

**The Inclusion of Women in Clinical Trials:  
Are We Asking the Right Questions?**

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**Women and Health Protection**

**March, 2006**

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Women and Health Protection is financially supported by the Women's Health Contribution Program, Bureau of Women's Health and Gender Analysis, Health Canada. The views expressed herein do not necessarily represent the views of the Bureau of Women's Health and Gender Analysis, Health Canada.

Également disponible en français.

ISBN 0-9738701-8-4

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## PROLOGUE

When drugs are an appropriate option for the treatment of a diagnosed medical problem, women want to know that the substance(s) they will take are of proven effectiveness and safety. Have the drugs prescribed for women been tested on sufficiently large – and representative – groups to provide the information needed to assess the potential benefits and harms of their use and allow a woman to make an informed decision? Is there information to show that a drug is, in fact, the best option for dealing with a condition of concern? These are the questions that need to be asked – they are essential to improving the quality of the regulation and management of drugs.

Guidelines and recommendations about the inclusion of women in clinical trials of drugs have been developed in response to concerns that women may have been taking drugs that had only been tested in males and might, therefore, not work, or work differently, in them. However, while including women in clinical trials may begin to provide data that address biological differences between males and females with regard to drug metabolism, kinetics, etc., the dictum “to include” glosses too quickly over gender differences that may play a substantial role in how women use and respond to drugs. As well, wider questions about whether drugs are the best way to deal with a problem are left unexamined by a singular focus on the “inclusion of women.” These questions may actually be more relevant to women’s health protection and health promotion. This report, therefore, addresses both the narrow and the wider issues evoked in considering the inclusion of women in clinical trials, highlighting especially where gender, even more than sex, is pertinent.

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**Sex** usually refers to the biological, anatomical, and physiological characteristics that distinguish females and males. **Gender** refers to the various socially constructed roles, expectations, and relationships that society differentially ascribes to males and females across their life spans and that intersect with other social and culturally determined factors such as ethnicity, ability, sexual orientation, etc. Both sex and gender are determinants of health; their interactions help explain some of the gendered patterns of disease and health care we observe. Thus, we find that some diseases/conditions are unique to women; some are more prevalent in women than men; and even when men and women have the same diagnosis, the care they receive may differ. To promote and protect women’s health, we need to understand fully the influence of biology and of gender, and to assess as well, differences among women that reflect their varying experiences. (Doyal, 2003)

## INTRODUCTION

Women have different relationships with drugs than do men, with the differences based in gender at least as much as in biology.<sup>1</sup> For example, women are more likely than men to be poor and following a prescribed medication regimen may, for cost reasons alone, be quite difficult and lead to pill splitting or skipping.<sup>2</sup> Women are also more likely than men to live longer and, in consequence, experience more chronic diseases needing

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<sup>1</sup> Broyles et al (2005) provide an insightful discussion of some of these issues in the context of “medication practice” and “adherence” to treatment for HIV/AIDS.

<sup>2</sup> Lippman, 2005

treatment with a range of medications, opening the door to an increased risk of harmful drug interactions. As well, the marketing of drugs is often geared primarily to women and girls, so they may be preferentially exposed to misleading information.<sup>3</sup>

Biological differences between males and females affect how a drug functions within the body, once it is consumed.<sup>4</sup> As Health Canada's gender-based analysis (GBA) policy observes, used consistently GBA "makes for good science and sound evidence by ensuring that biological and sex differences between women and men are brought into the foreground." Wizemann and Pardue note that "It is increasingly apparent that many normal physiological functions—and, in many cases, pathological functions—are influenced either directly or indirectly by sex-based differences in biology."<sup>5</sup> Increasingly, data are showing that patterns of gene expression differ, on average, between males and females, and this could lead to biological sex differences in how drugs are handled in the body.

These biological differences have implications for the development of drugs and other interventions for health and thus for clinical trials. For example, four previously approved potassium-channel blockers (withdrawn by the US FDA in the late 90s) showed that "women had a much greater risk for developing ventricular arrhythmias in response to these drugs."<sup>6</sup> Recent research<sup>7</sup> on the sex differences in the role of aspirin in cardiac events highlight the need for basic science to take 'gender and sex' into account.

In addition, because of average weight differences, a "standard" medication dose for a man may be excessive for a woman. Similarly, because of the concomitant use of hormonal contraceptives, the metabolic action of the same drug may differ between males and females.

For these and other gender and sex-based reasons, how, and by whom, drugs are tested and managed before and after marketing are important considerations, with questions about the inclusion of women in clinical trials perhaps receiving the most attention. However, this focus must be sufficiently broad to ensure that the context in which trials are carried out is also examined. The context has great bearing on whether or not the mere presence of women in research to establish the efficacy and safety of a drug is sufficient for promoting women's health – or whether clinical trials, even when women are included, might themselves be harmful, especially when they focus solely on drugs.

## **BACKGROUND**

This report was commissioned to learn what had happened in Canada since 1997 when *guidelines* about the inclusion of women in clinical trials (specifically of medications) were published by Health Canada. These guidelines advocated the inclusion of women of childbearing potential and post-menopausal women at all stages of research to develop drugs, and urged their inclusion *in sufficient numbers to enable the "detection of*

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<sup>3</sup> Mintzes, 2004

<sup>4</sup> US Institute of Medicine report edited by Wizemann and Pardue, 2001

<sup>5</sup> Wizemann and Pardue, 2001

<sup>6</sup> Heinrich, 2001

<sup>7</sup> See, for example, Berger et al, 2006 and Stramba-Badiel and Priori, 2005

*clinically significant sex-related differences in drug response.*” In other words, investigators were not only to bring women into studies, but to analyze the results by sex so that if there were any male/female differences, these could be identified. This section outlines how this came about and where we are now.

### **Women and pharmaceutical research: A brief overview**

Following the thalidomide and DES disasters of the 1950s and 60s, when it was recognized that major damage could be done to offspring of women exposed to drugs during pregnancy, it became common practice (for research purposes) to assume all women between the time of first menstruation until menopause were “potentially pregnant.” Thus, in the late 1970s, the US FDA adopted a policy of exclusion that basically prohibited all women – irrespective of their status with regard to sexual activity, sexual orientation, etc. – from pharmaceutical research for fear of causing foetal harm. While this was supposed to refer only to Phase 1 trials (done either on healthy people or those at the terminal stages of some disease to determine toxic levels of a drug), it wasn’t long before the rule was applied to ALL pharmaceutical research.<sup>8 9</sup>

In the 1990s, various women’s health advocates, recognizing that women were taking medications that had been tested for effectiveness and safety only on men, began to lobby for inclusion in clinical trials. As well, health care professionals, who wanted more options for their female patients, pushed for including women in clinical trials and for trials of drugs to treat conditions that affected primarily women – and not only in their reproductive capacities. A consensus developed fairly rapidly that women had to be included in trials so that they could share in any resulting benefits.

In response, the National Institutes of Health (NIH) in the US began to formulate guidelines, and then policies, for the inclusion of women in clinical trials. The NIH Revitalization Act, adopted in 1993, specifically required that research funded by the NIH include women as subjects in all clinical studies.<sup>10</sup> It also required that NIH-funded clinical trials be adequate in size to allow analyses to determine if women were differentially affected by whatever was being studied. Parallel to this policy was one developed by the US FDA, but unlike the NIH approach, including women was not made mandatory.

Canadians, too, were attentive to the possible harms and injustices to women if they were excluded from clinical trials and later took – or were precluded from taking – drugs that had not been tested in them.<sup>11</sup> In 1997, the Canadian Minister of Health, Alan Rock, announced a *guideline* on “Inclusion of Women in Clinical Trials.”<sup>12</sup> Unlike the NIH policy in the US, this guideline only sought to “*encourage*” (my emphasis) the inclusion of women; it did not make this a requirement. It also proposed that “patients of both

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<sup>8</sup> Stevens and Pletsch, 2002

<sup>9</sup> See Abergel, 2000, for a discussion of risk management at Health Canada.

