important cause of action for a research participant injured in a placebo-controlled trial because malpractice law has generally ignored traditional fiduciary concerns, such as physicians' financial conflicts of interest. A physician may be receiving financial benefits to recruit or conduct a clinical trial. There are also professional rewards, such as publications, promotion and high regard by one's peers for conducting research. These other interests of the investigator create the potential for conflict with duties to the patient. Although in some cases patients will benefit from trial participation (e.g., when there is no established effective therapy), trials are not designed with a placebo arm specifically to benefit the patients in that trial. They are designed in the interest and for the benefit of others, whether for future patients, pharmaceutical sponsors, investors, or others. Therefore, a patient in the placebo arm of a clinical trial whose condition deteriorates from lack of treatment may have a cause of action for breach of fiduciary duty if other interests are put above those of the patient.

Studies have looked at the role of trust in patients' decisions to participate in research. They show that patients trusted that their physicians would never endorse options that were not in their best interests,[63] thus demonstrating the importance of the physician/investigator's fiduciary role in clinical trials.

3. Professional Misconduct

Professional regulatory bodies use disciplinary actions to promote compliance with standards and to sanction unacceptable behavior on the part of their members (McNamara et al, 2002).[64] Regulatory bodies such as the Canadian provincial medical colleges or the American boards of medical examiners govern the conduct of physicians, including their use of substandard medical treatment. Regulatory bodies have found physicians in breach of the norms of professional conduct even when they clearly have their patients' interests in mind if their actions do not conform to the prevailing standard of care. (Re Ravikovich, [1995] O.C.P.S.D. No 16, para. 164) - untested uses of histamine injections; (Re Guess, 393 S.E.2d 833 (S.C.N.C. 199), 833-42 – homeopathy). It is generally not open to the doctor and the patient to bargain away this "guaranteed" level of professional competence. In effect, society paternalistically prevents us from "choosing" to obtain substandard care, even if that is what we knowingly wanted.[65]

B. Professional Responsibility of Physicians

It does not matter whether we are looking at negligence and the duty/standard of care, breach of fiduciary duty or professional misconduct, the law does not allow physicians to "opt out" of their

[60] Picard, E. and Robertson, G., *Legal Liability of Doctors and Hospitals in Canada*, 3rd ed. (Toronto: Carswell, 1996).
[61] *McInerney v. MacDonald* (1992) 93 D.L.R. (4th) 415 (S.C.C)
[62] *Norberg v. Wynrib* (1992), 92 D.L.R. (4th) 449 (S.C.C.)
[63] Advisory Committee on Human Radiation, *The Human Radiation Experiments* (New York: Oxford University Press, 1996
[64] McNamara, L., Nelson, E. and Windwick, B., in J. Downie, T. Caulfield and C. Flood (eds), *Canadian Health Law and Policy*, 2nd ed. (Markham, Ontario: Butterworths, 2002), 91-109.
[65] Menikov, J., *Law and Bioethics: An Introduction* (Washington, D.C.: Georgetown University Press, 2001.

professional obligations because they are researchers in addition to being physicians. In fact, being a researcher adds obligations to those existing already by creating a heightened standard of care (*Neufeld*, 1979[66]; *Halushka*, 1965[67]; *Cryderman*, 1977[68]; *Coughlin*, 1987[69]).

Even with the patient's informed consent (discussed further below), physician-investigators have no professional or legal mandate to prescribe substandard therapies. If the same rules of medical law apply to research that evaluates therapeutic interventions on ill patients, treatment consistent with competent medical practice cannot be sacrificed. This will apply for all clinical research offered to patients for whom treatment is appropriate, whether the issue is introduction of an experimental drug in a clinical trial or use of placebo in the control arm. There is no such thing as "contracting" for what would otherwise be considered negligent practice. The law protects individuals from making such poor health care choices because patients may be vulnerable. Such vulnerability may arise because of illness. Patients have a relationship of trust with their physicians and are in a situation of power imbalance since physicians have greater medical knowledge.

1. Consent as a Defense

A person who is harmed by participation in a placebo-controlled trial may have a cause of action against an investigator. However, there are potential defenses available to an investigator. Chief amongst them is an appeal to the autonomy of the patient in choosing to participate in the trial. Both law and medicine put a high premium on individual autonomy. Some may therefore claim that so long as patients are competent, well informed and can act freely, the choice to participate should be theirs. A substantial amount of contemporary medical case law has involved the notion of informed consent and the importance of insuring that any risks involved in medical interventions are assumed in an informed, voluntary fashion. The law further allows for a voluntary assumption of risk, in which case the plaintiff can waive the defendant's duty to observe a required standard of care. The notion of allowing altruistic patients to take on extra risk as research participants for the benefit of future patients has a certain appeal.

There are a number of arguments against an unlimited "appeal to liberty". The law allows for voluntary assumption of risk, but only in very limited circumstances and with limits on allowable risk. Some statutes specifically disallow the waiver of liability for negligent infliction of bodily harm. (e.g., *Civil Code of Québec*).[70] Further, defendants cannot use such a waiver to escape responsibility for the consequences of negligence unless it is unequivocally clear to all what is being waived. A consent form would have to make clear that participants were waiving their right to compensation even for negligently inflicted harm.[71]

A public policy argument can also be made that asking patients to waive physicians' professional obligations to treat, will have a negative impact upon the practice of medicine and public

[66] *Neufield* v. *McQuitty* (1979). 18 AR 271
[67] *Halushka* v. *University of Saskatchewan* (1965), 53 D.L.R. (2d) 436.
[68] *Cryderman* v. *Ringrose*, [1977] 3 W.W.R. 481 (Alta. C.A.).
[69] *Coughlin* v. *Kuntz* (1987), 17 B.C.L.R. 365; [1990] 2 W.W.R. 737.
[70] *Civil Code of Quebec*, S.Q., 1991, Articles 1474, 1477.
[71] Prosser, Keeton, *The Law of Torts*, 5th ed, W. Page Keeton, (ed) (St. Paul. Minn.: West Publishing Co, 1984)

health.[72] People do not have unlimited discretion to choose whatever medical treatment they wish. The law protects people from making certain poor choices on the theory that people are vulnerable to making such choices when it comes to health matters.[73]

The notion that patients/participants should fully understand the choice they make to enter a trial is also an ideal that is not always met. Studies demonstrate that even with good explanations of randomization many trial participants do not believe that chance is involved in their allocation. Many patients believe that they are allocated on the basis of their doctors' assessment of their individual therapeutic needs.[74]

Legal arguments are frequently made in the alternative, assuming that one line of thinking may be successful while another might fail. Suppose that an informed consent could provide legal justification for what would otherwise be considered medical negligence in leaving patients untreated. What must such a consent form contain to be truly informative, in addition to the usual description of the nature of the protocol, its risks of harm and potential benefits, and so forth?

- Must it clearly state that established effective intervention exists for the patient's condition, but that by entering the trial, there is a 50% chance that they will not receive it? And further, must prospective participants be informed that outside the trial, they could receive treatment?
- Must all of the potential disadvantages of remaining untreated, including those that are remote, be specified?
- Should participants be told that, in some circumstances, withholding treatment would be considered substandard clinical medical practice?
- Must prospective participants be told that scientific experts disagree about the necessity/desirability of a placebo trial design?
- Must they be informed, when it is the case, that the treatment under study does not offer a more effective therapy, but is a "Me Too" drug and the benefit of the study is to allow the sponsor to capture a share of the market?
- Should the consent form disclose the fact that the recruiting physician or investigator will be remunerated for participating in the trial, and if so, should the amount be disclosed?

Even if the answers to these questions are affirmative and a carefully drafted consent form provides a good legal defense to negligence, breach of fiduciary duty or professional misconduct, a moral standard that puts the health and well-being of research participants first would preclude asking them to make the compromises required by some trials.

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[72] Waring, D. and Glass, K.C., "Legal Liability for Harm to Research Participants: the Case of Placebo Controlled Trials", in New Directions in Biomedical Research: Regulation, Conflict of Interest and Liability, T. Lemmens, D. Waring (eds) (Toronto: University of Toronto Press, forthcoming)

[73] Menikov, J., *Law and Bioethics: An Introduction* (Washington, D.C.: Georgetown University Press, 2001.

[74] Applebaum, et al, False Hopes and Best Data: Consent to Research and the Therapeutic Misconception, *Hastings Center Report*, 1987; 17: 20-24; Snowdon, J., Garcia, D. and Elbourn, N., Making Sense of Randomization: Responses of Parents of Critically Ill Babies to Random Allocation of Treatment in a Clinical Trial, *Social Science and Medicine*, 1997; 45: 1337-55; Advisory Committee on Human Radiation, *The Human Radiation Experiments* (New York: Oxford University Press, 1996.

2. **A Defense of "Meeting the Standard of Care"**

Is it possible to argue that placebo-controlled trials do meet the legal standard of care, even if established effective therapy is withheld? After all, in an active control trial, half the patients, those on the experimental arm, also have established effective therapy withheld from them. Further, they are exposed to an unapproved therapy that might carry risks, including the risk that it will be ineffective for the condition under study. While the analysis in this chapter is aimed at clarifying the legal situation for placebo controlled trials, as noted above, the same legal regime that applies to clinical care also applies to clinical research, no matter the choice of control. However, for trials of new agents, there must be sufficient pre-trial information to create uncertainty about the comparative merits of each arm of the trial as the preferred intervention in a defined population.[75] Such information includes animal studies, tests on healthy volunteers, case studies or information from similar pharmacological entities. In the best judgment of those designing the trial, participants should have an equivalent opportunity to benefit no matter which arm they are in. Both placebo and active control trials that do not meet this standard might be found to be "substandard medicine" by a court, with investigators not meeting the appropriate legal standard of care.

Do participants in a placebo arm have "equivalent opportunity to benefit" from the trial as those in the active treatment arm? While there is some "weak clinical evidence" from meta-analysis to suggest that clinical trials have a positive effect on the outcome of participants, the evidence comes mainly from cancer trials, and "inferences should perhaps be restricted to such trials" (Braunholtz, Edwards, Lilford, 2001).[76] There is no evidence to support the existence of a positive effect for those on placebo in a clinical trial. Braumholz *et al.*'s meta-analysis supports the notion that randomized clinical trials are "more likely to be beneficial than harmful". This conclusion is stronger "where the experimental treatment turns out to be more effective than the control, which is difficult to predict, or where there is a pre-existing effective treatment that is included in the protocol." Such evidence does not support the notion that patients have an "equivalent opportunity to benefit" or that they will not be harmed by participating in the placebo arm of a clinical trial. Without this evidence, it would be very difficult to argue that physicians enrolling patients in placebo-controlled trials are meeting the legal standard of care.

C. **Conclusion**

The legal subcommittee has not explored all possible aspects of legal liability in placebo-controlled trials. Nor has it gone beyond the realm of physician liability. However, it does make the case that physician/investigators may have liability for harm to patients/participants who are randomized to the placebo arm of a trial. While there have been no legal claims directly on point, and it is not possible to predict whether there will be any, it is prudent to advise clinicians/investigators, institutions, Research Ethics Board members, regulators and sponsors of the potential for legal liability.

[75] Freedman, B., Equipoise and the Ethics of Clinical Research, *N Engl J Med* 1987; 317: 141-145.
[76] Braunholtz, D.A., Edwards, J.L., Lilford, R.J., "Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect", J. Clin. Epidemiol. 2001; 54(3): 217-24

6. Regulatory Perspective

Patricia Huston, Jim Wright and Vratislav Hadrava

There is resounding consensus that there is a dual imperative to conduct research that reflects both good ethics and sound science. This is reflected in the:

- *ICH guidelines*
- *Division 5 of the Food and Drug Regulations (Canada's Clinical Trial Regulations*)
- *Declaration of Helsinki*
- *Council of International Organisation for Medical Sciences (CIOMS) guidelines* and
- *Tri-Council Policy Statement*

Specifically, in regulatory guideline ICH E6 on *Good Clinical Practice*, it states:

"The rights, safety and well-being of the trial participant are the most important considerations and should prevail over interests of science and society [and] clinical trials should be scientifically sound."

And in Canada's clinical trial regulations it states that Health Canada will authorize a trial to proceed only when good clinical practices are followed and:

(a) the use of the drug for the purposes of the clinical trial will not endanger the health of a clinical trial subject or other person;
(b) the clinical trial is not contrary to the best interests of the clinical trial subjects;
(c) the objectives of the clinical trial will be achieved.

Thus, the contentious issue in the use of placebos in clinical trials is when:

- established therapy is not given for the duration of the trial; and
- the safety and well-being of the research participant is ensured.

Is it wrong to respect patient autonomy when there is no increased risk of harm? The *Tri-Council Policy Statement* suggests that even if there were no risk, it is inappropriate to give a placebo when standard treatment exists. Thus, it recommends patients' choice to join a trial be ignored even when there is no harm that could come from it. International research ethics guidelines, and ICH guidelines suggest that when there is no additional risk of harm patient autonomy can be respected, which is consistent with Canada's Charter of Human Rights. A placebo-controlled trial may be the most scientifically rigorous and efficient way to assess the safety and efficacy of a new treatment, and if it poses no increased risk of harm, it is ethical to respect a patient's informed choice whether to participate in it or not.

We believe that it is unnecessary to limit patient autonomy when a clinical trial is safe and scientifically appropriate. The placebo remains a valuable tool in the clinical research armamentarium, and can be used under specific and controlled conditions which protect the safety of all participants in a trial. Without placebos, erroneous assumptions of efficacy can

occur. An example of this was recently demonstrated for arthroscopic surgery[77] after years of practice. It was only by conducting a placebo-controlled trial that it was shown patients made the same level of improvement in both the treatment and placebo groups. The assumption that arthroscopic surgery was more effective than "nothing" would never have been disproved if a placebo-controlled trial had not been done.

The experimental drug bears all the risks associated with withholding established effective treatment, in addition to all the safety risks for potential adverse reactions. Any discussion on appropriate use of placebos in clinical research and proposed guidelines cannot be separated from parallel consideration of the experimental compound.

The objective of clinical research designed to assess the effectiveness of an experimental drug is not necessarily the same objective as a clinician wanting to know which of two marketed drugs is better. We agree that Phase IV trials should in general be active control trials in order to give clinicians direct comparative efficacy data about two treatments. But this is a much different objective than the regulators and scientists who are assessing the absolute efficacy of an experimental treatment where little to nothing is known about its safety and efficacy. It may not be possible to establish the safety and efficacy of an experimental treatment with a non-inferior active control trial. Thus, it is sometimes necessary to have a two-step process:

- establish the safety and efficacy of an experimental treatment and then,
- compare the new treatment with established effective therapy.

In this chapter we will outline some of the special considerations in early clinical drug trials of experimental treatments, and then review the *ICH E-10* guideline. We will identify the growing consensus internationally regarding appropriate placebo use in both research ethics and regulatory guidelines and identify the opportunity that Canada has to clarify and strengthen this consensus.

A. **Issues Relevant to Early Clinical Drug Trials**

Any discussion on appropriate use of placebos in clinical research and proposed guidelines cannot be separated from the parallel consideration of the experimental treatment – as there are risks involved with each. Thus, any proposed methodological, regulatory or institutional constraints on placebo use which could increase the exposure of subjects to experimental drugs should involve a careful and comprehensive risk/benefit evaluation.

The following is a list of some of the issues that guide the design and conduct of early phase drug trials:

- Risk to volunteers and/or patients must be minimized,
- The early stages of drug administration to humans involve unknown risks,
- Drugs are capable of causing both immediate and delayed serious adverse events,

[77] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Broday BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *NEJM* 2002; 347:81-87.

- First doses in humans must be very small,
- Subjects must be monitored very closely,
- The number of subjects exposed must be kept to a minimum,
- The duration of exposure must be kept to a minimum,
- Subjects with co-morbid conditions or those taking other drugs are often excluded, and
- Women who are pregnant or who are at risk of pregnancy are usually excluded.

Based on these and other issues, most Phase I trials involve 10 to 20 young healthy male volunteers studied in a hospital or specialized Phase I trial unit setting. At the end of Phase I, safety has only been established in a handful of normal healthy male volunteers and little or nothing is known about efficacy. Therefore, all of the same issues continue to apply, particularly to the Phase II trials designed to establish efficacy. Phase II trials usually involve only a small number of well-defined closely monitored patients treated for a short duration of time. Non-inferiority active control comparative trials are normally not conducted in early Phase II. A superiority active control trial may be done if withholding treatment would pose a safety risk to the research participant. However, when it is safe to do so, a placebo-controlled trial is often done to minimize the risk of experimental drug exposure.

B. **ICH E-10**

ICH E-10: Choice of a Control Group and Related Issues in Clinical Trials provides specific information on trial design with respect to establishing efficacy of investigational new drugs. It identifies that the type of trial design, and therefore the type of question that can be answered, is the defining feature in assessing a trial's ability to establish efficacy. Specifically, trial design is more important than type of control.

No general preference for giving placebos is noted in *ICH E-10*. Multiple design options are carefully considered with advantages and disadvantages of each. *ICH E-10* states very clearly in its conclusion that:

"In most cases, evidence of efficacy is most convincingly demonstrated by showing superiority to a concurrent control treatment. If a superiority trial is not feasible or is inappropriate for ethical or practical reasons, and if a defined treatment effect of the active control is regularly seen (e.g. as it is for antibiotics in most situations), a non-inferiority or equivalence trial can be used and can be persuasive."

ICH E-10 distinguishes two main types of trial design:

- ***Superiority trials*** that can answer the question: Is "A" better than "B"? and
- ***Non-inferiority trials*** that can answer the question: Is "A" not much worse than "B"?

Superiority Trials

In a superiority trial, if "A" is the investigational treatment and it is better than "B," then given that the trial is a fair comparison, evidence of efficacy with a defined level of confidence can be determined. This is true whether "B" is established effective therapy or placebo. If however, "A"

is no different than "B," then several possibilities exist and no firm conclusions can be reached. If "B" is placebo, this could be taken as sufficient evidence to abandon further development of the drug and thus limit undue exposure of subjects to an experimental treatment. *ICH E-10* promotes the use of superiority trials to establish efficacy, noting that they can be either placebo or active control trials. Active control superiority trials can offer compelling evidence of efficacy, as long as they are "fair" comparisons. Fair comparisons mean the dose of both the investigational and comparison drug should be optimal, the patient population should be appropriate, as should the selection and timing of measurement of outcomes.

Non-Inferiority Trials

In a non-inferiority trial, if "A" is the investigational drug and is found to be "not much worse" than "B," where "B" is a marketed treatment, then one can generally assume that "A" is similar to "B." These trials generally require larger number of patients than a superiority trial. Non-inferiority (sometimes called "equivalence") trials are designed when the expected result is that "A" is about the same as "B." Yet, in such a trial, a finding of similarity could be due to four (4) possible explanations:

- both drugs were equally effective,
- both drugs were equally ineffective,
- both drugs were equally harmful, and
- one drug was better than the other, but this was not demonstrated.

When multiple explanations are possible, one has less confidence in the conclusion that "A" is effective and equal to "B." It may be surprising that an established treatment could be ineffective or harmful in a trial. This can happen due to a number of circumstances. As noted earlier, some treatments like arthroscopy get established in clinical practice before they have been tested for efficacy by a randomized placebo-controlled trial. It is also possible that some treatments, such as anti-depressants, may have variable effectiveness, so will show a significant benefit in some trials, and not in others.[78] Finally, some drugs that are marketed for one thing may be used "off label" for something else. This was the case with the CAST trial, where anti-arrhythmics approved for uncomplicated arrythmias were being commonly used to suppress premature ventricular contractions post-myocardial infarction. When a new anti-arrhythmic medication was compared with what has become the "established treatment", flecainide and encainide, and a placebo in a randomized controlled trial, it was discovered that flecainide and encainide increased mortality as compared to placebo[79]

Therefore active control non-inferiority trials only give good evidence of efficacy when other possible explanations can be ruled out. *ICH E-10 Guidelines* identify the features of active control non-inferiority trials that give compelling evidence of efficacy. To state it simply, to assume that similarity means both treatments are effective, one must be pretty sure that

[78] Walsh BT, Seidman SN, Sysko R, Gould M. Placebo Response in Studies of Major Depression: Variable, Substantial, and Growing. *JAMA* 2002; 287:1840-1847.
[79] The Cardiac Arrhythmia Suppression Trail (CAST) Investigator. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *NEJM* 1989; 321:406-412

established treatment has a consistent treatment effect, which has been established by more than one trial, and those trials are similar to the proposed active control trial.

C. Common Features of International Research Ethics and Regulatory Guidelines

There has been growing international consensus regarding what constitutes appropriate placebo use. Changes have been made to the placebo policy in two international research ethics guidelines: the *Declaration of Helsinki* from the *World Medical Association* and the *Council of International Organizations for Medical Sciences (CIOMS)* international research ethics guidelines from the *World Health Organization (WHO).* These changes have made them consistent with *ICH* guidelines.

There are three common features between the *CIOMS* guidelines, the *Declaration of Helsinki*, and *ICH E-10*:

1. *All guidelines note that active control trials are preferable in some circumstances*. *CIOMS* and the *Declaration of Helsinki* begin with the general rule that active control trials are preferable when there is an established effective intervention. *ICH E-10* notes a preference for superiority trials, which includes active control superiority trials.

2. *All guidelines suggest or specify that active control trials are unreliable in other circumstances.* One of the most important revisions to both the *Declaration of Helsinki* and the *CIOMS* guidelines is the explicit acknowledgment that active control trials are more likely to lead to incorrect conclusions. This respects the first principle that there is a dual imperative for research to be both ethically and scientifically sound before it is acceptable. People should not be asked to participate in inconclusive research.

3. *All suggest or specify that placebos can be used when it involves withholding proven treatment if there is no increased risk of harm.* All international guidelines are concerned about the rights, safety and well-being of the research participant. There is also an acknowledgment that there are risks in clinical research because it involves uncertainty. There are no guarantees of good outcome from either standard or experimental treatments. What is important is that known unacceptable risks such as serious harm are disallowed, and uncertain risks are minimized and mitigated by the choice of participants, the duration of the trial, and the safety features built into the trial.

D. The Ethical Basis for International Research Ethics and Regulatory Guidelines

The ethical basis for international research ethics and regulatory guidelines is founded on the ethical principles of minimizing harm and respecting autonomy and meeting the duty of care.

Minimize harm

As noted, placebos are not used when there is a risk of serious harm, such as when testing cancer treatments, human immunodeficiency virus (HIV) treatments, serious infections, etc. What is important is not only that serious harm is disallowed, but also that all potential risks are considered and minimized. No international regulatory or research ethics guidelines that include specific instances where it is appropriate to give placebo in the context of established effective therapy support an undue risk or sacrifice of a few individuals for the good of the majority. Every detail of the trial is examined to see how safety can be optimized and risk minimized, while maintaining the scientific integrity of the trial. This includes:

- examination of the inclusion/exclusion criteria to ensure no high risk patients are exposed,
- assessment of the number of patients in the trial and its length,
- close monitoring of patient progress, the establishment of stopping rules or criteria for discontinuation from the study,
- follow-up protocols and consideration of the need for a data safety or efficacy monitoring board.

There are situations when placebo control trials would decrease the exposure of large numbers of people to experimental treatment and possible serious harm as would occur in non-inferiority active control trials.

Respect Autonomy

International research ethics and regulatory guidelines assert that under the proper conditions, placebo use is consistent with respecting the rights, safety and well-being of the research participant. It also suggests that the patient should determine, to some degree, what is in his or her best interests. This does not mean that informed consent can make any or all risks acceptable. It does mean that after unacceptable risks have been eliminated and reasonable risks minimized, individual choice, based on accurate and complete information, should be respected. It acknowledges that a patient's best interest may include a willingness to assume a reasonable risk for the benefit of others.

Meet the duty of care

The moral obligation of a physician is to care for his/her patients. Pharmacotherapy is an important, but many times not the only, therapeutic option. Adequate treatment does not necessarily mean prescribing medication on the first patient visit. Prescribing an effective established treatment should be the result of a mutual decision based on the therapeutic alliance established between the patient and the clinician. Therefore, temporary withholding of the established effective treatment may be considered ethical, and not breaching the physician's duty of care when:

- the therapeutic alliance is maintained,
- the patient is not exposed to unreasonable risk,
- the patient provides his/her informed consent,

- the patient knows established effective treatment is an option that can be given instead of trial participation,
- the patient can stop their participation in the trial at any time and receive established effective treatment,
- the trial methodology minimizes the risk of withholding such treatment and any other risks associated with the experimental drug.

In essence, the duty of care in clinical trials is met by following Good Clinical Practice guidelines which include ensuring the rights, safety and well-being of each and every research participant.

E. Recommendation: Be Consistent with International Guidelines

Clinical research often occurs in multi-centre trials in an international context. The quality of evidence arising from these trials is critical for patients, physicians, researchers, research ethics boards, the pharmaceutical industry and regulators. It is important that there be consistency in the rules concerning placebo-controlled trials to ensure the safety and protection of research participants. Such consistency will strengthen the ability to enforce these rules and prevent abuses in local, national and international contexts.

It is important that a common placebo policy in Canada be consistent with international guidelines. The greater the clarity and international consistency regarding what is appropriate placebo use, the more likely that potential abuses of placebos can be identified and stopped.

If Canada stands alone in maintaining a different and possibly more restrictive research ethics view of placebos, this could:

- limit the number of placebo-controlled clinical trials performed in Canada,
- decrease the clinical research conducted in Canada,
- place regulatory authorities in a difficult situation with respect to considering evidence from placebo-controlled trials from other countries that met international research ethics standards, but not Canadian standards, and
- decrease access of Canadians to new treatments, which are available in other countries

Canadian guidelines should be based and built upon international guidelines. This would ensure continued participation of the Canadian public and health professionals in international research. And it would utilize this important opportunity to clarify and strengthen the international consensus on appropriate placebo use.