<sup>10</sup> Several authors (e.g., Prout and Fish, 2001; Baird, 1999, Corrigan and Williams-Jones, 2003; Mastroianni, et al, 1994; 1999; Merkatz, 1998) have detailed the historical events leading up to this decision and will not be repeated here.

<sup>11</sup> Sue Sherwin (1994) has written most eloquently about this.

<sup>12</sup> [www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/wominct\\_e.html](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/wominct_e.html)

sexes... be included in the same trials in numbers adequate to allow detection of clinically significant sex-related differences in drug response,” but here, too, there was nothing in the guideline to make this mandatory. Interestingly, the guideline DID acknowledge the importance of including, and then examining for differences, women using oral contraceptives or “estrogen replacement therapy.”<sup>13</sup>

As this brief summary indicates, in both Canada and the US, “inclusion” referred almost exclusively to being research subjects; there was no serious mention of the need for inclusion of women in the community of researchers or in the decision-making groups that set research agendas.<sup>14</sup> It is, perhaps, also worth noting that the calls for inclusion were not always attentive to the particular role in drug research that had been played by women with disabilities and racialized and other marginalized women over the years. In fact, women in these groups actually *had*, all too often, been included in research studies and equally all-too-often, included without having given proper informed consent.

Internationally, the issue of including women in clinical trials of drugs has also been addressed, in particular by the International Conference on Harmonization (ICH).<sup>15</sup> However, while the ICH has specific *guidelines* on the conduct of clinical trials in geriatric and paediatric populations, reasoning that, because of age effects (both groups) and the effects of “concomitant medications” (geriatric populations), these two populations warranted special attention in drug development, there is nothing that specifically addresses women. In fact, following a review of existing policies from the US, the EU and Japan, as well as of its own “good practice guidelines,” the ICH concluded that no specific guidelines addressing gender issues were required despite requiring that a study population represent the target patient population.<sup>16</sup>

On first glance, the various policy announcements on the inclusion of women appear straightforward – and non-controversial. But, as Epstein<sup>17</sup> has pointed out elsewhere, they actually raise some important questions about just what “differences” between men and women are seen as requiring the inclusion of women in clinical trials. In other words, what is being claimed about the “medical consequences of sex, gender?” Biological differences? Social concepts? A combination? Why, and for what reasons, has “taking account of difference... come to seem like a good thing?”<sup>18 19</sup>

At first, most of the clinical trial policy recommendations from 1993 on seemed to be based on the notion of distributive justice. Women needed to be included in the trials of

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<sup>13</sup> Interestingly, Section 7 of the Tri-Council Policy Statement on Research Ethics is silent with regard the inclusion of women in such studies.

<sup>14</sup> Something, beyond mere inclusion, that women wanted was good research on the problems that were most prevalent among us, as well as studies to learn if medications already marketed were safe and effective. These wants remain mostly unaddressed.

<sup>15</sup> See *Women and Health Protection*, 2005 for details and for evidence of how women’s groups monitor and advocate on these issues.

<sup>16</sup> Guideline E8, 2004

<sup>17</sup> Epstein, 2004

<sup>18</sup> Epstein, 2004, page 189

<sup>19</sup> A relevant question to address, in this light, is whether disaggregating data by sex is of primary importance or if applying the concept of risk stratified analysis might be richer – and more informative for making inferences. See Hayward et al, 2005, for a discussion of these types of analyses.



interventions that might be applied to them to ensure they could properly benefit from any advances – and to ensure that any risks associated with being in a study were distributed fairly and not just falling on one group. With time, and the growing numbers of women in trials, some shifts in emphasis occurred to underline how effects needed to be assessed separately in women if the goals were truly to be met.

### **Inclusion of women in clinical trials:<sup>20</sup> Current status**

Over the past several years, various investigators have attempted to capture what is happening to fulfill these guidelines and regulations.<sup>21</sup> The most vigorous has been the General Accounting Office in the US. It is perhaps thanks to its reports that policies have become increasingly explicit and binding so that today, investigators in the US may not obtain NIH funding if their plans for including and separately analyzing data on women are not spelled out in protocols submitted for support.<sup>22</sup>

Non-governmental groups and individuals have also assessed the inclusion of women in trials. Some focused on specific health problems, while others have looked at trials in general. Overall, they have generally found a continuing under-representation of women, with this especially clear when ethnic and minority status intersect with gender.<sup>23</sup>

In a major project, Bartlett et al.<sup>24</sup> explored the “social, legal and ethical contexts of trial exclusion” in the US and the UK. They documented “disparities between people included in trials, those using the drugs and those in need of treatment;” explored the “effects of exclusion on the generalizability of trials” with regard to the effectiveness of statins and the adverse effects of NSAIDs; and “developed a theoretical model for the causes and effects of exclusions.”

Among their major conclusions relevant here was that, while there continues to be under-representation (of women, older people and ethnic minorities), this may not always affect the external validity<sup>25</sup> of *relative* effect estimates. However, the same cannot be said about *absolute*<sup>26</sup> effect estimates in different sociodemographic groups; these ARE likely

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<sup>20</sup> This report uses the term ‘clinical trials’ to refer primarily to Phase 3 trials in which subjects are randomly assigned to receive either the test medication or a comparison drug (or placebo) with the overall goal of determining the efficacy of the new(er) product. These trials are geared primarily to meeting the needs of regulatory bodies, more than for testing some innovative scientific hypothesis and must be understood in this light. The other clinical trial phases consider such things as the safety, absorption, metabolism and activity of a drug in usually healthy people (Phase 1); short-term effects on selected outcome measures in patients (Phase 2); safety and effectiveness in the general population of users post-marketing (Phase 4).

<sup>21</sup> [www.democrats.reform.house.gov/Documents/20040830110302-93240.pdf](http://www.democrats.reform.house.gov/Documents/20040830110302-93240.pdf) There has also been some research to explore factors related to women’s participation (or not) in clinical trials (see Fullerton and Sadler, 2004, for an overview of some of these).

<sup>22</sup> [http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm)

<sup>23</sup> See, for example, Heiat et al, 2002; Killien et al, 2000

<sup>24</sup> Bartlett et al, 2005

<sup>25</sup> Epidemiologists speak of “external” validity to refer to the generalizability of a study’s results to the overall population. “Internal” validity, by contrast, refers to whether the study is itself sufficiently well done and bias-free to provide valid, trustworthy results.

<sup>26</sup> Most simply, *relative* effects are what is seen when one group is compared to another. For example, a two-fold difference, a relative measure, would be found if side effects occurred in 40/100 patients taking a drug compared to occurring in 20 of 100 people not treated, as well as if there were side effects in 40/100,000 users vs 20/100,000 non-users. However, the *absolute* difference between groups would be quite different: 20/100 more affected in the first case, only 20/100,000 in the latter.

to be biased, but the nature and extent of this bias cannot be modeled with current understandings and data.

Others, too, have given a mixed report card on the inclusion of women in drug trials:<sup>27</sup> while more women are apparently being enrolled in trials overall, there has been little, if any, in-depth presentation or use of sex-disaggregated data – and perhaps even less clarification of the use of gender and ethnic categories or their conceptualization. And very little work has examined in depth the implications (besides age) of various inclusion and exclusion criteria that define which women in the “base” population may actually get into a trial.

In February 2003, Joseph Caron submitted a paper as background for a “Think Tank” sponsored by the CIHR Institute of Gender and Health (IGH) in which he examined “initiatives and evaluations” carried out to “promote or support research taking into account gender and sex differences.”<sup>28</sup> His focus was on the degree to which existing guidelines and regulations were being monitored, and among his findings, two are of most relevance here:

1. While there have been major efforts in the US to increase the numbers of women in clinical trials, there are no data to show “beyond doubt” that these efforts have “resulted in the desired quantitative objective” (page 66).
2. There is still insufficient disaggregation by sex of research findings, indicating that not much has changed in the past decade.

With regard to Canada, Caron notes that the Women’s Health Strategy of Health Canada promised in 1999 to monitor the clinical trials policy on the inclusion of women but that, at the time of his writing, nothing systematic had yet been put in place to do so. And this remains the case today. (By contrast, it might be noted that another commitment in the Women’s Health Strategy, to have Gender-based Analysis (GBA) integrated into policy and program development, has begun to be implemented in Health Canada.)