Table 6.1: Comparison of Guidelines for placebo use from various sources (CIOMS, *Declaration of Helsinki* (DOH), *ICH E-10* and *Tri-Council Policy Statement*).

CIOMS	DOH	*ICH E-10*	*Tri-Council Policy Statement*
As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention.	**Consistent with DOH**: "The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current...therapeutic methods."	**Consistent with *ICH E-10*** "Evidence of efficacy is most convincingly demonstrated by showing superiority to a concurrent control treatment. If a superiority trial is not feasible... and if a defined treatment effect of the active control is regularly seen... a non-inferiority...trial can be used."	**Consistent with *Tri-Council Policy Statement*** - *Tri-Council Policy Statement* states the inverse: "placebo... generally unacceptable when standard therapies...are available".
In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or "no treatment".	**Consistent with DOH** Clarification states: "A placebo-controlled trial may be ethically acceptable, even if proven therapy is available under the following circumstances."	**Consistent with *ICH E-10*** "Whether a particular placebo-controlled trial is ethical may... depend ...on the particular circumstances of the trial."	**Consistent with *Tri-Council Policy Statement*:** "a placebo may be used as the control treatment in a clinical trial in the following circumstances"
Placebo may be used: - when there is no established effective intervention	**Consistent with DOH** "This does not exclude the use of placebo... in studies where no proven... therapeutic method exists."	**Possibly consistent with *ICH E-10*** Notes the inverse: "In cases where an available treatment is known to prevent serious harm... it is generally inappropriate to use a placebo control."	**Consistent with and expanded in *Tri-Council Policy Statement*:** a) no standard treatment b) standard therapy has been shown to be no better than placebo c) evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy d) In a population of patients who are refractory to standard treatment (no effective treatment)

CIOMS	DOH	*ICH E-10*	*Tri-Council Policy Statement*
Placebo may be used: - when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms;	**Consistent with DOH** Clarification states: "placebo-controlled trial my be ethically acceptable... where a... therapeutic method is being investigated for a minor condition... and the patients will not be subject to any additional risk of serious or irreversible harm."	**Consistent with *ICH E-10*** ICH states: "When there is no serious harm, it is generally considered ethical to ask participants to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment."	**Inconsistent with Tri-Council Policy Statement**: *Tri-Council Policy Statement* states: "Use is permitted...[when] patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy would not lead to undue suffering or the possibility of irreversible harm of any magnitude"
Placebo may be used: when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.	**Consistent with DOH** Clarification states: "Where for compelling and scientifically sound methodologic reasons its use is necessary to determine the efficacy or safety of a... therapeutic method... All other provisions of the *Declaration of Helsinki* must be adhered to."	**Consistent with *ICH E-10*** ICH is more specific in identifying when an active comparator would not yield scientifically reliable results (unfair comparison, or threats to validity of non-inferiority trials) noting acceptable when "withholding or delaying treatment will not result in harm". "There are occasional exceptions, however, such as cases in which standard therapy has toxicity so severe that many patients have refused to receive it".	**Inconsistent with *Tri-Council Policy Statement***: Not accepted as an exception in *Tri-Council Policy Statement*.

7. Research Ethics Board Perspective

John Fisk and Heather Sampson

A. Introduction

The response to the public consultation process was clear in identifying the Research Ethics Board as a crucial component of an accountable and trustworthy national system of research review that has the responsibility of balancing the principles of patient protection and autonomy.

In order to fulfill this mandate, Research Ethics Boards must ensure that placebo-controlled trials involving a new therapeutic device, agent or method in Canada are reviewed by individuals without conflict of interest and that they meet the requirements of scientific merit and ethical acceptability.[80] Regardless of the setting in which a placebo-controlled trial is conducted within Canada, this review process must be based on the application of consistent scientific and ethical principles.[81]

All placebo-controlled trials conducted in Canada must be reviewed and approved by a Research Ethics Board that employs those scientific and ethical principles which represent a Canadian national standard for the review of such trials. Consistency in the application of scientific and ethical principles by Research Ethics Boards requires that they:

- are appropriately constituted,
- are free of conflicts of interest
- have the resources necessary to conduct their activities,
- have access to all information that is relevant for their deliberations, and
- have clearly articulated the scientific and ethical principles that they employ in their review of placebo-controlled trials.

B. Areas of Concern

1. Inconsistencies in Standards for Protocol Review

Inconsistencies in decisions regarding protocol approval among Research Ethics Boards, and between Research Ethics Boards and Health Canada, may exist, in part, because of their use of different guidelines or standards for review.[82] The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Tri-Council Policy Statement)* was published in 1998 as a joint policy statement of the Medical Research Council (now CIHR), Social Sciences and Humanities Research Council and the National Sciences and Engineering Research Council, and compliance with this policy statement is required for all individuals and institutions who receive

[80] Beauchamp, T.L., Childress, J.F., *Principles of Biomedical Ethics*, fifth edition , Oxford University Press, 2001; Foster, Claire, *The Ethics of Medical Research on Humans*, Cambridge University Press, 2001

[81] Weijer, C., Dickens, B., Meslin, E., Bioethics for clinicians:10.Research Ethics *CMAJ* 1997;157(8) 1153-1157; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report* (Washington, DC: DHEW Publications OS 78-0012, 1978)

[82] Editorial, How Consumers Can and Should Improve Clinical Trials. *Lancet*; 2002, 357: 1721; Zlotnik Shaul, Randi Reviewing the reviewers: the vague accountability of research ethics committees, *Critical Care* 2002; 6: 121-122

funding from these agencies. Nevertheless, the *Tri-Council Policy Statement* does not represent a national standard for the review of all placebo-controlled trials.

While most Canadian academic centres employ the *Tri-Council Policy Statement*, Research Ethics Boards that are used by industry sponsors for the review of studies conducted outside of academic institutions are not required to do so. Health Canada and the pharmaceutical industry are most concerned that studies meet the *International Conference on Harmonisation (ICH)* standards which have been established as a joint regulatory/industry project. Their purpose was to "improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States, in order to facilitate the availability of these products to patients."[83] As a result, the standards employed in the review of trials conducted outside of academic centres are most often those of *ICH E-10*.

2. Patchwork of Research Governance

The research ethics review process in Canada is a fragmented one in which academic institutions, government agencies, and industries operate in relative isolation. This issue has been discussed extensively in previous Canadian national reviews of research governance and in reviews by other countries as well.[84, 85] As a result of the "patchwork" of research governance and different standards for the review of clinical trials, the sponsors of trials and the researchers who conduct them may incur the expense of meeting varied requirements for the preparation and submission of study protocols for review.[86] Research Ethics Boards and/or their host institutions also seem to be very reluctant to establish reciprocity agreements with other Research Ethics Boards/institutions.[87] This reluctance may, in part, reflect concerns about potential exposure to legal liability if the same standards of review are not applied at other institutions.[88] The process of open, transparent knowledge-sharing between Research Ethics Boards would facilitate study protocol reviews and potentially increase both patient safety and Research Ethics Board efficiency. At present, there exists no formalized mechanism by which REBs can determine whether a study protocol under their consideration is, or has been, reviewed elsewhere in Canada. While such information could benefit Research Ethics Boards, until such time as there is a clear national standard for the review of all human research in Canada and a governance framework to support this, the benefits of information sharing between Research Ethics Boards will be limited. The *Tri-Council Policy Statement* provides the policy framework for the ethical review of research involving humans at most, if not all, academic institutions in Canada. Given the extensive development process of the *Tri-Council Policy Statement* and its attempts at inclusiveness for all types of human research, it seems an appropriate basis for developing a national standard for the review of all placebo-controlled trials conducted in Canada.

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[83] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sop_ich_e.pdf, Page 6

[84] Cave, E., Holm, S., New governance arrangements for research ethics committees: is facilitating research achieved at the cost of participants' interest *J Med Ethics* 2002; 28:318-321,

[85] http://www.lcc.gc.ca/en/themes/gr/hrish/macdonald/macdonald_main.asp

[86] Bevan, Joan C., Towards the Regulation of Research Ethics Boards, *Can J Anesth* 2002; 4(9): 900-906; Beauchamp, T., IOM Report on the System for Protecting human Research Participants, *Kennedy Institute of Ethics Journal*, 2002; 12(4): 389-390

[87] Ashcroft, R., Pffeffer, N., *Ethics behind closed doors: Do research ethics committees need secrecy?* BMJ 2001; 332:1294-6

[88] Ferris, L.E., Industry-sponsored pharmaceutical trials and research ethics boards: Are they cloaked in too much secrecy?, *CMAJ*, 2002; 166(10): 1279-1280; Foster, Claire, *The Ethics of Medical Research on Humans*, Cambridge University Press, 2001

The Interagency Advisory Panel on Research Ethics (PRE) was established with a stewardship mandate for the *Tri-Council Policy Statement.* The mandate includes "responsibilities for its evolution and interpretation, educational implications, and its promotion and implementation".[89] It provides opportunities for the *Tri-Council Policy Statement* to be responsive to both national and international developments in the science and ethics of clinical trial design, treatment availability, and placebo use.

Currently, the *Tri-Council Policy Statement* recognizes that "investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals should also generally respect the *ICH Guidelines.*"[90] Furthermore, the "adoption, implementation and maintenance of *ICH* products" by Health Canada allows for the use of an addendum if Health Canada "or industry/stakeholders consider that the guidance lacks some clarity and/or sufficient detail."[91] Thus, it is within the jurisdiction of Health Canada to implement the *Tri-Council Policy Statement* in its current form or in a revised form as the policy framework for the review of placebo-controlled clinical trials in Canada. This would represent an important step in ensuring consistency in the standards of Research Ethics Board review of all human research in Canada and, in particular, of the review of placebo-controlled trials.

3. Presumed Necessity for Conduct of Placebo-Controlled Trials

The goal of industry-sponsored research is to achieve regulatory approval for their product in the most cost-effective manner. If regulatory approval requires demonstration of absolute efficacy, a placebo-controlled trial may be the most cost-effective means of doing so. One cannot reasonably expect that any study sponsors will engage in activities beyond those required of them unless there is obvious benefit to them. Thus, the placebo-controlled trial will often be the first and preferred option of researchers.

Unfortunately, what is often communicated to Research Ethics Boards is a presumption on the part of investigators/sponsors that placebo-controlled trials are necessary in order to provide a demonstration of efficacy that will meet regulatory requirements for approval. While this is not explicitly stated in the Canadian *Food and Drugs Act*, *ICH-E10* implies that a placebo-controlled trial is the preferred means of establishing absolute efficacy of a new therapy. Health Canada endorses many of the ICH guidelines although *ICH E-10* has not yet been formally adopted, pending the outcome of the current National Placebo Initiative. Nevertheless, as ICH represents international regulatory and industry standards, and since Health Canada is not in the practice of providing specific guidance regarding study design to investigators, a presumed necessity for the conduct of placebo-controlled trials in order to obtain regulatory approval of new products appears to have developed. From the perspective of Research Ethics Boards that are charged with reviewing study protocols, there often appears to be a lack of consideration for the relative scientific and ethical merits of alternative study designs in Research Ethics Board submissions.

The presumed regulatory requirement that absolute efficacy be demonstrated via a placebo-controlled trial seems to have also been interpreted by some investigators as implying that no further scientific/ethical justification of the trial design is required in the study protocols that are

[89] http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm, June 4, 2002
[90] *Tri-Council Policy Statement*, pg. 7.3
[91] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sop_ich_e.pdf, Page 9.

submitted to Research Ethics Boards. Research Ethics Boards reviewing such study protocols are often frustrated by lack of scientific and/or ethical justification of the use of a placebo comparator since this information is critical to their decision-making process.

Local investigators for multi-centre trials and many Research Ethics Board members may be uncertain of the regulatory requirements of Health Canada, thereby making informed discussion of these issues difficult. In particular, Research Ethics Boards have not been provided with information regarding the conditions under which active control, noninferiority trials can or cannot be considered sufficient evidence of efficacy to support the objective of the trial. Failure of Health Canada to adequately describe the regulatory requirements and their scientific review process to Research Ethics Boards means that the Research Ethics Boards members may view the regulatory review process as either irrelevant to their considerations or at odds with the issue of research ethics review.

4. Lack of Adequate Information in Research Ethics Board Submissions

As a background to the scientific and ethical justification of the trial design, comprehensive reviews of the new investigational therapy and of current established effective therapies (if any) are necessary for informed decision-making by Research Ethics Boards. This need, and the frequent lack of such information in Research Ethics Board submissions, was raised numerous times throughout the National Conference on the Appropriate Use of Placebos in Clinical Trials.[92] Although the *Tri-Council Policy Statement* currently requires that "patients or authorised third parties are fully informed about … the reasons why investigators deem a placebo-controlled trial to be necessary" these arguments are rarely presented in sufficient detail to the Research Ethics Board, let alone to the potential subject.[93]

A comprehensive review of the evidence on the efficacy of current established effective therapies for the condition under study is necessary in order to justify the selection of the comparator (placebo vs. active control) as well as the study design (superiority, equivalence, noninferiority). The conduct of systematic reviews is beyond the financial resources of local Research Ethics Boards and requirements for them to conduct such reviews would be likely to contribute to, rather than reduce, inconsistencies between them in their decision-making. When study protocols fail to provide comprehensive reviews of the investigational and established effective therapies, Research Ethics Boards are left to base their discussions on the personal knowledge of members. The issues are complex from a medical and scientific perspective and can lead to potential oversights in the deliberations regarding trial design options and the informed consent process. One example of the latter could be the failure to inform subjects in a placebo-controlled trial that they may be precluded from receiving specific approved treatments in the event of unforeseen future medical events (due to potential drug interactions) if they are in the treatment arm of the trial, but that if they are in the placebo arm, such treatments could be made available if the study code is broken.

[92] http://www.cihr-irsc.gc.ca/e/19301.html

[93] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sop_ich_e.pdf, Page 9.; Bernstein, M., Upshur, R.E.G., Framework for bioethical assessment of an article on therapy, J. Neurosurg 2003; 98:485-490

It is recognized that the introduction of a policy requiring sponsors and investigators to provide such reviews to Research Ethics Boards would have costs associated with it.[94] However, maintaining up-to-date systematic reviews of available treatments for patient populations of interest seems a necessary part of the development of new therapies and should ultimately be a cost-effective process for industry, regulators, and other sponsors. From the standpoint of the Research Ethics Board members who are reviewing a specific study protocol, a systematic review need not be an exhaustive compilation of all data on all available treatments for a given condition or of all published and unpublished studies of a given treatment. Rather, what is needed is an explicit justification of the study design, including the comparator being used, based on a thorough examination of the relevant available evidence, and conducted in a manner that is well described and reproducible.

Requests from Research Ethics Boards for more detailed information can be problematic if the local investigators for multi-centre studies lack the scientific or ethical expertise to adequately articulate a justification of the study design when asked to do so.[95] If sponsors of multicentre studies do not anticipate the need to prepare such documentation, responding to requests from individual Research Ethics Boards can be time consuming.

The potential human resource costs to sponsors of preparing such responses on a case-by-case basis may be sufficiently high to result in the withdrawal of study protocols from centres in which Research Ethics Boards make such requests. This in turn will undermine consistency in the research ethics review process and lead to inequitable distribution of the risks and benefits of research participation across Canada. Development of a national governance framework for human research in Canada that will require scientific and ethical justification of the trial design in all study protocol submissions to both Health Canada and Canadian Research Ethics Boards seems reasonable.

ICH E-10 clearly articulates the scientific and ethical issues regarding selection of a comparator in clinical trials. The same explicit requirement for scientific and ethical justification of placebo-controlled trials should be more clearly stated in the *Tri-Council Policy Statement* as well if it is to serve as the policy framework for the ethical review of placebo-controlled trials in Canada. It could be argued that this is implied in the *Tri-Council Policy Statement* statements regarding the:

- need to provide such information to potential subjects,
- need for "clinical equipoise" at the start of a trial, and
- basic requirement of scientific validity in all studies.

However, reaffirming this requirement explicitly in the context of clinical trials (*Tri-Council Policy Statement*, Section 7) seems warranted since such information is rarely provided in sufficient detail to Research Ethics Boards.

[94] Weijer, Charles, Continuing review of research approved by Canadian research ethics boards, *CMAJ*, 2001; 164 (9): 1305-1306

[95] Silverman, H., Hull, S.C., Sugarman, J., Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med* 2001; 29(2):235-41

C. Consideration of a Central Review Process for Clinical Trials

The development of national or regionally-based Research Ethics Boards focused on multi-centre trials for specific health conditions has a number of potential advantages, not limited to the context of placebo-controlled trials, that warrant consideration. Research Ethics Boards with a broader geographical mandate should not replace the role of the local Research Ethics Board that must ensure that issues of local concern are addressed. However, national or regional Research Ethics Boards may provide a number of advantages, including greater opportunity for the participation of patients, patient advocates, and other citizens. The experience of regional Research Ethics Boards that are currently being developed in Canada should be examined, as well as the experiences of regional Research Ethics Boards in other countries. In particular, the potential that such a process could simply add an unnecessary layer of bureaucracy and impede, rather than facilitate, the research process must be examined carefully.[96]

1. Multi-Centre Trials

The "central review" of clinical trials by provincial or national affiliations of institutions has recently been developing as an approach to research ethics review in Canada. If organized properly, this process should facilitate, but not replace or impede, the review of protocols at the local Research Ethics Board level[97,] A responsibility of the local Research Ethics Board is the reflection of local community values and this cannot be abdicated to a "central" Research Ethics Board. It is possible that a regional or national review process could be viewed with skepticism by some Research Ethics Boards at large academic institutions. Others however, particularly those at smaller centres, might welcome a "central" review of multi-centre trials that provide a thorough evaluation of the scientific validity of the study and the ethical justification of a placebo as comparator.

The effectiveness of any central review process will depend on ensuring adherence to a national standard for Research Ethics Board composition and review, including freedom from conflicts of interest. Since it necessarily adds a layer of bureaucracy, central review must have a "value-added" component that would address explicit needs of the local Research Ethics Boards, such as allowing for an expedited review process at the local Research Ethics Board level. For a variety of conditions (e.g. cancer, HIV/AIDS, heart disease and stroke, Alzheimer's disease, multiple sclerosis, diabetes, mental health, and others) partnerships between the central Research Ethics Board, relevant non-governmental organizations, and possibly governmental research funding agencies as well, might be feasible. Such partnerships could provide the best means of having a national perspective on difficult scientific and ethical issues such as the accepted standard of care, the efficacy of available treatments, and the implications of treatment refusal for a given condition.

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[96] Beauchamp, T., IOM Report on the System for Protecting human Research Participants, *Kennedy Institute of Ethics Journal*, 2002; 12(4): 389-390; NHS Executive. *Ethics committee review of multi-centre research, HSG(97)23. London: NHS Executive, April 1997*

[97] http://www.corec.org.uk Central Office for Research Ethics Committees, National Health Service, 1998; http://www.ncicirb.org The Central Institutional Review Board (CIRB) Initiative is a pilot project sponsored by the National Cancer Institute (NCI), in consultation with the DHHS Office of Human Subjects Protections (OHRP).

2. Patient Perspectives

Another important potential of a central Research Ethics Board would be the opportunity to include the perspective of patients and/or their advocates in the review process.[98] While such input was clearly called for in the response to the public consultation process, it is not feasible for most local Research Ethics Boards which will typically review studies involving a wide range of patient groups. Local Research Ethics Board members may have a very limited knowledge of a particular medical condition and its personal consequences. As such, arriving at a consensus opinion about the scientific justification and ethical acceptability of a study can be very difficult.[99] For example, the conditions under which a person with terminal cancer and a person with their first episode of psychosis can make an informed decision about participation in a placebo-controlled study of a new investigational drug can differ dramatically.[100]

Even within specific patient populations, the conditions under which informed decision-making is possible may vary significantly (e.g. early versus late stage Alzheimer's disease) and the perspectives of patients and their representatives could facilitate the decision-making of the Research Ethics Boards. Expecting consistency in local Research Ethics Board review of protocols that deal with diverse issues encountered on an infrequent basis may be asking too much. However, one must also recognize a contrasting potential problem facing local Research Ethics Boards: that regular exposure to a specific patient population and specific trial designs may lead to a narrowing of their perspective on the ethical concerns in studies with this population. While this latter issue would also apply to the central review of studies, processes that ensure regular turnover of both Research Ethics Board membership and patient/advocate representation could reduce the likelihood of this occurring.

Despite the goal of improving opportunities for specific patient groups or their advocates to participate in research review through a centralized process, Non-Governmental Organisations may be unwilling to take on the potential legal liability and the costs of insurance for participation. Moreover, well-organized patient and/or patient advocacy groups with national representation are not common. Thus, securing appropriate representation of consumer perspectives on a majority of national multi-centre trials will not be a simple process even if central Research Ethics Boards are established. Nonetheless, obtaining such representation at the local Research Ethics Board level is already problematic and the potential for having relevant patient, advocate and citizen representation in the research ethics review process may be greatest with a central process.

3. Credibility of Central Review Process

The potential problems arising from a central review process must also be recognized. In particular, ensuring the credibility of this process is essential if it is to be effective and the absence of conflicts of interest between those designing/funding the studies and those reviewing them must be assured. Local Research Ethics Boards are unlikely to accept the opinions of a central review unless it is clear that the central review has been conducted:

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[98] Editorial, How Consumers Can and Should Improve Clinical Trials. *Lancet*; 2002, 357: 1721

[99] Weijer, C, Shapiro, S., Fuks, A., Glass, KC., Scrutkowska, M., Monitoring Clinical Research: an Obligation Unfulfilled, *CMAJ*, 1995; 152: 1973-80; Zlotnik Shaul, Randi Reviewing the reviewers: the vague accountability of research ethics committees, *Critical Care* 2002; 6: 121-122

[100] Ferguson, P.R., Patients' perceptions of information provided in clinical trials. *J Med Ethics* 2002; 28: 45-48

- in accordance with common standards,
- by individuals who are free from conflicts of interest, and
- by individuals who are knowledgeable of the specific topic addressed by the study.

Without such assurances, local Research Ethics Boards may in fact be even more skeptical of protocols approved by a centralized process and be biased against accepting the recommendations of a central Research Ethics Board. If this were to happen, the result would be a delayed, rather than a facilitated, research review process. Once again, open and transparent communication and knowledge-sharing between Research Ethics Boards will be essential. Any centralized review process will require formal "feedback loops" that ensure the central Research Ethics Board is aware of and responsive to local Research Ethics Board deliberations and concerns.

D. **Recommendations**

1. A national governance framework should be established for Research Ethics Boards in Canada.

The establishment of a national governance framework would facilitate consistency in the scientific and ethical review of placebo-controlled trials for all Canadian Research Ethics Boards. This governance framework, through a process of accreditation, could ensure that Research Ethics Boards reviewing placebo-controlled trials:

- have procedures in place to ensure that the review process is free of conflicts of interest,
- are constituted with a membership that provides appropriate scientific and ethical expertise,
- have the resources necessary to conduct their review process, and
- have formal processes in place for knowledge-sharing with other Research Ethics Boards, and
- operate through a process that applies those scientific and ethical principles that reflect the current national standard for the review of placebo-controlled trials.

2. Clearly stated information regarding the regulatory approval process should be published and widely disseminated by Health Canada.

The Research Ethics Board review process would benefit from the availability of such information. Barriers in the communication between Research Ethics Boards and Health Canada with respect to the review of placebo-controlled trials must be eliminated in order to ensure consistency in the principles for determining the scientific validity of a study design between Canadian Research Ethics Boards and Health Canada. The process of Health Canada's regulatory approval of new therapeutic products is in many respects separate from the Research Ethics Board approval process. However, Health Canada requires that all placebo-controlled trials conducted in Canada have Research Ethics Board approval, and both Health Canada's regulatory approval process and the Research Ethics Board review process require that clinical trials be scientifically valid. As the regulatory body, dissemination of information regarding the regulatory process is the mandate of Health Canada. However, with the development of a national governance framework for research ethics review, a single integrated package of

information describing the framework of regulatory and ethical review in Canada could also be developed.

3. Studies submitted for Research Ethics Board review must include comprehensive reviews of available information regarding *both the new therapy under investigation and other available treatments for the condition under study* in order to provide both scientific and ethical justification for the study design.

This information must be made available to Research Ethics Boards. Consistency in the Research Ethics Board review process for placebo-controlled trials requires that they have all of the information necessary to determine that the study design is scientifically valid and that the use of a placebo is ethically justified. The study design (superiority, equivalence, non-inferiority) and the choice of a comparator (active control, placebo) must be justified on both scientific and ethical grounds.

The present requirements that industry sponsors provide all relevant information regarding the new therapy under investigation should be retained. This, however, does not necessarily provide scientific or ethical justification of the use of a placebo as a comparator in the study design. Providing a thorough, systematically conducted review of other available therapies for the condition under study requires additional efforts on the part of investigators beyond current requirements and it is difficult for Research Ethics Boards to implement such a requirement on an individual basis. One mechanism by which this could be achieved would be the establishment of a policy by Health Canada requiring that the above information be included in all Clinical Trial Applications, which currently must be filed with Health Canada prior to initiation of any clinical trials. This same information could then also be required for all Research Ethics Board submissions. This recommendation is made with the recognition of the limitations of publicly available information on clinical trial results that can exist due to the publication bias against negative study results and the proprietary nature of industry-sponsored trial results.[101] However, release of unpublished study results to researchers by regulatory agencies is possible in other countries and may become a possibility in Canada. Analyses of such data clearly have the potential to inform debate about the use of placebos and we would concur with the opinion of Khan and colleagues, who conducted one such analysis, that: "the risks of placebo treatment do warrant the serious considerations they have received. The elimination of placebo controls calls for serious consideration as well. It is in the public interest for both matters to be informed not only by broad ethical and scientific principles but also by the available data."[102]

4. In an effort to improve consistency in the Research Ethics Board review process for placebo-controlled trials in Canada, consideration should be given to the development of national or regionally based Research Ethics Boards focused on multi-centre trials for specific health conditions.