In sum, then, in Canada, there are general guidelines from Health Canada encouraging the inclusion of women in clinical trials as well as a federal government commitment to the application of GBA to policy and program development. In addition, the Tri-Council policy on the ethical conduct of research involving humans states (Section 5.B, Article 5.2) that, “Women shall not automatically be excluded from research solely on the basis of sex or reproductive capacity” (although there is nothing specifically about the inclusion of women in the section addressing clinical trials). Nevertheless, a review of the peer-reviewed and “grey” literature and a policy scan reveal that there is no *mandate* in Canada to include women in clinical trials (despite the commitment to monitor this policy made in the 1999 Women’s Health Strategy). Moreover, there is still more adjustment for, than analysis by, sex in reported research. And finally, while much has been written<sup>29</sup> about where and how women and men differ biologically in ways that could underlie sex

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<sup>27</sup> Evelyn et al, 2001

<sup>28</sup> Caron 2003

<sup>29</sup> e.g., Wizemann and Pardue, 2001

differences in drug availability and action, there continues to be almost NO attention to gender matters – other than to reduce these to questions of biological sex.<sup>30</sup>

Thus, it is possible to conclude that despite the good intentions of the 1997 Canadian guidelines, there is no systematic monitoring of conformity to them. Nor is there strong evidence from reported research that the appropriate inclusion of women in drug trials is happening.<sup>31</sup>

However, also to be considered is the potential for a focus merely on the inclusion of women in trials and on sex-disaggregated analyses to actually distract from obtaining the kinds of information many women actually need, information about non-drug or holistic ways of addressing their problems. For example, as they age, women are likely to have more than one chronic condition and to be living with these for many years. Even if drug treatments for each of these are studied in clinical trials, the very set-up of the trials (short-term exposures one at a time, often with potential participants excluded if they are taking other medications or have other disorders) cannot answer the questions women have about how to manage their individual situations.<sup>32</sup> As well, we need to consider that clinical trials are but one way to get the information we need about how to respond to women's health problems.

## **GENERALIZABILITY/EXTERNAL VALIDITY**

### **Why do we need to include women?**

In epidemiological terms, demands for including women in clinical trials often reflected concerns about the external validity or generalizability of the research on drugs; if those who would eventually take the drug had not been studied in its development, how did we know the drug would work and be safe for them? And the past few years have shown, without doubt, the importance of studying drug effects in women separately from in men. For example, in March 2005 it was shown that, contrary to expectations based on studies in males, aspirin had effects in women unlike those in men with regard to primary protection against stroke and fatal heart attacks.<sup>33</sup>

Calls for inclusion have both justice and “scientific” rationales, and these don't always fully overlap. While inclusion is “right” to ensure that the benefits of research are shared by all and that the risks, too, are distributed fairly, including a group because they are identified as women needs to be justified on other grounds: are sex/biology or gender questions to be addressed? Further, if expectations of biological differences are the basis

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<sup>30</sup> And according to a recent report [Simon et al, 2005], apparently there is minimal attention even to studying sex differences in NIH-supported research.

<sup>31</sup> Further complicating what is to be learned from reported clinical trials are a series of revelations in recent years that have exposed serious problems with the doing, reporting, and reviewing of pharmaceutical industry-supported drug trials – and most drug trials ARE now supported in whole or part by the industry. These revelations, combined with recalls of (or, as in the US, black box warnings for) major drugs, because of serious harms that had not been reported or identified in the data on which marketing approval for them had been given (Vioxx, SSRIs, Depo-Provera, etc.), give renewed urgency to a broad examination of the general topic, “women and clinical trials.”

<sup>32</sup> See Tinetti et al, 2004

<sup>33</sup> Ridker et al, 2005

for inclusion, are there reasons to anticipate that differences between sexes will be more important than those within a sex? In other words, while the biological impact of sex differences must be considered, we must also be cautious and not assume all women are alike and/or that there is something fundamental (“essential”) about being a woman that pertains to all females.<sup>34</sup> As well, we need to guard against making false assumptions that all male/female differences are necessarily biologically determined. Most important to avoid are assumptions that arbitrary biological traits are markers of innate differences between males and females.

### **Trials and drugs for the elderly**

It is well documented that there are very few, if any, trials of drugs for the elderly that have compared a new active medication with one being used in current practice. The lack of these trials is of a particular interest to women, given the higher numbers of women in this population. These “head-to-head” trials are not required for Health Canada approval and there is little incentive for pharmaceutical companies to mount them, in part because such comparisons might reveal the new entity to be no better, or even worse, than the existing one. In addition, such trials are more expensive to run because it is easier to show a difference between an experimental drug and a placebo than between an experimental drug and an active control: more patients are required in the latter type of trial and that means greater cost. But without these comparison trials, the health and well-being of the elderly may be put at especial risk, exposing aging women to drugs that, though they have shown efficacy in placebo-controlled trials, may not be safe. This is particularly the case when there is more than one drug in a class and it is assumed, with no scientific basis, that they are interchangeable.<sup>35</sup>

For example, it has been pointed out by many that drug trials almost always have an upper age limit for participants and that researchers continue to exclude older people, leaving what McMurdo et al. (2005) call a “yawning chasm between patients in the real world and patients who participate in clinical studies.” Paula Rochon (1998) and others have noted how this is particularly prejudicial to women who, on average, develop some diseases later in life than men, take more medications as they get older, and also live longer than men. Thus, merely to include women in a study without taking into account WHICH women will be likely to use a drug if it is approved is not sufficient. An arbitrary cut-off at age 75, for example, means that drugs could be prescribed for an ever-growing population of women for whom the safety and effectiveness of those drugs is unknown. Clearly, then, gender is an important consideration in assessing the generalizability of a clinical trial.

This issue is of specific relevance with regard to cardiovascular disease (CVD) and the development of drugs to treat or prevent it.<sup>36</sup> Because women tend to develop CVD at later ages, on average, than men,<sup>37</sup> and because the probability of having other chronic

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<sup>34</sup> For example, studying males and females separately may be of less importance in a drug study than separating subgroups on the basis of weight or some other feature related to how a drug may work.

<sup>35</sup> Zarowitz, 2005

<sup>36</sup> Stramba-Badiale and Priori, 2005; Jochmann et al, 2005

<sup>37</sup> Re: CHD in women, see Mikhail, 2005. As well, the later diagnosis of CVD in women compared to men probably has both sex and gender determinants. The former are more easily proposed (e.g., the influence of

diseases that may require medication also increases with age, it is not unlikely that women with CVD will have other conditions for which they are taking drugs (e.g., osteoporosis, high cholesterol). Polypharmacy is to be expected in women living in their own homes in the community – as well as in women living in care-giving facilities. Yet, clinical trials are still set up to examine one product at a time, with those taking other medications often excluded from trials. This raises the fundamental question of whether this kind of trial has any real relevance (i.e., generalizability may be quite limited). This limitation was illustrated clearly following a recent advisory from the US FDA about increased mortality among elderly patients using “atypical antipsychotic medications.” Many physicians switched patients to older drugs, but this decision had no empiric basis, since there were no data on the elderly who, it turned out, not only were mostly women, but actually did as poorly on the old as on the newer drugs.<sup>38</sup>

### **Efficacy vs. effectiveness**

The discussion above illustrates why it is important not just to look at the “inclusion of women in clinical trials,” but to question the very nature of trials and how they are designed and analyzed. It also emphasizes why information about a drug’s *efficacy* may be of limited clinical relevance; the transition from efficacy (how a drug works in an ideal[ized] situation) to effectiveness (how it works in the “real world”) is neither necessarily smooth nor linear – or one way. This leads to potentially unavoidable detours in going from “bench to bedside” and to a possible clash between “evidence-based medicine” (EBM) and “knowledge transfer”<sup>39</sup> to the clinic. As framed today, EBM requires clinical trial data (i.e., efficacy data). But of what use is “transferring” this knowledge if it is of limited, if any, generalizability? And these limitations may be the rule more than the exception, raising concerns about the difficulties – if not harms – of applying average results obtained in ideal circumstances (as clinical trials provide) to individual patients in the real world.<sup>40</sup> In consequence, there are increasing calls for effectiveness and “practical” trials. As well, approaches that integrate behavioural and social science research or that are designed to incorporate previous knowledge and experience (Bayesian trials<sup>41</sup>) are being explored with regard to improving the usefulness of research for clinical and policy decision making.<sup>42</sup>

In a similar vein, we need to examine the increasing emphasis on the use of “clinical practice guidelines” (CPG) to improve the care physicians give patients as well as their use as standards for assessing quality of care and, in some instances, whether or not there will be reimbursement for a medical encounter. These guidelines usually are written by experts, often under the auspices of a professional organization, and are supposed to be based on the best available evidence, usually that from clinical trials. The CPGs are usually constructed one disease at a time, but, for example, women with disabilities and

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estrogen levels, the differing physiologies, etc.) while the latter are more interesting and hidden: different socially-patterned eating and physical activity behaviours; social influences on seeking and getting medical care; mistaken diagnoses because of gendered patterns of physician/patient interaction; etc.).