[101] Ferguson, D., Glass, K.C., Waring, D., Shapiro, S., Turning a Blind Eye: the Success of Blinding Reported in a Sample of Randomised, Placebo Controlled Trials, *BMJ, BMJ,doi:10.1136/bmj.37952.631667.EE(published January 22, 2004)*

[102] (A. Khan, S. Khan and W.A. Brown "Are placebo controls necessary to test new antidepressants and anxiolytics?" International Journal of Neuropsychopharmacology (2002) 5: 193-197.).

Research Ethics Boards with a broad geographical mandate should not replace the role of the local Research Ethics Board that must ensure that issues of local concern are addressed. However national or regional Research Ethics Boards may provide a number of advantages including greater opportunity for participation of patients, patient advocates and other citizens. The experience of regional Research Ethics Boards that are currently being developed in Canada should be examined as well as the experiences of regional Research Ethics Boards in other countries. The potential that such a process could add an unnecessary layer of bureaucracy and impede the research process must be examined carefully.

5. A Canadian national formulary should be developed.

This recommendation has broad jurisdictional (i.e. federal/provincial) and economic implications for health care provision that go well beyond the issue of placebo-controlled trials and health research in general. Feedback to the previous draft report produced skepticism that this recommendation could be implemented and concerns that the inherent difficulties in implementing it would be an impediment to the implementation of other recommendations. However, we felt that this recommendation would fulfill the need of eliminating inconsistent access to approved therapies across jurisdictions, an issue that has implications which are clearly within the mandate of the National Placebo Working Committee. We also felt that the difficulties in implementing this recommendation do not affect our other recommendations.

Debate about the ethical acceptability of the use of a placebo comparator in a clinical trial often revolves around the availability of established effective therapies for the condition under study. When such therapies are available to some but not all members of the population due to high cost, the acceptability of offering those people who cannot afford the established effective therapy enrolment in a placebo-controlled trial of a new therapy can be a subject of considerable ethical debate.

This is a difficult ethical issue and is one that is most often discussed in the context of international studies. However, inconsistencies between Canadian provinces in access to approved therapies because of the costs to the individual, can provide similar situations within Canada. A Canadian national formulary could eliminate these inconsistencies. This, in turn, would provide more consistency in the ethical issues that Research Ethics Boards must consider when reviewing the acceptability of placebo-controlled trials that are taking place at multiple centres across Canada.

6. An Educational Guidance Document on the issues surrounding placebo-controlled clinical trials should be developed for Research Ethics Boards.

As the Interagency Advisory Panel on Research Ethics (PRE) has a stewardship mandate for the TCPS that includes "responsibilities for its evolution and interpretation, educational implications, and its promotion and implementation."[103] PRE, with the assistance of Health Canada, should prepare a guidance document for dissemination to all Canadian Research Ethics Boards for their use in the evaluation of clinical trials. This guidance document should identify the key questions to be asked by Research Ethics Boards in their evaluation of the scientific merit and ethical acceptability of clinical trials and should incorporate both international and national standards.

[103] http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm, June 4, 2002

While a "decision tree" approach such as that presented in *ICH E-10* would be difficult to implement, a set of common questions to be applied to placebo-controlled studies could be developed. An expectation of "right or wrong" answers to the questions would be overly simplistic. Nevertheless, ensuring that each is considered in the review process could establish the expectation that decisions will be based on common sets of information and the rationale for the decision could be clearly articulated to others.

7. The Interagency Advisory Panel on Research Ethics (PRE) should consider revisions to Section 7 of the *Tri-Council Policy Statement: Ethical Research Involving Human Subjects* that will facilitate its implementation as a Canadian amendment to *ICH E-10* by Health Canada.

Such a revision would address some of the interpretative difficulties posed by the current wording and position the *Tri-Council Policy Statement* as a potential policy framework for use in the review of all placebo-controlled trials conducted within Canada. The *Tri-Council Policy Statement*, presently under the stewardship of PRE provides a policy framework that can be applied to the scientific and ethical review of all human research in Canada, including those studies involving the use of placebos. However, at present, there is no requirement for the use of this framework outside of institutions that receive funding from CIHR, Social Sciences and Humanities Research Council of Canada (SSHRC) and Natural Sciences and Engineering Research Council of Canada (NSERC). As a basis for the development of a Canadian national policy on the review of placebo-controlled trials, the *Tri-Council Policy Statement* seems most viable since it represents a broad national perspective on research ethics as well as the required standard for ethical review at most Canadian academic centres, and since it has an established oversight body whose mandate includes updating the policies in accordance with changes in national and international ethical standards.

It is well recognized that extensive efforts have been devoted to the development of the *Tri-Council Policy Statement*. It is clear however that there is at least some dissatisfaction with current wording of Section 7. Indeed, the perceived discrepancies between the wording of *Tri-Council Policy Statement*, Section 7 and *ICH E-10* were at least part of the rationale for the formation of the National Placebo Working Committee. Differences in these documents are to be expected since *ICH E-10* and the *Tri-Council Policy Statement* represent differing viewpoints (industry/regulators, scientists/ethicists) and have different applications (harmonisation of international regulatory processes, protection of human research subjects in Canada).

Section 7 of the *Tri-Council Policy Statement* states that "clinical investigators undertaking research intended for use in seeking regulatory approval for pharmaceuticals, should also generally respect the *ICH Guidelines* which were developed by the United States, Europe and Japan and have been adopted by Canada."[104] Despite the differences between the two documents there is cross-referencing.

It is important to recognize that adoption of the *Tri-Council Policy Statement* as the policy framework for the review of placebo-controlled clinical trials can be implemented by Health Canada without jeopardizing Canada's compliance with *ICH* guidelines. The "adoption, implementation and maintenance of *ICH* Guidelines" by Health Canada allows for the use of an

[104] (*Tri-Council Policy Statement*, p. 7.3)

Addendum if Health Canada "or industry/stakeholders consider that the guidelines lack some clarity and/or sufficient detail."[105] However, the introduction of Section 7 of the *Tri-Council Policy Statement* in its current form as an amendment to the *ICH E-10* could prove difficult.

Some individuals view the *Tri-Council Policy Statement* as a "flexible" document that allows for a range of interpretations of the policies regarding placebo use. Others view the *Tri-Council Policy Statement* as relatively rigid, prohibiting the use of placebos in other than a few exceptional circumstances. This disparity of opinion was obvious from presentations and discussions at the *National Conference on the Appropriate Use of Placebos in Clinical Trials.*[106] Such comments are not unique to the *Tri-Council Policy Statement*, however. The same has been said of the recent revision of the *Declaration of Helsinki* and its subsequent "*Note of Clarification.*"[107]

One concern that has been raised regarding adoption of the *Tri-Council Policy Statement* as a national standard for the review of placebo controlled trials centers on its emphasis of the concept of "clinical equipoise."[108] In particular, the current statement in Section 7 that "Clinical equipoise means a genuine uncertainty on the part of the expert medical community about the therapeutic merits of each arm of a clinical trial,"[109] may not be clear to all. While some individuals profess to have a clear understanding of the meaning of this term, others do not and interpretation in an overly restrictive manner that is inconsistent with most current views of the ethical analysis of risk in a clinical research context is possible. While the concept of equipoise as defined by Freedman (B. Freedman, "Equipoise and the ethics of clinical research." New England Journal of Medicine, 1987; 317:141-145) is incorporated in international policy guidelines (**see references provided by Weijer to NBAC and CIOMS**) emphasis on the use of this term as the "moral foundation" for the review of clinical trials in Canada, without a more clearly understood definition, can be taken construed by some as representing a unique approach to the ethical considerations of clinical trials. [110, 111]

From a regulatory perspective, the emphasis on the use of an inadequately defined concept of "clinical equipoise" by the *Tri-Council Policy Statement* and the absence of this specific term from international guidelines, such as the *Declaration of Helsinki*, can be problematic. Once again, an imprecise understanding of this term and its application to the ethical review process can lead to the misunderstanding that the ethical review of clinical trials in Canada does not correspond to existing international ethical guidelines. The term "clinical equipoise" need not be removed from the *Tri-Council Policy Statement*, but greater clarification of the moral foundation

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[105] http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sop_ich_e.pdf , (Page 9)

[106] http://www.cihr-irsc.gc.ca/e/19301.html

[107] http://www.wma.net/e/policy/b3.htm

[108] Freedman, B., C. Weijer, et al., Placebo orthodoxy in clinical research. I: Empirical and methodological myths. *Journal of Law, Medicine and Ethics, 1996.* 24(3): 243-51.

[109] Tri-Council Policy Statement, p. 7.1

[110] Weijer C. The ethical analysis of risks and potential benefits in human subjects research: history, theory, and implications for U.S. regulation. In: U.S. National Bioethics Advisory Commission. *Ethical and Policy Issues in Research Involving Human Participants. Volume II: Commissioned Papers and Staff Analysis.* Bethesda, MD, 2001: P1-P29; U.S. National Bioethics Advisory Commission (NBAC).

[111] *Ethical and Policy Issues in Research Involving Human Participants.* Bethesda, MD: NBAC, 2000: pages 69-95. Website: http://bioethics.georgetown.edu/nbac/human/overvol1.html; Date accessed: July 7, 2003

of ethical review of clinical trials in Section A of the *Tri-Council Policy Statement* seems warranted.[112] Specific suggested wording changes for section 7.4 of the *Tri-Council Policy Statement* are presented in the NPWC Policy Recommendations section below.

Table 7.1: Educational Guidance Document

Suggested Questions

A guidance document jointly prepared by Health Canada and Interagency Advisory Panel on Research Ethics (*PRE)* could incorporate the *ICH: GCP* and *Tri-Council Policy Statement* considerations and help develop consistency within and between the Research Ethics Board and regulatory review processes. While a "decision tree" approach such as that presented in *ICH E-10* may prove difficult, a set of common questions to be applied to placebo-controlled studies could be developed. An expectation of "right or wrong" answers to the questions posed below would be overly simplistic. Nevertheless, ensuring that each is considered in the review process could establish the expectation that decisions will be based on common sets of information and the rationale for the decision could be clearly articulated to others.

(i) Are approved therapies available for the population and study target and, if so, what is the known efficacy (note that the availability of approved treatments is not the same as a "standard of care")?

(ii) Would the risk-benefit ratio for the individual patient/participant be optimized with an active control trial?

(iii) Could a superiority, active control trial be done (i.e. can it be reasonably expected that the investigational therapy will be better than established effective therapy)?

(iv) Do existing studies demonstrate sufficient "constancy of effect" for available therapies to consider active-control equivalence or non-inferiority trials as sufficient evidence of efficacy (e.g. for the purposes of regulatory approval)? (Note that if an active comparator is being used, rather than placebo, the design of the trial must allow for a reasonable estimation of the efficacy of the active comparator).

(v) If the purpose of the placebo is blinding, what is the likelihood that blinding can be maintained or that blinding is necessary to demonstrate treatment efficacy (e.g. if the primary outcome is mortality, is blinding relevant)?

(vi) How do the available therapies contribute to a "standard of care" for the condition of interest?

(vii) If there is a standard of care for the condition under study, does it include withholding treatment with available therapies? If so, under what conditions (e.g. for specific sub-populations or time frames, or with close monitoring of symptoms)?

[112] Weijer C. The ethical analysis of risk. *Journal of Law, Medicine & Ethics* 2000; 28: 344-361

(viii) Do the study procedures (e.g. individual subject monitoring, “early escape” procedures, overall data safety monitoring and reporting) represent a reasonable standard of care for all subjects?

(ix) Will all subjects in the trial receive established effective therapy (i.e. is this an add-on trial with a placebo arm)?

(x) Are study participants required to discontinue a therapy for which they have had a satisfactory response (as determined by either the subject or the clinician caring for them) in order to participate in the study?

(xi) What are the consequences of discontinuing or withholding available therapies?

(xii) Is refusal of the available therapies common?

(xiii) Would a study that includes only individuals who refuse the available therapies be scientifically valid and would such as study limit the approved indications for the therapy if the study successfully demonstrates treatment efficacy?

(xiv) Is the risk/benefit ratio of the trial such that informed refusal of the available therapies is sufficient justification for the subject’s participation in a placebo-controlled trial?

(xv) Can informed, autonomous decision-making by potential subjects regarding participation in a placebo-controlled study be ensured (e.g. are the recruitment methods appropriate and are the appropriate subjects being recruited)?

(xvi) Is the use of a placebo in the study clearly evident to potential participants (e.g. in the study title)?

(xvii) Is the concept of a placebo, the reason for its use, and its potential risks and benefits adequately explained in the consent documentation?

8. Recommendations and Unresolved Issues

The National Placebo Working Committee (NPWC) has made considerable progress in its discussions on the use of placebos in clinical trials. A consensus of opinion has been achieved around some of the principles that should form, or continue to form the foundation of placebo policy in Canada. However, arriving at consensus was a cumbersome process as there were many opposing views within the Committee. That said, it is of particular importance to note that the NPWC debated the question extensively, rigorously taking into account feedback from the stakeholder and public consultation reports. In brief, these discussions helped the Committee to arrive at a balance of recommendations that it thought added value to the advancement of the placebo debate both nationally and internationally. This section of the Report identifies the principles and recommendations that the NPWC has agreed upon. It also identifies those areas of discussion around which the committee did not achieve a full consensus.

The formulation of these recommendations was undertaken by the following process. On May 5-6 2003, the NPWC met and each subcommittee presented the modification made to its chapter and its recommendations. Following that exercise, each recommendation was looked at by the NPWC. Three situations were possible: (1) all members agree with the wording of the recommendation, then, that recommendation was removed from its original chapter and introduced in Chapter 8 as a **NPWC recommendation.** (2) all members agreed that the questions/issues could not be resolved at this time and require further discussion in a broader community, therefore that recommendation was put in Chapter 9 as an **unresolved policy issue**.. Finally, (3) some members of the NPWC disagree on the recommendation as stated, then that recommendation was kept in its original chapter and kept its status of a subcommittee's recommendation. The NPWC met again on February 12-13, 2004 to reconfirm the above recommendations and unresolved policy issues.

The views expressed in this chapter do not necessarily reflect the views of Health Canada or CIHR, but are the views of the members of the NPWC. The two ex-officio members do not hold voting privileges on the committee; their role is to ensure due process, to provide expert knowledge, and to represent their federal affiliation.

Therefore, this chapter contains areas of consensus that give rise to recommendations (based on principle and some administrative in nature) but also agreements on some issues that remain unresolved. In this last case, pro and con are presented to illustrate the difficulties associated with this specific issue.

A. Areas of Consensus

1. Statements of Principle

The principles set out below are generally accepted by diverse research disciplines.

- Respect for human dignity,
- Respect for free and informed consent,

- Respect for vulnerable persons,
- Respect for privacy and confidentiality,
- Respect for justice and inclusiveness,
- Minimizing harm, and
- Maximizing benefit.

The consequences of adhering to these principles requires:

- Research should provide useful information to inform patients, scientists, regulators, clinicians and other key stakeholders about the efficacy/effectiveness of health care interventions,
- Use of placebos should remain firmly grounded in fiduciary obligations of physicians (clinical investigators) toward patients as stated in Article 3 of the *Declaration of Helsinki*,
- Access to all available information is essential
  - for research subjects to facilitate informed consent, and
  - for Research Ethics Boards, scientists and regulators to assist with the evaluation of trials

2. Policy Preamble

The National Placebo Working Committee endorses the need to clarify Canada's current policy framework regarding the use of placebo in clinical trials. The committee supports the adoption of one clear and consistent policy direction. No consensus has yet been reached however with respect to all aspects of the most appropriate choice of policy framework for Canada.

3. NPWC Policy Recommendations

> The NPWC agreed that as a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic or preventive intervention should receive an established effective therapy.

Use of Established Effective Therapy

For the NPWC, ***an established effective therapy*** is defined for a specific group of individuals with a specific condition in terms of the examination of the *totality of evidence* derived from either:

a) Systematic reviews of randomized controlled trials measuring outcomes that are relevant to the patient and carried out in that population (even though there may be just one trial). In most instances evidence that is based on surrogate markers will not be accepted as evidence of established effective therapy,

b) "All or none" evidence (when, in a universally fatal condition, the therapy is followed by survival; or when some other adverse outcome is totally eliminated following therapy).

It is possible that in some circumstances there could be established effective therapy in the absence of a) and b) above.

- Standard Treatment and Standard Therapy

The terms "standard treatment" and "standard therapy" should be removed from reference in the *Tri-Council Policy Statement*. These terms do not appear in international guidelines and are open to wide interpretation. As an alternative, the term "established effective therapy" is recommended.

> NPWC recommends to revise section 7, Article 7.4 of *Tri-Council Policy Statement* and recommend its use as the Health Canada Addendum to *ICH-E10* as follows:

Amendments to *Tri-Council Policy Statement*, Article 7.4

> Article 7 should be amended to read:
>
> "The use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate study design when *established effective therapy or therapies exist* for the population and indication under study." Additionally,
>
> "A placebo comparator is acceptable in the following situations:
>
> a) There are no established effective therapies for the population and for the indication under study,
> b) Existing evidence raises substantial doubt regarding the net therapeutic benefit of available therapies,
> c) Patients are refractory to the available therapies by virtue of their past treatment history or known medical history
> d) The study involves adding a new investigational therapy to established effective therapies, (established effective therapy + new therapy vs. established effective therapy + placebo)
> e) Patients have determined that the response to the established effective therapies for their condition is unsatisfactory to them,"*.
> f) Patients have previously refused established effective therapies for their condition."*

* For articles (e) and (f) the determinations of response satisfaction and refusal of treatment must take place outside of the context of recruitment for the clinical trial and prior to the offering of trial participation to the potential subject, and be documented in a standardised manner. Under these conditions, study subjects would not necessarily be considered "refractory" to the available therapies since the choice to discontinue available therapies is based on their own opinion and values, not those of the clinicians responsible for their care. As such, regulatory approval of the therapy under investigation would not necessarily be restricted.

B. Unresolved Policy Issues

There are several concepts that have been used to evaluate the ethics of placebo-controlled trials – risk of harm, clinical equipoise and fiduciary duty. Some regulatory documents employ the concept of risk of harm. Others employ the concept of clinical equipoise or fiduciary duty. This dichotomy is the underlying issue in the debate about the use of placebos in clinical controlled trials. This dichotomy is reflected in the unresolved issues among committee members. A number of issues remain unresolved in relation to whether there are additional specific circumstances under which it is acceptable to use placebos in clinical trials. As noted previously in this section of the Report, the NPWC has reached consensus and are recommending specific circumstances under which it is acceptable to use placebos for comparative purposes in clinical research trials.

Other than the situations (a-f) under Article 7.4 on which the committee has reached consensus, there are four other situations on which the committee has not been able to reach consensus. These situations are outlined below along within a commentary about the supporting and opposing views.

1. Treatment of "Minor" Conditions

Use of a placebo control is acceptable, when withholding an established effective intervention for a minor condition would expose subjects to, at most, temporary discomfort or delay in relief of symptoms.

Supporting View

- Placebo-controlled trials are acceptable because ethics should not be concerned about trivial risk, and
- Patients should be permitted to participate in a trial if they choose to do so.
- Placebo-controlled trials are necessary to measure assay sensitivity.

Opposing View

- There is no agreed definition of "minor" conditions,
- Undermines the duty of care that physicians owe to patients by exposing patients to an intervention known to be ineffective.
- Begins to qualify acceptable level of risk.
- The comparison of the new treatment to placebo is not of interest.

2. Early Phase Clinical Trials

Placebo controlled trials are acceptable in early phase II trials in some circumstances beyond those listed above.

Supporting View

- Active control trials are generally larger than placebo-controlled trials. An active control trial in early drug development implies many more patients are exposed to an experimental treatment. The number of people exposed to risk could be minimized with a placebo-controlled trial.

Opposing View

- The agreed upon amendments to c,e, and f of Article 7.4 sufficiently identify patient populations in which early phase II placebo-controlled trials would be acceptable.

3. Informed Refusal of Established Effective Therapy

It is acceptable to conduct placebo-controlled trials when patients have provided an informed refusal of established effective therapy in conditions for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.

Supporting View

- The fully-informed patient should have the right to refuse established effective therapy within those limiting conditions.

Opposing View

- The terms “undue suffering” cannot be easily defined.
- The use of the term “irreversible harm of any magnitude” sets the threshold of harm too low to support patient autonomy.

4. Cost Constraints or Limited Supply of Established Effective Therapy

It is acceptable to conduct placebo-controlled trials in situations where established effective therapies are not available to the population under study due to cost constraints or limited supply.

This issue is currently addressed in *Tri-Council Policy Statement* and *CIOMS* but not *ICH E-10*. However, the NPWC did not formulate a view on this issue because it lacked the time to adequately study it.

C. Administrative Recommendations

The complexity of regulatory requirements and mounting workloads make it increasingly difficult for Research Ethics Boards to carry out the responsibilities vested in them. Varying degrees of scientific and ethics expertise exist among centres engaged in the evaluation and approval of clinical research such that the appropriateness and consistency of decision-making is

now of concern. The NPWC discussed many of these issues and the contributing circumstances, and reached a consensus on a number of remedial steps that should be taken nationally. The consensus is reflected in the following recommendations:

The National Placebo Working Committee recommends that*:*

1. All research protocols, submitted to Health Canada (for example, as part of the Clinical Trial Application (CTA) process) and/or to a Research Ethics Board should include:

- justification of the study design (superiority, non-inferiority, equivalence) and the choice of comparator (active control or placebo on both scientific and ethical bases), and
- systematic reviews of the new investigational therapy and other established effective therapies for the condition under study, sufficient to support the justification of the study design.

At the present time in many circumstances, it is not possible to conduct a comprehensive systematic review of controlled trial evidence. This is due to the inability to know how many trials have been done, inaccessibility to complete data from published trials and inaccessibility to any data from unpublished trials.

2. In order to facilitate the comprehensive systematic review of controlled trial evidence, the policies and regulations of Health Canada should be changed to allow researchers and research ethics boards to have access to all protocols and clinical data from trials that are on file with the government, consistent with the fair information principles for protecting personal data. Health Canada should also assist in obtaining additional trial data from the sponsor or manufacturer if necessary.

3. Health Canada should do everything possible to assist the development of a comprehensive International Trial Registry as soon as possible.

4. Patients should be made aware on an active basis that all information filed with the trial sponsor and available to the Research Ethics Board must be available to them through the primary research investigator. Patients should be informed that they have a right to receive all information that may materially affect decisions to participate in trials.

5. The research participant should have available to them, a participant advocate, free of any conflict of interest with whom they can discuss any aspects of trial participation.

6. A safety monitoring function proportionate to the level of risk and external to both the investigator and sponsor should be established for all randomized trials including placebo controlled trials. This function is currently not always being met.

7. A national framework governing all Research Ethics Boards should be established to facilitate consistency in the scientific and ethical review of placebo-controlled trials. This governance framework would help ensure that Research Ethics Boards are free of conflict of interest, are

constituted with a membership consistent with currently accepted standards of appointment, have resources to support the review process and apply the current national standards when evaluating and approving all clinical trials, including placebo-controlled trials.

8. Health Canada should develop and publish a document that clearly identifies the criteria for authorizing the release of a therapeutic product for the purpose of a clinical trial. This includes the particular instance of a placebo-controlled trial when, there is an established effective therapy.

9. An Educational Guidance Document should be developed by Health Canada and CIHR and distributed to all Research Ethics Boards across the country. The document should identify the key questions that should be posed by the Research Ethics Board in the evaluation of the scientific merit and ethical acceptability of clinical trials. The questions should be constructed so as to account for both national and international standards and policy.

Conclusion/Next Steps

The National Placebo Initiative process represented a substantial intellectual give and take involving the public and stakeholders. We have addressed important issues of the advancement of scientific knowledge and the protection of research participants. Our recommendations will be presented to Health Canada and CIHR. Our expectations will be that these recommendations will be translated into action for the benefit of the Canadian Public in an expeditious manner. We do recognize the complexity of implementing the Administrative Recommendations in particular.

Appendix 1

A. Clinical Drug Development and Regulation

Patricia Huston

Drug development is a long and complex process. New drugs[113] are typically developed over many years by multinational pharmaceutical companies, based on research that takes place in countries around the world. In Canada, the regulation of new drugs, and the regulation of human trials involving new drugs, falls under the responsibility of Health Products and Food Branch of Health Canada, as outlined in the *Food and Drug Act* and its *Regulations.*[114] This section provides an overview of the drug development process and the regulatory structure at Health Canada to ensure that both the drugs and the drug development process are safe and scientifically sound.

1. The Drug Development Process

New drugs are discovered in a number of ways, including the purification of herbal remedies, laboratory testing and computerized simulations. Most experimental drugs do not make it to market. Experience has shown that approximately one in a thousand new chemical entities assessed for human use actually make it to market.