<sup>38</sup> Wang et al, 2005

<sup>39</sup> A critique of EBM is beyond the scope of this report. Interested readers can find some relevant articles in the Fall 2005 issue of *Perspectives on Biology and Medicine*.

<sup>40</sup> For an informative discussion of this and related points, see Kravitz et al, 2004.

<sup>41</sup> Berry, 2006

<sup>42</sup> e.g., Tolley and Savery, 2006; Tunis et al, 2003; Glasgow et al, 2003

older women often have multiple co-morbidities and are already taking medications for other diseases. In such circumstances, any specific guideline could be difficult to apply or even harmful, if the interactions with other interventions are not taken into consideration. These latter could not only influence the way in which the new medication is handled, but complicate what may be an already complex drug-taking regimen leading to adverse effects.<sup>43</sup>

Clearly, the inclusion of a range (in age, in pre-existing conditions, etc.) of women *in appropriate, well-designed, ethical* clinical studies IS important prior to a drug receiving approval. Important, too is the development of independent, thoughtful, specific processes for the post-marketing investigations and surveillance of approved drugs. However, we do need to ask if randomized controlled trials (RCTs), even with rigorous monitoring of marketed drugs, are the only way to get useful, valid information of the kinds needed to promote and protect women's health.

### **RESEARCH CLIMATE AND THE COMMERCIALIZATION OF RESEARCH**

It has been estimated that worldwide over 20,000 new trials are begun every year.<sup>44</sup> In the US alone, "total grant spending for clinical trials involving human subjects [in 2002] was approximately \$5.6 billion."<sup>45</sup> Of this, more than 70% came from the biopharmaceutical industry.<sup>46</sup> This kind of monetary investment gives this industry great power in setting research agendas, influencing the questions that will be asked, the ways in which answers will be sought, and the extent and nature of the results that are disseminated.

The growth in Contract Research Organizations (CRO) that design and carry out studies, offer in-house ethical review of protocols, and even provide writers for research publications, is one sign of how pervasive the clinical trial industry is becoming.<sup>47 48</sup> Another is the frequency of ads in community newspapers and on the radio seeking participants for clinical trials run by these private groups.

This kind of heavy industry investment leads to the development of clinical trials that are designed more with patents and profits than with women's health in mind.<sup>49</sup> Compounding this is the extent to which academics are pressured into research partnerships with industry, so that even work supported with public funds – as from the CIHR<sup>50</sup> or provincial agencies – is privileged if it will bring benefits back to the

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<sup>43</sup> see O'Connor PJ, 2005; Boyd et al, 2005

<sup>44</sup> Sim and Detmar, 2005

<sup>45</sup> Personal communication, Joel Lexchin, M.D., School of Health Policy and Management, York University.

<sup>46</sup> AMA Council on Scientific Affairs, Report 10, June 2004

<sup>47</sup> It has been claimed that the clinical trial has *itself* become an industry [JA Greene, unpublished paper]; certainly there is evidence of this in the burgeoning number of CROs and the billboard ads at bus stops and in community newspapers offering high payments for research recruits.

<sup>48</sup> See Bloomberg News for information suggesting that 75% of drug tests are contracted out to private test centres by the pharmaceutical industry (Bloomberg 2005) [www.bloomberg.com]

<sup>49</sup> e.g., drug combinations, repackaging two standard drugs in one [BiDi]; Serafem – "Prozac in pink," where, finding/claiming a new use for an old medication is sufficient to get further prolonged patent protection for money-making drugs. Cf Brophy, 2005.

<sup>50</sup> The CIHR funds 30-35 new trials per year. In 2005, 140 were active. However, over 50% of these were non-drug trials. (Karmela Krleza-Jeric, Canadian Institutes of Health Research, Ottawa, personal communication. 2 December 2005)

university.<sup>51</sup> For example, the GlaxoSmithKline (GSK) CIHR Research Chair Award Competition notice mentions, as a specific objective, establishing chairs in disciplines where GSK has a “clear scientific interest” and fields that are “important to specific elements of development and commercialization...” (CIHR website: [www.cihr-irsc.gc.ca/e/27725.html](http://www.cihr-irsc.gc.ca/e/27725.html))

If we consider only drugs being developed to treat what probably all would agree are “real” diseases (such as breast cancer, for example), we find a pro-trial bias is also being created at the *individual patient* level. In the face of headlines telling scary stories about the state of the health care system (long waits, physician shortages, inattentive care, etc.), those with an authentic disease may believe, even be told that, participating in research is the only way to get a timely diagnosis, expert care, state-of-the-art treatment, etc. In such circumstances, a woman’s overall reluctance to be a “guinea pig” may be overridden by what she sees as her health needs. And with trials and consent forms written in ways that may lead to what has been called a “therapeutic misconception”,<sup>52</sup> over-stating the possible advantages of being in a study, one can raise questions about whether consent is truly informed. Pro-trial attitudes are further advanced by assumptions that women “always want to help”<sup>53</sup> and so may feel they must conform to this expectation.

By contrast, when a woman *does* express resistance to participation in a trial despite all the lures dangled before her, and makes an informed decision not to take part, she may find herself treated as a second-class patient, if not overtly criticized.<sup>54</sup>

It is essential that trials not be viewed as a default option by women who might otherwise not have access to proper care.<sup>55</sup> At the same time, it is important to recall that this “default” can be inequitably distributed: women with disabilities may be seen as ineligible for trial participation and relegated once again to what is perceived as “lesser” care – as well as prevented from knowing just what drugs are effective and safe for them to take.

What seems needed to ensure the possibility of authentic informed choice about participating in a trial, therefore, is the prior assurance of quality care for all women with the condition for which a drug is being tested. This must include assured access to whatever high-tech equipment (MRI, PET scans, etc.) is clearly required to determine eligibility for research and or to monitor progress in a study. Trial participants must not be allowed to jump to the head of the queue or cause delayed access for others.

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<sup>51</sup> Shelly Krinsky has referred to the pharmaceutical business as a “vertically-integrated industry” in which drug development, guideline development, physician education, drug promotion, etc., are all under the same aegis (Krinsky, 2003).

<sup>52</sup> Lidz and Appelbaum, 2002

<sup>53</sup> A particularly problematic paper suggesting that “scientific research is a moral duty” by John Harris in the March 2005 issue of the *Journal of Medical Ethics* is further cause for concern.

<sup>54</sup> Anonymous personal communications from 3 women.

<sup>55</sup> Although of interest here is a recent report [Melnikow et al, 2005] that in fact very few women actually signed up to take part in prevention trials, even when they were given extensive “risk counselling.”

## Prevention trials

The situation described above pertains to those with serious medical problems who are “invited” into clinical trials that can be termed THERAPEUTIC trials: these trials test a product for its ability to cure, or delay or interfere with the progress of a disease, or because it might be easier to take or have fewer side effects than existing products or a placebo. However, research today probably focuses as much on “treating” *risk factors* as on treating disease, so that one may find a pro-trial bias<sup>56</sup> also elicited at the individual level when researchers and the media hype the benefits of drugs, the “miraculous” panaceas needed to ward off the chronic conditions that await us all (especially, for women today, breast cancer and osteoporosis). The constant messages of rescue and of hope, in the face of all the “risks” with which we live, mean that individuals are likely to assume there are more benefits than harm to participating in these PREVENTIVE clinical trials.<sup>57</sup>

Primary prevention trials raise special concerns with regard to potential harms and safety, since they involve giving potent drugs to healthy individuals. This alone must influence any “risk/benefit” balancing; it certainly should influence what is considered as adequate for the size of a study population. Prevention trials, it can be argued, must be larger than therapeutic trials because here, especially, adverse effects must be identifiable before marketing is approved.<sup>58</sup> But, paradoxically, this size requirement for clinical trials focusing on “treating” risks may actually turn them into marketing devices (also known as “marketing” or “seeding” trials”). Their very size and the need to recruit healthy participants can become a way to make a brand name known, and seem a desirable product, even before the drug has been approved for sale!

## POLICY ENVIRONMENT AND CLINICAL TRIALS<sup>59</sup>

Complementary to how the research environment influences the nature of clinical trials is the impact of the policy environment. Most important, perhaps, is the ongoing overall restructuring of Health Canada – and other branches of government – under the umbrella of “smart regulations.”<sup>60</sup> Space limits preclude discussion of this major policy shift here, but some have suggested that this move to join economic growth with the development of “safe” drugs and devices is neither smart nor a plan for health protecting regulations and can only set the stage for what Sue Sherwin has called “incoherence” in policy values with respect to drug regulation: can government commitment to health and well-being be

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<sup>56</sup> Perhaps the strongest contributor to a “pro-trial” bias is the reification of “evidence-based” care, policy, decision-making, et al., and the general assumption that only randomized trials can provide the “evidence” needed for these bases. The importance of this issue notwithstanding, it is beyond the scope of this paper other than the earlier discussion.

<sup>57</sup> Although not limited to drug trials, it is of interest that some recent work shows that participants in clinical trials do not necessarily fare less well, or better, than those who get the same treatment outside of a trial. (Vist et al, 2005).

<sup>58</sup> Taylor and Wainright (2005) suggest that open label extension studies, which follow the completion of RCTs and allow *all* (their emphasis) participants to take the study medication are not only rarely published, but may actually be marketing ploys to promote drug use rather than being research.

<sup>59</sup> For a more detailed discussion of the issues raised in this section, see J. Downie, 2006.

<sup>60</sup> See comments by Janice Graham (2005) in CMAJ.



compatible with its support of industry and the economic development of the biotech/pharmaceutical sector?<sup>61</sup>

The answer is probably obvious when we learn that the use of cost-recovery mechanisms and decreases in the time for drug approvals, components of “smart regulations,”<sup>62</sup> lead not only to reduced vigilance in testing the safety of drugs and devices, but to a host of policies and mechanisms that favour industry over the individual.<sup>63</sup> Thus, the new clinical trials regulatory framework that became active in 2001 had, as an explicit goal, a decrease in the time for the review of new drug applications to give Canada “improved” access to innovative therapies. This came at the same time as the safety of people in clinical trials was to be increased!

This climate provides at least a partial explanation for the lack of adequate surveillance and monitoring of drugs on the marketplace, a lack especially relevant to women, since of the 10 drugs recalled recently in the US because of dangers they posed, 8 were substances that caused greater risks for women than for men.<sup>64</sup> It is true that even if there had been women in all the pre-marketing trials of these drugs, harm might not have been seen until after the substance was in wide use in the population. But with “smart regulations” aimed at getting faster drug approvals, tending to lead to trials of very limited size, carried out in homogeneous populations, and of short duration, uncommon harms may not be revealed before a drug is put onto the market (assuming that trial data have actually been presented honestly and in toto). Clearly, this underscores the importance of vigilance after, as well as before, a drug is marketed, especially drugs for women. The regulatory system is woefully remiss in doing Phase 4, or post-marketing, trials after a drug is on the market and being taken by those who have probably not been represented in earlier study populations. Thus, recent initiatives by Noralou Roos and others to develop improved mechanism for managing clinical trials and for the post-marketing surveillance of drugs represent important steps. It will be of interest to see where these lead: hopefully to a process independent of, though funded by, the pharmaceutical industry (e.g., through pooled contributions to a research network of experts in pharmacovigilance).<sup>65</sup>

## **NEOMEDICALIZATION<sup>66</sup>**

Any consideration of women and clinical trials must be attentive to the socio-political context of medical research, the changing regulatory system, and the pressures on women to join what may be problematic studies. But we also need to be attentive to an even larger context, one that can be subsumed under the label of neomedicalization.<sup>67</sup>

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<sup>61</sup> cf the report of the Standing Committee on Health, *Opening the Medicine Cabinet*, 2005, as well as the UK Health Committee report (2005).

<sup>62</sup> See the working group paper on the ICH.

<sup>63</sup> Lexchin, 2005

<sup>64</sup> Simon, 2005

<sup>65</sup> Proposal by the Canadian drug policy development coalition, communication from Noralou Roos.

<sup>66</sup> Adele Clarke et al. (2003) have developed a concept they call “biomedicalization” and it bears many similarities to what I have named “neomedicalization.”

<sup>67</sup> Lippman, 2004

Neomedicalization is an expansive incarnation of disease-creation.<sup>68</sup> This process involves the corporate-driven creation and marketing of diseases to sell drugs, as well as the framing of natural experiences as *causes* of future diseases. In other words, the emphasis is on one's supposed *risk* of developing a problem, and, in its most pernicious form, it makes being “at risk” itself a disease state.<sup>69</sup>

Neomedicalization fits seamlessly into two currents of contemporary North American society: neo-liberal economic policies and their consumer orientation, and the increasing emphasis on “risk” and its management. If the economics of neo-liberalism can be said to embrace corporatism, consumerism, and capitalism, these same forces nourish neo-medicalization. And to underscore this, one need only read some recent documents that refer to “health services as . . . . a leading edge economic sector for employment, innovation, research and exports” or that talk about health care as a “dynamic engine of economic growth” as well as an “export platform with economic spin-offs.”<sup>70</sup>

In neomedicalization, the owners and makers of medical knowledge are not only physicians, but also corporate entities, government, the media and consumers.<sup>71</sup> Neomedicalization has a broader reach than medicalization, since we all can be found to have some behaviour, some characteristic, some “marker” – genetic or otherwise – that can be called a “pre-disease.” This is increasingly likely as more and more distant features in a possible disease-causing chain are being labelled for treatment: BMI (body mass index) as a “pre-disease” for diabetes; BMD (Bone Mineral Density) as one for hip fracture; etc. The increasing applications of genetic testing will only enhance this.<sup>72</sup>

As well, neomedicalization is both a cause and an effect of the growing use of imaging technologies that reveal things one is not even aware of. These “things” (including DNA patterns, brain images, etc.) are not just early stages of a disease (which could, in some limited situations, be good to find early). More often, they (e.g., ductal carcinoma in situ [DCIS], prostate-specific antigen [PSA] levels) are either of unknown or of limited meaning with regard to a person's future health. This includes those variations labelled as genetic susceptibilities.<sup>73</sup> Given this, we might even identify the creation of “pseudo-diseases” as one component of neomedicalization.<sup>74</sup>

Neomedicalization grows out of – and itself nourishes – the current emphases (in North America) on “risk” and its management, and on individual “choice” and the offer of multiple “options” to women. Like the neo-liberalism that fertilizes it, it constructs health as a commodity, a resource needed for economic growth. Both emphasize augmenting women's choices (via the creation of tests, screening exams, etc.). Further, by framing life experiences as causes of disease, neomedicalization generates a whole “Selling

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<sup>68</sup> cf Conrad and Leiter, 2004

<sup>69</sup> For a recent example, see Moynihan and Cassels, 2005, and also Pollack in the 9 May 2005 NY Times, “marketing a disease, and also a drug to treat it.”