There is tremendous uncertainty whenever a new chemical entity is considered for human use. To manage this uncertainty, a careful step-wise approach is undertaken. First, in-vitro or laboratory studies are conducted. If promising results are seen, then small animal studies are conducted, and if those are promising, larger animal studies are undertaken. Animal studies are carried out to determine what effects the drug has, including both potentially beneficial effects as well as how, and at what dose, the drug becomes toxic. Animal studies also help determine how the drug is absorbed, distributed in the body, metabolized and excreted. If everything looks promising, all this information is then used to help plan the first human trials. Animal studies are not regulated or reviewed by Health Canada, but are reviewed by institutional animal care committees to ensure they meet animal care guidelines produced by the Canadian Council on Animal Care.[115]

The Phases of Human trials

Once basic information on a new drug has been established in animals, and the drug exhibits acceptable indicators of safety and potential for benefit, then human trials can commence. There is a logical, step-wise approach to the development of drugs in humans that involves exposure of

[113] The term "new drug" has an extensive definition found in C.08.001 of the *Regulations* and includes not only drugs for which marketing approval is being sought for the first time in Canada, but also new indications for already approved drugs, generic versions of approved drugs, etc. Unless otherwise specified, it is generally used here to refer to experimental drugs that have not yet received market approval

[114] *Food and Drugs Act*, SRC c.F-27; *Food and Drug Regulations*, CRC, c.870

[115] http://www.ccac.ca

the new drug to small numbers of healthy people first, to gather information which will support larger, more conclusive clinical trials. In general, there are four phases of drug development. [116]

Phase I Trials

Phase I or "human pharmacology" trials test a new chemical entity (also called an investigational new drug) for the first time in humans. Animal data is used to establish the initial dosing. The objectives of Phase I trials are to assess safety (adverse effects), pharmacokinetics (absorption, distribution, metabolism and elimination) and to estimate drug activity. Phase I trials typically involve healthy adults who are paid for their participation in these trials.

Phase II Trials

Phase II or "therapeutic exploratory" trials explore the use of an investigational drug for a specific use or indication (for example, the treatment of hypertension in adults). They are usually of short duration in a well-defined patient population and may test a variety of clinical outcome measures. Phase II, III and IV trials typically involve volunteer patients.

Phase III Trials

Phase III, "therapeutic confirmatory" or "pivotal" trials are generally large, well-controlled studies designed to establish the efficacy and safety profile of an investigational drug for a specific indication in a specific population.

Phase IV Trials

Phase IV, "therapeutic use" or "post-marketing trials", begins after drug approval. These trials include active comparator, epidemiological and pharmacoeconomic studies. These trials help to refine the understanding of the drug and its ideal conditions of use following regulatory approval.

Drug development is an iterative activity where each stage or phase offers information and evidence that informs the next phase. These phases may not always be sequential. Studies may be a combination of phases, such as trials that combine Phases I and II, or II and III. It is also possible that when a Phase III study has been completed, sponsors will return to Phase I or II trials to help explain an unexpected feature found during the ongoing development of the drug or to assess the use of the drug in new age groups, subpopulations or for other indications and conditions of use. A placebo-controlled trial can be conducted in any phase, but is usually conducted in Phase II or III

2. The Regulation of Drugs by Health Canada

The ultimate goal in drug development is getting a drug on the market. The regulation of drugs is the sole responsibility of Health Canada under the provisions of article C.08.002 of the *Food and*

[116] ICH Harmonized Tripartite Guideline: *"General Considerations for Clinical Trials (ICH E-8)"*: www.ich.org/pdfICH/e8.pdf

Drug Regulations. There are clinical trial regulations that assess trials before they are conducted,[117] and new drug regulations that assess the results of those trials (and other information), in determining the appropriateness of a drug for the Canadian market.[118] The area of Health Canada that conducts these assessments is part of the Health Products and Food Branch. It includes the Therapeutic Products Directorate, the Biologics and Genetic Therapies Directorate, or the Medical Devices Directorate, depending on the type of therapeutic agent.

Health Canada is a participant in the International Conference on Harmonisation: Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH includes regulatory authorities and experts from the pharmaceutical industry who work together to develop technical guidelines and requirements for drug development and approval. This is done to promote an "economical use of human, animal and material resources, and [eliminate] unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health".[119]

2a. **Regulatory Review of Clinical Trials**

No clinical trial on an experimental drug can proceed in Canada unless and until it has passed regulatory review by Health Canada.

The goal of the regulatory review process is not to "approve" the design of the trial. Rather, it is to authorize the sponsor (most often the drug manufacturer) to release the drug to the researcher for the purpose of the trial. In all trials that are reviewed by Health Canada, a drug is being used for a previously unapproved use. This could either be for Phase I, II, and III trials of experimental drugs or for new indications of already approved drugs. Health Canada does not authorize the use of drugs for Phase IV trials because these involve drugs that are already on the market and are being tested for approved indications.

Health Canada has teams of physicians and PhD scientists who work full-time in reviewing clinical trials to assess whether trials meet the requirements of the *Regulations* and the international regulatory guidelines, as set out by the International Conference on Harmonisation (ICH).

According to the regulations, a clinical trial cannot be undertaken in Canada if:

- there is insufficient information to "assess the safety and risks of the drug or the clinical trial" or
- there are reasonable grounds to believe that:
  a. "the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person" (safety risk)
  b. the clinical trial is contrary to the best interests of a clinical trial subject, or
  c. the objectives of the clinical trial will not be achieved." [120]

[117] *Food and Drug Regulations*, Part C, Division 5.
[118] *Food and Drug Regulations*, Part C, Division 8.
[119] See the ICH website: www.ich.org
[120] *Food and Drug Regulations*, C.05.006

In addition, there must be research ethics board approval for each clinical trial site.

The regulations identify that both a research ethics and regulatory review are needed. If a proposed clinical trial is not approved by an REB, or not authorized by Health Canada, the implications are different. The jurisdiction of an REB is site-specific; the jurisdiction of Health Canada is national. So, for example, if an REB does not approve a trial, then the trial cannot proceed at that one site and the sponsor, usually a drug company, will have to inform Health Canada of this refusal.[121] If it does gain Health Canada authorization and REB approval at other sites, the trial can proceed at the approved sites. However, if a trial is not approved by Health Canada, it cannot proceed in Canada no matter how many local REBs have approved the trial.

In summary, the responsibility for choosing and devising a scientifically and ethically appropriate methodology is the responsibility of pharmaceutical companies and the institutions that are testing a new drug. Health Canada does not mandate specific clinical research methodologies. However, it will not allow a trial to proceed in Canada if there is insufficient information on safety, the trial will not meet its research objectives, it risks endangering the health of research subjects, or it is contrary to their best interests.

There are no specific clinical trial regulations addressing placebo use. However, all placebo-controlled trials must meet the requirements of the clinical trial regulations and international regulatory guidelines such as the good clinical practices identified in ICH.[122] In other words, placebo-controlled trials are authorized by Health Canada only when the rights, safety and well-being of research participants are ensured.

2b. **The Regulation of Drugs in Canada**

The Regulations specify that a new drug cannot be sold in Canada unless the manufacturer has submitted a New Drug Submission that has resulted in a "Notice of Compliance" from Health Canada. A New Drug Submission contains all the information that is known about a new drug. This includes a detailed list of its ingredients, as well as its manufacturing processes, to ensure the potency, purity and stability of the drug. It includes the results of all animal studies and all human trials (Phase I, II, and III) conducted to date, in Canada or abroad, to establish the safety and efficacy of the drug. This often translates into literally hundreds of volumes of data. There are numerous departments within the Directorates that have full-time physicians and PhD scientists reviewing new drug submissions. This review process typically takes a year.

The Regulations do not require that clinical trials be conducted in Canada in order to submit a New Drug Submission, nor do they specify what type of trial is needed to establish efficacy. It states that there must be "substantial evidence" and that this evidence must be related to its recommended conditions of use. Conditions of use include the indication (or condition for which the drug is to be used) as well as the patient population, any contraindications (when the drug

[121] *Food and Drug Regulations*, C.05.005d
[122] ICH E-6: *Harmonized Tripartite Guideline: Guideline for Good Clinical Practice E6* see: *www.ich.org/pdfICH/e6.pdf*

must not be used), warnings, precautions, adverse effects, potential interactions, recommended dosage and any other circumstances for its use.

Once the evidence for the quality, safety and efficacy of a new drug are reviewed and found to meet the regulatory requirements, a Notice of Compliance (NOC) is issued. The NOC means that an assessment has been completed and a conclusion has been arrived at, based on assessment of the information given, that the drug meets regulatory requirements for the indications specified in the New Drug Submission. Thus, a drug is approved for a specific patient population and a specific condition. The NOC can be withdrawn at any time if additional evidence becomes available that brings into question the quality, safety or efficacy of the drug.

B. The Placebo Debate and the Major Players **Thérèse Leroux**

The following is a short introduction to five major actors in the debate on the Appropriate Use of Placebo in Clinical Trial.

1. Canadian Institutes of Health Research (CIHR)

CIHR, as Canada's premier federal agency for health research, is "promoting, assisting and undertaking research that meets the highest international scientific standards of excellence and ethics and that pertains to all aspects of health, including bio-medical research, clinical research and research respecting health systems, health services, the health of populations, societal and cultural dimensions of health and environmental influences on health."[123]

As a pre-condition to funding, universities signed a memorandum of understanding (MOU) with the three major federal funding agencies (CIHR, Natural Sciences and Engineering Research Council of Canada [NSERC] and the Social Sciences and Humanities Research Council of Canada [SSHRC]). The MOU stipulates that for all research involving humans under their auspices, the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (*Tri-Council Policy Statement*) must be applied (http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm). *Tri-Council Policy Statement*, Chapter 7, contains rules applicable to clinical trial and article 7.4 states the criteria for the acceptance of the use of placebo.

2. Council for International Organizations of Medical Sciences (CIOMS)

CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. Its membership includes 48 international member organizations, representing many of the biomedical disciplines, and 18 national members mainly from academies of sciences and medical research councils (http://www.cioms.ch/index.html). Last year, CIOMS published its updated document concerning the experimentation with human subjects, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Geneva 2002). *Guideline 11: Choice of control in clinical trials*, refers specifically to the use of placebo.

[123] *Canadian Institutes of Health Research Act*, SC. 2000, c 6, a. 4 e

3. Health Canada

Health Canada is the federal jurisdiction responsible for helping the people of Canada maintain and improve their health.[124]

The *Food and Drugs Act* (SRC, c. F-27) applies to all food, drugs, cosmetics and medical devices sold in Canada, whether manufactured in Canada or imported. The purpose of the *Act* and *Regulations* is to ensure safety and prevent deception in relation to foods, drugs, cosmetics and medical devices by governing their sale and advertisement, in addition to setting out the labeling requirements for food.

Health Canada is responsible for examining the proposed clinical trials to be sure that they are scientifically and ethically sound (*Food and Drug Regulations*, C.05.005).

4. International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH)

ICH was established in 1990 as a joint regulatory/industry project to improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States, in order to facilitate the availability of these products to patients. Canada, through the Therapeutics Products Programme, sits as an Observer to the ICH Steering Committee (*Guidance for Industry: Standard Operating Procedure - Adoption, Implementation and Maintenance of ICH Products*, International Policy Division, Bureau of Policy and Coordination, Therapeutic Products Programme, Version Date: October 1999, http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/sop_ich_e.html).

As stated in ICH's website: "The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health." (http://www.ich.org). Since ICH was initiated, many guidelines were produced, among them, the *Good Clinical Practice: Consolidated Guidelines* (E-6). More recently, a new guideline was proposed to complete E-6, which focuses on the methodology of the trial: *Choice of Control Group in Clinical Trials* (E-10). In this last document, a section is dedicated to the use of placebos.

5. World Medical Association Inc (WMA)

The World Medical Association is an international organisation of physicians from more than 70 countries. Established in 1947, the WMA aims to "achieve the highest international standards in medical care, ethics, education and science." (http://omni.ac.uk/whatsnew/detail/8006088.html). The *Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects* is one of the WHA's best known statements. Paragraph 29 of the updated Declaration as well as a Note of Clarification added in 2002 pertains to the use of placebo in medical research involving human subjects (www.wma.net/e/policy/b3.htm).

[124] *Department of Health Act*, SC. 1996, c.8

Appendix 2: Acronyms

ACT	Active control trial
ACNIT	Active control non-inferiority trial. Non-inferiority trials answer the question: Is "A" not much worse than "B"?
ACST	Active control superiority trial. Superiority trials answer the question: Is "A" better than "B"?
CIHR	Canadian Institutes of Health Research
CIOMS	Council for International Organizations of Medical Sciences
EET	Established Effective Therapy
HC	Health Canada
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MRC	Medical Research Council of Canada
NGO	Non-governmental organization
NPWC	National Placebo Working Committee
NSERC	Natural Sciences and Engineering Research Council of Canada
PCT	Placebo-Controlled Trial
PRE	Interagency Advisory Panel on Research Ethics
REB	Research Ethics Board
RCT	Randomized Controlled Trial
SSHRC	Social Sciences and Humanities Research Council of Canada
TCPS	Tri-Council Policy Statement
TPD	Therapeutic Products Directorate of Health Canada

UNESCO United Nations Educational, Scientific and Cultural Organization

WHO World Health Organization

WMA World Medical Association

Appendix 3: Glossary

Active Comparator: A control or "benchmark substance" with active ingredients that is used for comparative purposes in a clinical trial.

Aggregation: Massing of materials together as in clumping.

Altruism: Unselfish regard for, or devotion to the welfare of others.