<sup>70</sup> Courchenne, 2003

<sup>71</sup> see Timmermans and Kolker, 2004

<sup>72</sup> see Bureau of Women's Health and Gender Analysis, March 2005

<sup>73</sup> And raises concerns about iatrogenic harm, if the intervention on these “early” findings itself has adverse effects and/or leads to unnecessary treatment.

<sup>74</sup> See Hoffmann, 2003 on technological paternalism.

Sickness”<sup>75</sup> industry to create “pills for prevention,” in the words of the UK Health Committee report, a “pill for every ill.”<sup>76</sup> And by further manufacturing – through their marketing strategies – new diseases for old drugs, grounds are established for the extension of patent protections on existing products and continued profitability of “old” drugs.

Neomedicalization encourages “risk management” by individuals rather than the public health application of the precautionary principle. Pharmaceutical companies encourage the use of pills to manage these risks. Because the environment gets identified as a seemingly non-manageable “trigger” that leads to illness in those who are “susceptible,” one’s biochemistry, hormones, and lifestyle alone are seen as manageable – with a pill to “fix” each of these conditions. This framing de-politicizes the determinants of health and shifts the emphasis to the individual who must work to be well – to manage her risks. In fact, “risk” itself becomes medicalized, with its management a social obligation – albeit an obligation that not all have the resources to carry out.

The economic roots of neomedicalization nourish the expansion of drug interventions to manage risks. Given that there are more healthy than diseased people in the world, offering a product that is claimed to help manage their risks can capture increasing numbers of those in need of some treatment. Finding the “not-yet-sick” and the “worried well,” who could be offered some drug or device, is the goal. And, since likely we are all “at risk for” something, this means everyone! As well, it means we could all be potential candidates for some clinical (“prevention”) trial.

Taking a drug that appears to affect the course of a well-defined disease and then doing trials of the drug in a healthy population, to see if it will lower their chances of getting this disease, is an increasingly common symptom of neomedicalization. Beyond the potential of direct harm to the women in such studies from the trial drug, we also need to be mindful of indirect effects (deflecting attention from upstream causes of a problem; further “disease mongering”), but also what could be called the “opportunity costs”: those things not studied (as causes or interventions) because funding is directed only to pharmaceutical fixes.<sup>77</sup> Perhaps for each trial we see proposed, we should demand an accounting of all these possible opportunity costs, and include them in our analyses of cost/benefit.

### **Neomedicalization and offers of “choice”**

Neomedicalization involves not just the translation of being “at risk” into a disease, or the marketing of drugs to manage risks, but the manipulation of the concept of “choice” to create the markets for these drugs and the tests that will uncover our risks.<sup>78</sup> This conception of choice is problematic, being perhaps more an illusion than a promotion of

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<sup>75</sup> Moynihan and Cassels, 2005

<sup>76</sup> House of Commons, 2004

<sup>77</sup> Related here is the concept of “fidelity” discussed in a recent paper by Woolf and Johnson (2005). They argue that we might do more for public/population health by improving how we deliver/manage existing drugs than by developing yet newer ones for the same problems. Or, as the title of an accompanying (though critical) editorial put it (Kravitz, 2005): we may need to do things better than do better things.

<sup>78</sup> Lippman, 1999

authentic autonomy. And this illusion can be harmful, particularly when it distracts us from looking upstream at the sources of the problems for which a set of response choices are offered.

Pharmaceutical companies – and others – have borrowed feminist language and converted it to consumer dialect. Most prominent here, perhaps, is the huge expansion of direct-to-consumer advertising (DTCA), whether this be with actual ads for specific drugs or “awareness” campaigns that encourage us to “ask the doctor” about some problem or to fill in some survey in a magazine that will tell us what problem(s) we have.<sup>79</sup> For example, how many fill out the depression or the osteoporosis questionnaires in popular magazines without experiencing a “My god, I have it” reaction?

Women's demands for “empowerment” have led the biopharmaceutical industry to create “choices” of pills we can take to maintain/promote our health, products we can purchase that will “empower” us to remain active consumers – all in the name of giving us choices. But when we look to see how our autonomy has been advanced, what we mostly find is a simplified menu of drug options: not only drugs to treat real diseases (cancer, diabetes), but also pills for prevention and for “lifestyle” reasons (e.g., to stop periods, etc.) or, perhaps more accurately, for the medical conditions industry has created for their use. For example, as many as 18 drugs are currently in clinical trials to treat something labelled “female sexual dysfunction,”<sup>80</sup> and world-wide sales for the three major erectile dysfunction drugs reached \$2.4 billion in 2004, about 0.5% of total prescription drug spending.<sup>81</sup> Do these figures reflect health needs, or commercial ones?

### **Alternatives to “Pills for Prevention”**

Do we need to support clinical trials, to find potentially problematic drugs for healthy women? Are pills for prevention what the ads recruiting study participants say they are, or are they more likely to be “pills of substitution,” substituting one disease for another?<sup>82</sup> Why focus on untried medicines of unproven safety and effectiveness, when documented safe approaches to prevention are available, approaches that are easier on women’s bodies and cheaper (e.g., dietary, environmental, and other changes).

Clearly, in considering the inclusion of women in clinical trials, we must look beyond the mere enrolment of women in ethical and scientifically valid drug trials, even beyond merely monitoring adherence to inclusion policies and analyzing data in ways that take account of sex and gender. While all this is important and may be necessary, it is certainly not sufficient to attain the real goal of recognizing and meeting women’s health needs. Safe, effective medicines are important, but pharmaceutical products are not always the best response to women’s health problems. Sometimes, they may actually damage rather than benefit health.<sup>83</sup>

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<sup>79</sup> see, for example, Mintzes, 2003

<sup>80</sup> Enserink, 2005.

<sup>81</sup> Berenson, New York Times, 4 December 2005

<sup>82</sup> Batt, 2001

<sup>83</sup> It has been estimated that only about 20% of drugs that begin human trials are eventually approved. This would suggest that 80% of participants in trials are in a trial that may not lead to any benefit in the end. If so,

In the case of heart disease, for example, a major killer of women, drugs may have some therapeutic role after disease develops, but what about other approaches to its *prevention*.<sup>84</sup> Many women know what issues threaten their health and of ways to eliminate these threats. But rarely are these interventions studied in the randomized clinical trials to which “evidence-based medicine” turns for developing practice guidelines. Parker (2005) echoes these concerns and suggests that “A skew toward therapeutic interventions and away from preventive ones, and to pharmacological ones and away from complex social care, are significantly driven by EBM methodology and the related financial rewards.” Perhaps if women’s health advocates were among those setting research agendas, structural determinants of health might get more attention. Women would likely ask different questions in seeking solutions to these problems, such as: “What improvements in neighbourhood facilities will promote increased time in physical activity? What policies help to reconcile paid/home work demands?” Where are the clinical trials of – and other research on – these kinds of interventions?

Even for medical diseases, studies that ask potentially “wrong” questions abound. Perhaps the best evidence is provided by breast cancer activists who have pointed out the enormous imbalance in drug-treatment research versus research that would identify environmental and occupational causes of the disease, thereby leading to primary prevention. In this category, too, is the news that a request for about 1.3 billion dollars (US) is in the works to support a human cancer genome project! Just think how much of the environment we could map with these funds. And then prevent cancer (and other diseases), not merely identify already transformed cancerous cells.

After years of fighting the medicalization of their lives, women are now experiencing more sophisticated, technologically-based forms of neomedicalization as clinical trials seek out women to test drugs for conditions of daily life (sadness, menstruation, etc.) newly made into diseases, with these processes undoing many of the gains women have made to reclaim their natural experiences.

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this would argue for ensuring that the “right” trials are done, that the “right” people take part, and that the “right” questions are asked.

<sup>84</sup> Mention must be made here of the class of drugs called statins. Their use exemplifies at least two serious trials-related problems. One is that they are being prescribed for women, even though women have not been included in sufficient numbers in clinical trials to determine the safety or effectiveness of these medications for primary or secondary prevention. The other is that the group for whom these drugs are being recommended keeps expanding, with no lower limit, it seems, to what a “normal” cholesterol level should be.

## **CLINICAL TRIAL ISSUES OF PARTICULAR RELEVANCE TO WOMEN: SOME RECOMMENDATIONS<sup>85</sup>**

Concerns about clinical trials – and about all aspects of the pharmaceutical industry and its regulation – are multiplying daily. Parliamentary committees (in Canada and the UK), journalists, and academic scholars, are all examining and critiquing what has been going on, most recently focusing on SSRIs (and hidden risk of suicide information) and Vioxx. How most clinical trials are funded, the length of the clinical trial, what is used for comparison with a study drug, and what outcomes (endpoints) are considered relevant are among many issues that remain as sources of concern. But even those who have voiced these concerns tend to do so as if they were “gender neutral”. Yet medicines, clinical trials, and all their intersections are profoundly gendered, and not only because women take more drugs, live longer, or have more chronic diseases than men. Thus, correcting the gaps and errors in what trials are done and how they are regulated has special meaning to women.

Solutions for some of the problems that have been identified have generally emphasized the full reporting of trial data,<sup>86</sup> as well as an open/public registry of the protocols of all drug trials on an easily accessible website.<sup>87</sup> In a similar vein, the former Canadian Minister of Health, Ujjal Dosanjh, agreed in May 2005 to make the adverse drug reaction reporting database of Health Canada open to all, perhaps to improve post-marketing surveillance capacity. Furthermore, industry itself appears to have taken to heart the general dismay at the current situation with clinical trials insofar as PhRMA, the umbrella organization for the major pharmaceutical companies in the US, has set up its own, industry-sponsored database, the “Clinical Study Results Database,”<sup>88</sup> which will provide study results separate from a registry of ongoing trials. These are clearly all necessary steps, but they are not sufficient – even if there were not already signs of non-compliance and of limited transparency.<sup>89</sup> To begin to address specifically gender-related concerns about clinical trials of drugs, the following comments and recommendations are offered for consideration.

### **Beyond numbers**

Most studies related to inclusion have focused on the numbers of women in trials. This focus is far from sufficient. Not only must women be included in studies of all drugs of potential use by them, but all resulting data must, at a minimum, conform to existing guidelines and be sex-disaggregated when they are presented, so that “lessons” for

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<sup>85</sup> Ray and Stein (2006) have outlined a 3-part reform of the current drug regulatory system for the USA. Separating approval and post-marketing studies from each other, and from a “drug information” process, they argue for three independent centres. Their ideas, and how they would address serious limitations in current processes and policies, warrant close attention and consideration.

<sup>86</sup> See Mohar references on the “CONSORT” guidelines.

<sup>87</sup> e.g., [www.clinicaltrials.gov](http://www.clinicaltrials.gov) operated by the NIH in the USA, with such registration recently becoming a requirement for consideration of later publishing of results by peer-reviewed medical journals (DeAngelis et al, 2004)

<sup>88</sup> [www.clinicalstudyresults.org](http://www.clinicalstudyresults.org)

<sup>89</sup> Zarin et al, 2005

women can be obtained.<sup>90</sup> There must be sufficient numbers in any subgroup to be analyzed for the data to be robust and useful, and these analyses must be planned in advance to avoid the false inferences that can come from “data dredging”: under-powered analyses may do more harm than good if the results are seen as definitive. Moreover, other relevant features (ethnicity, class, age, etc.) need to be accounted for in study protocols and described in published studies in *meaningful ways* that capture whether sex or gender (or both) is at issue. This will mean, at the least, not assuming that any female/male differences that may be found are necessarily biologically based. As well, gender-based designs and analyses must take into account the diversity among women and carefully conceptualize how gender, sex, and associated covariates are to be understood.

Further, if women are under-represented in a trial, we must be told why: were they not asked to take part? Were they asked but declined? Were they appropriately ineligible? Did they lack the resources that would allow participation? Etc. Without knowing *why* there is under-representation (overall or only of some groups of women), appropriate remediation is impossible, as is the ability to make valid inferences from the data presented. And judging the nature of under-representation will require an integrated gender-based analysis.

***Consequently, we recommend that:***

- ***Health Canada and the CIHR transform the current “guidelines” about the inclusion of women in clinical trials and for sex-disaggregated analyses into mandatory requirements that must be met for regulatory approval consideration (HC) and for funding decisions;***
- ***CIHR require a gender analysis of all research projects it manages or funds;***
- ***conformity with these regulations be monitored and exceptions specifically justified;***
- ***annual reports summarizing the state of affairs be made available to the public in a timely manner;***
- ***sex and gender issues be addressed separately as appropriate, with particular attention to how these interact with each other and with other salient characteristics of a woman;***
- ***standards for gender-based analyses be established by Health Canada, and training in their use be provided for researchers, policy analysts, peer reviewers, and all others involved in any way in the clinical trials of drugs, including post-marketing surveillance and adverse drug reporting.***

### **Tracking inclusion of diverse groups of women in trials**

“Women” are a diverse lot, and attention to sub-groups and socially relevant features that may be operative in women's health studies must also be given attention. There is some excitement about the recently announced policies about trial registration (by the CIHR, by peer-reviewed professional journals, et al.) and the requirement for the prior submission of complete protocols that indicate clearly the endpoints to be analyzed in a

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<sup>90</sup> Because there can be basic biological differences between males and females at all levels, from cells to the whole organism, the possibility of sex differences even needs to be considered when cell or non-human animal models are employed in the development and testing of drugs in the laboratory.

study must be enforced.<sup>91</sup> But it is not clear that these practices, necessary as they are, will facilitate the kinds of tracking needed to monitor the status of women in clinical trials. Registering trials in a *global register*, provided sufficient data are included, will provide a “snapshot”, but an active process for tracking the research is needed.

*Consequently, we recommend that:*

- *ALL clinical trials be registered (in accord with the 2005 Ottawa statement: <http://ottawagroup.ohri.ca/>);*
- *consent forms and patient information handouts should indicate whether or not a trial has been registered, and if so, note where, providing the unique trial number;*
- *Health Canada and the CIHR continue their efforts to develop and/or ensure the full registration of all clinical trials carried out in Canada or by Canadian investigators, public and private, and that resources for tracking trials are assured;*
- *there be a global mechanism so that there is a unique number for all trials accessible in one place;*
- *registers give priority to providing easily-understood information about trials, but not in ways that privilege their use as recruitment methods;*
- *the clinical trials registry provide data by sex.*

#### **Exclusion/inclusion criteria as gender issues**

Numbers alone cannot cover the absence from trials of women (older, with co-morbidities, etc.) for whom the intervention being studied may be most relevant. With most trials of limited size, carried out in homogeneous populations, and of short duration, harm cannot be revealed before a drug is put onto the market. Only when it is in “real world” use will the true colors be seen (assuming the data from trials is presented honestly and in toto).

*Consequently, we recommend that:*

- *independent post-marketing studies of new therapeutic drugs be made mandatory for all new drugs and be funded by industry. These follow-ups should be appropriate to the approval status of the drug involved, with those approved conditionally required to show they actually produce a clinical benefit; and those approved under a priority approval followed for determination of their safety in populations other than those initially studied by whatever methods are most appropriate (including registries and observational studies as well as randomized trials);*

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<sup>91</sup> Plans for the registration of clinical trials must not be seen as a panacea for the protection of women – and their interests – in clinical trials. The public recording of all protocols, no matter the funding source, as a prerequisite to funding and to institutional ethical board approval, or the subsequent publication of papers, should be mandatory. But, registration per se will not actually facilitate the kinds of tracking needed either to monitor the status of women in clinical trials or to ensure that gender – or justice (as in outsourcing trials) – matters are addressed. Moreover, as evidence mounts that post-marketing studies are essential, it is not clear that the various proposals about trial registration suggested to date will guarantee these are done. In fact, other regulations or policies will be needed.