A Priori: Characterising that kind of reasoning which deduces consequences from definitions formed, or principles assumed, or which infers effects from causes previously known.

Bioethics: Branch of ethics, philosophy and social commentary that discusses the life sciences and their potential impact on our society.

Clinical Equipoise: An honest professional disagreement in the community of expert practitioners as to the preferred treatment.

Clinical Trial: Research study conducted with patients, usually to evaluate a new treatment or drug. Each trial is designed to answer scientific questions and to find better ways to treat individuals with a specific disease.

Clinical Trial Effect: The impact on the subject of a clinical trial simply as a result of participating in the trial.

Clinical Trial Hypothesis: The underlying question or assumption around which the clinical trial is designed.

Co-morbid: Co-existing diseases or medical conditions.

Concomitant Therapy: Therapy that is given along with another.

Consistency: Without contradiction.

Credibility: The condition of being credible or believable.

Diagnostic Method: A means of determining the cause of an illness or condition.

Derogate: To deviate from standard expectations. To take away or detract.

Epistemology: The theory or science of the method or grounds of knowledge.

Established Effective Therapy: Drug or therapy previously proven to be effective and safe for the condition and patient population under study.

Effective: Producing the intended result.

Efficacy: The ability of a drug to control or cure an illness.

Ethics: The philosophy or code pertaining to what is ideal in human character and conduct.

Fiduciary: A person entrusted with power or property to be used for the benefit of another and is legally held to the highest standard of conduct.

Fiduciary Duty: To act in the best interests of patients, not allowing personal interests to conflict with those of the patient.

Harmonisation: Bring into consonance or accord.

Histamine: Responsible for the early symptoms of life threatening allergic reactions or anaphylaxis.

Homeopathy: A system of medical practice that treats a disease especially by the administration of minute doses of a remedy that would in healthy persons produce symptoms similar to those of the disease.

Hypothesis: A supposition that appears to explain a group of phenomena and is advanced as a basis for further investigation.

Immunodeficiency: Inability to mount a normal immune response. Immunodeficiency can be due to a genetic disease or acquired as in AIDS due to HIV.

Meta-Analysis: The systematic collection, review, combination and analysis of multiple trials/research results.

Methodology: The mode or manner or orderly sequence of events of a process or procedure.

Neurological Disorder: Disturbance in structure or function of the central nervous system resulting from developmental abnormality, disease, injury or toxin.

Patient Advocate: An individual who advocates for the patient and his rights and interests.

Pharmacoeconomics: The study of the economics of drug therapy.

Pharmacokinetics: The action of drugs in the body over a period of time, including the processes of absorption, distribution in tissues, biotransformation and excretion.

Placebo-Controlled Trial: A clinical trial in which an investigational new therapy is tested against a placebo.

Platelet Inhibiting Drug: Medication that, like aspirin, reduces the tendency of platelets in the blood to clump and clot.

Prophylactic Method: A preventative measure or medication.

Protocol: A formula, treatment recipe or approach to a clinical trial.

Psychosis: A mental disorder characterized by gross impairment in reality testing as evidenced by delusions, hallucinations etc.

Randomized Controlled Trial: A clinical trial in which the treatments being delivered are selected by a random process, such as the use of a random numbers table.

Refractory: Non-responsive to therapy.

Regression to the Mean: If, for a symmetrical population with a single mode, a measurement, selected because it is extreme, is repeated, on average the second reading will be closer to the first.

Reliability: The degree of stability exhibited when a measurement is repeated under identical circumstances.

Surrogate: Something that functions as a substitute.

Therapeutic Method: Of, for, or contributing to the cure of disease.

Utilitarianism: Implying the greatest happiness of the greatest numbers.

Validity: The extent to which a measurement, test or study measures what it purports to measure.

Variability: The quality, state, or degree of being variable or changeable.

Appendix 4: List of Tables

Appendix 5: Biographical Notes of NPWC Members

Heather Sampson; Toronto, Ontario: Chair

Ms. Heather Sampson is the director of the Clinical Research Program Radiation Medicine, Princess Margaret Hospital, Toronto, Ontario since 2000. Ms Sampson has been involved in clinical research from protocol development to grant writing and trial facilitation. Previously she was responsible for the Clinical Research and Outcomes Measurement Unit: initiation and responsibility for all aspects of clinical research and outcomes measurement in the Division of Urology, Toronto General Hospital, University Health Network. She serves on two Canadian Research Ethics Boards and one U.S. Research Ethics Committee. In addition to which in initiating the Understanding Clinical Trials, Patient Public Education Program at the Princess Margaret Hospital, she has developed an open dialogue of what the public perception of placebo-controlled studies in oncology is at the present time.

Penny Brasher; Calgary, Alberta

Dr. Penny Brasher is a Biostatistician with the Alberta Cancer Board. She is an adjunct associate professor in the Departments of Oncology and Community Health Sciences at the University of Calgary. She has been involved in the design and conduct of randomized clinical trials. She has also reviewed clinical trials for NCIC, CIHR and the Alberta Cancer Board. She is a member of the Research Ethics Review Committee of the College of Physicians and Surgeons of Alberta.

Kathleen Cranley Glass; Montréal, Québec

Dr. Glass is the Director of McGill's Biomedical Ethics Unit, Associate Professor in the Departments of Pediatrics and Human Genetics, and Clinical Ethicist at The Montréal Children's Hospital. She holds a doctorate in health law and ethics from the Institute of Comparative Law at McGill and is a member of the Bar of Québec. Her research, which has been funded by CIHR, Social Sciences and Humanities Research Council of Canada, NCE and Genome Québec, concerns children, the elderly, psychiatric patients and research subjects as well as the design, review and implementation of clinical trials. She is currently co-chair of the Research Ethics Board of The Montréal Children's Hospital.

John D. Fisk; Halifax, Nova Scotia

Dr. Fisk is a psychologist with Capital Health and Dalhousie University in Halifax, Nova Scotia who has clinical expertise in the neuropsychology of neurodegenerative disorders and dementia. He has served as a member and chair of local research ethics committees for over ten years. Dr. Fisk has been a past member and chair of the Alzheimer Society of Canada's Task Force on Ethics and their Research Policy Committee. He currently serves as a member of the Health Research Review Committee of the Multiple Sclerosis Society of Canada and as a Scientific Peer Review Committee member for the National MS Society (USA). Dr. Fisk's research includes the development and evaluation of measures of cognition, health outcomes and quality of life, as well as studies of the economic consequences of neurodegenerative disorders and their treatments.

Vratislav Hadrava; Montréal, Québec

Dr. Hadrava is the Director of Clinical Research at Pfizer Canada. He has extensive experience in basic and clinical sciences and designing and management of pharmaceutical clinical trials. Over the last years, he has collaborated in numerous projects with clinical researchers from academia, mainly in the area of mental health disorders, and has been exposed to various perspectives on the placebo use from several stakeholders including investigators and study nurses, regulators, statisticians, ethics committees and health economists. He is author of numerous articles in peer reviewed journals in the domain of vascular smooth muscle proliferation, mechanism of action of antidepressants and anxiolytics and clinical psychopharmacology.

Patricia Huston; Ottawa, Ontario

Dr. Huston was Acting Senior Medical Advisor in the Therapeutic Products Directorate at Health Canada until February 2004. Previously she worked in the Bureau of Pharmaceutical Assessment in the Clinical Trials Unit and was Chair of the National Research Council's Ottawa Research Ethics Board. She has extensive experience in clinical trial design, research ethics and critical appraisal. She is an adjunct professor in Epidemiology and Community Medicine at the University of Ottawa's Faculty of Medicine, and Scientific Editor of the Canadian Journal of Public Health.

Bernard Keating; Québec City, Québec

Professor Keating teaches biomedical ethics at Université Laval in Québec City in the theology and pharmacy programs. His interest in bioethics is focused mainly on two particular life stages: the beginning of life and the end of life. He participates in the work of many clinical and research ethics committees. His approach to ethical issues is one in which he is particularly sensitive to the governing philosophical visions.

Thérèse Leroux; Montréal, Québec

Dr. Leroux was Director of the Ethics Office at the Canadian Institutes of Health Research until March 2003, and the Special Advisor to the President from March to November 2003. At that time, she was replaced by Patricia Kosseim, an Acting Director of the CIHR Ethics Office in her capacity as an-officio member of the NPWC. Dr. Leroux is a full professor and senior researcher at the Centre de recherche en droit public, Faculty of Law of the University of Montréal. She serves on both clinical ethics and research ethics committees in hospital, university and provincial settings. She was a member of the National Council on Ethics in Human Research and the president of the Canadian Bioethics Society. Her current research projects include a focus on legal and ethical aspects of human experimentation, allotransplantation and xenotransplantation, biotechnology and biodiversity.

David Sackett; Irish Lake Ontario

Dr. David L Sackett is the Director of the Trout Research & Education Centre at Irish Lake. He is a hospital specialist in internal medicine who has been involved in approximately 200 randomized clinical trials as a study patient, an investigator, a methodological consultant, an ethics committee (or Institutional Research Ethics Board) member, and as a member or chair of a Trial Monitoring Committee (TMC or DSMB). As a trial monitor he ensures that placebo patients also continue to receive excellent medical care. He has started a "Cochrane Review" of the world literature that compares the outcomes of patients treated inside randomized trials with that of similar patients treated outside these trials. Thus far the evidence shows that patients, including premature babies, enjoy better outcomes inside randomized trials, including lower death rates.

Stan Shapiro, Montréal, Québec

Dr. Stan Shapiro, a Professor in the Department of Epidemiology & Biostatistics at McGill University, is a clinical trialist who holds a PhD in statistics. He is a founding member of the Clinical Trials Research Group at McGill, and a consultant to the Randomized Clinical Trials Unit at the SMBD Jewish General Hospital in Montréal. He has participated in the design, conduct, analysis and reporting of a wide variety of randomized trials, including studies of pharmaceutical agents, medical devices and behavioral interventions. His clinical trial experience also includes oversight activities as a member of data safety and monitoring committees, research ethics committees and scientific review committees. He is co-editor of a volume on clinical trials, Clinical Trials Issues and Approaches.

Maureen Smith; Ottawa, Ontario

Ms. Smith has twenty years experience as a teacher and obtained a Masters Degree in Educational Psychology. Her interest in research ethics stems from numerous years as a patient at the forefront of endocrine research in Montréal and Toronto subsequent to being diagnosed with a rare condition in 1966. Ms. Smith has a long history of active collaboration with the Canadian research community and has been a subject in placebo-controlled research. She is the layperson on the newly created Panel on Research Ethics (CIHR, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada) and is enthusiastic about its role as the steward for the *Tri-Council Policy Statement* on the Ethical Conduct for Research Involving Humans.

Phil Upshall; Guelph, Ontario

Mr.Phil Upshall is a founding member and current chair of the Canadian Alliance for Mental Illness and Mental Health (CAMIMH), and President of the Mood Disorders Society of Canada. He is a member of the advisory board to Statistics Canada's Canadian Community Health Survey - Mental Health Supplement and the Disabilities Committee of the Canadian Psychiatric Association. He is a member of the Advisory Board for the Institute of Neurosciences, Mental Health and Addictions for the Canadian Institutes of Health Research and a member of the expert panel for Health Canada's Mental Health Strategy. Mr. Upshall is a member of the Mental Health Implementation Task Force for Toronto and Peel. He has co-chaired the Specialized Services and Supports Sub-Committee and currently co-chairs the Support Services Sub-committee.

George C. Webster; Winnipeg, Manitoba

Dr. Webster is a Clinical Ethicist with the Health Care Ethics Service, St. Boniface General Hospital in Winnipeg, Manitoba. He has worked as a Clinical Ethicist since1982 in Toronto and Winnipeg. He established and was Director of the first full-time hospital based Ethics Service in Canada. George is an Assistant Professor in the Faculty of Medicine, University of Manitoba and an Adjunct Professor in the Department of Philosophy, University of Manitoba. He is a member of the Committee on Ethics, Canadian Anesthetist's Society and the Committee on Mental Health Ethics, Winnipeg Regional Health Authority. Last year, he was appointed to the American Society for Bioethics and Humanities, Clinical Ethics Task Force. He has served on the Research Ethics Board at St. Michael's Hospital in Toronto and the University of Manitoba, Faculty of Medicine, Biomedical Research Ethics Board. He currently chairs the National Research Council of Canada Winnipeg Research Ethics Board. He was recently appointed to the Canadian HIV Trials Network National Ethics Review Committee.

James M. Wright; Vancouver, BC

Dr. Wright is a Professor in the Departments of Pharmacology & Therapeutics and Medicine at the University of British Columbia. He is a practicing Clinical Pharmacologist and Internist, and has many years of experience with various aspects of clinical drug trials. He is presently the Coordinating Editor of the Cochrane Hypertension Review Group, Editor-in-Chief of the Therapeutics Letter, and Managing Director of the Therapeutics Initiative (TI). The TI's objectives are independent assessment and dissemination of therapeutic evidence. The TI acts in an advisory role to BC Pharmacare.