- *conditional licensing (i.e., the use of Notice of Compliance with conditions) approvals for new products that have only limited pre-marketing testing be greatly improved to ensure it is a transparent process with close monitoring of what companies are doing to comply;*
- *there be mandatory special labelling to indicate if a drug has been given accelerated approval, with information on the numbers, sex and age of those who have been studied in clinical trials included, so that users can be warned in advance of the very minimum testing it has received;*
- *there be NO advertising (to physicians or to the public) of a drug that has received accelerated approval until post-marketing studies have established its safety and effectiveness;*
- *“prevention” trials be subjected to the most stringent regulatory overview and monitoring with advertising completely prohibited until long-term studies have established safety and effectiveness.*

### **Pregnancy and pregnant women**

Concerns about pregnancy and foetal exposures have been an exclusion criteria for women but not men. This gendered inequality is most obvious in phase 1 and phase 2 trials. Paradoxically, it may be safer to expose women in phase 1 and 2 trials (as opposed to phase 3 trials), since these trials are often very short in duration making it unlikely that a woman would conceive during such a trial. Yet, without the basic physiologic and other data these early stage trials provide, the medication dose to which women in phase 3 trials are exposed may be inappropriate.

Furthermore, concerns about possible foetal harms have diverted attention from the potential harms of excluding women from trial participation, those that might occur if safe drugs for treating a pregnant woman for an established medical condition are not developed. With maternal age at first pregnancy increasing, it is becoming more and more likely that a woman will be pregnant and have some problem needing medication at the time.<sup>92</sup> Thus, for medical reasons, as well as to ensure women are not treated with a “lack of trust” with regard to being able to make decisions about their sexual activities and contraceptive use,<sup>93</sup> trial criteria for in/exclusion must be based on individual realities not false assumptions about women – and their sex lives and capacity for responsibility.

### **Consequently, we recommend that:**

- *standard consent forms respect women's rights to make decisions for themselves and allow a woman to decide for herself how to balance the possible risks to her, her pregnancy, or her foetus, with the possible advantages of participating in a clinical trial;*
- *pregnancy exclusions should apply equitably to men and to women.<sup>94</sup>*

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<sup>92</sup> Frederiksen, 2002

<sup>93</sup> Butler and Downie, 2003

<sup>94</sup> There is evidence that damage to a foetus can be transmitted via sperm and so only focusing on maternal risks as a reason to eliminate women from trials is inequitable. (see DeLap et al, 1996)

## **What does and does not get studied**

It is not clear that the frequency of drug trials corresponds with the conditions most prevalent among women for which there is most need for safe, effective pharmaceutical intervention.<sup>95</sup>

### ***Consequently, we recommend that:***

- ***regulatory agencies take into consideration the added value of new drugs in approval decisions, as well as the degree to which they are meeting unmet and real needs;***
- ***especially rigorous standards for judging safety and effectiveness be applied to drug trials that involve “me-too” formulations;***
- ***regulatory agencies consider both the “therapeutic importance” of a new drug and its cost-effectiveness. This will often require comparison, NOT placebo, trials and adequate funding/resources/mechanisms for this research that is not biased by commercial interests.<sup>96</sup> “Non-inferiority” trials should not be used as the sole basis for marketing approval;***
- ***there be no public funding of trials unless they address important health questions and are unbiased by commercial interests in their design, implementation, analysis and reporting.***

## **Consent forms and literacy are clinical trials issues for women**

Ensuring that informed choices about participation in trials are more than pro forma is essential. This requires attention to informed consent material, and the informed consent process. Given literacy levels of women and the complexity of forms, there are serious doubts that women can give truly authentic consent to trial participation. And even with women who are print literate, other factors related to expectations of medical care, understanding of random assignment, placebos, and of probability, can compromise the ability to give truly informed consent.<sup>97</sup>

With the increasing use of languages other than English and French in Canada, the common requirement for women to be able to read/write in one of the “official” languages may be an inclusion criterion that keeps many out of a study, and this may in turn lead to under-representation of minorities.<sup>98</sup> In addition, given gender- and class-based differences in doctor-patient relationships, one needs to be attentive to the possibility of gender-based differences in how the informed consent process is carried out.

### ***Consequently, we recommend that:***

- ***work be done to make consent forms “user friendly” without sacrificing the informational content needed to make the ability to give consent a reality;***

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<sup>95</sup> Ostrzenski and Ostrzenski, 2005; Cochrane et al, 2005.

<sup>96</sup> In contrast to this recommendation for testing new drugs against existing ones is the policy suggested by Barton and Emanuel (2005) that this be done only post-approval. They argue that comparative testing would “significantly increase the costs of clinical trials.” However, they do also suggest that FDA approval might be “conditional on results of at least one randomized trial with a comparator in the same class.”

<sup>97</sup> Stead et al, 2005

<sup>98</sup> Macleans, 2005

- *Health Canada ensure that reader-friendly summaries of trial protocols are made easily accessible;*
- *the plans of the Cochrane Consumer Network to prepare reader-friendly summaries of all reviews be supported and that these summaries be made easily accessible;*
- *multiple means of communication (Internet, print, oral, multiple languages, etc.) be developed and used to ensure all women can have access to all information and related materials.*

### **Trials as a way to better care and “outsourcing”**

Against a background of media reports about growing waiting lists, a shortage of physicians and nurses, etc., it is essential that clinical trials do not become a “default” option for women who might otherwise not have access to proper care. Thus, any hospital that participates in clinical trial research must ensure that no woman’s care is jeopardized in any way by not taking part in research. Related to this, there must be evidence that trials originating outside of Canada are not taking place here for financial reasons (e.g., to save medical care costs for patients that would add to research costs elsewhere but that are covered by the public system in this country).

Over the years, there has been an increasing “outsourcing” of research<sup>99</sup> to lower wage markets, and a growing enrolment in trials in Canada by women seeking paid employment. Drug companies may move trials (to test interventions that will be used by privileged women) to “emerging” markets under the cover of “good business” to allow for cheaper drug development. This will, however, shift harms and burdens onto poor and otherwise vulnerable women, women from whom, experience has shown, informed consent is not always obtained and who are less likely to have access to the drug if it eventually reaches the market.<sup>100</sup> Women in Canada should not gain at the expense of others.<sup>101</sup>

### **Consequently, we recommend that:**

- *Health Canada (and the CIHR, as appropriate) carefully monitor trials carried out outside of Canada and that data from these trials entered for regulatory decisions be scrupulously assessed to ensure trials were ethical; that participants gave truly informed consent, not compromised by direct or indirect financial inducements; and that arrangements have been made for follow-up treatment in situations where a drug has been found to be effective;*
- *Health Canada monitor the financial inducements offered by CROs and other private research organizations in advertisements for trial and other research participants.*

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<sup>99</sup> Outsourcing takes several forms, including the running of trials by CROs, ghostwriting of medical papers, and the hiring of paid spokespeople to promote company products (Healy, 2005).

<sup>100</sup> Mulay, 1997

<sup>101</sup> Hirschler, 2005. See, too, Mudur (2005) and Jayaraman (2006)

## **SUMMING UP – and further recommendations**

Merely involving (more) women in clinical trials must not be the sole concern in examining the relationship(s) between women and clinical trials. Fundamental, is first asking WHY a drug trial is being proposed, whether gender and sex have been taken into account in the development of a drug, and whether a drug is the most appropriate means for addressing a problem, with this concern particularly relevant in prevention and marketing trials. Only when a drug trial seems appropriate as the answer to a specific problem do technical questions about the trial protocol (recruitment of participants and analyses, et al.) become relevant. Even the best of trials may be wrong if they are not suited to the actual problem women face.

*Consequently: clinical trials should not only accommodate gender differences, but also become a site for the transformation of gender relations in the biomedical/healthcare world. Training and development of those carrying out trials to privilege the involvement of women; promotion of user/patient input into choosing questions, designing studies, and performing analyses; challenging all inferences from men to women; study endpoints that are gender sensitive; and ensuring that interventions recognize the social positions of women participating in trials are but some of the issues requiring attention in this regard.*

For RCTs to contribute to better health and disease management for women, this research must address intersectional gender issues in design, implementation, monitoring and evaluation, and ensure that the RCT does not promote or maintain inequitable gender roles or relations. This may be of particular relevance when trials are “outsourced.”

*Consequently, gender concerns should be addressed in choosing study questions as well as in study design so that women do not face either improper inducements encouraging participation, or structural barriers preventing participation. Furthermore, specific attention must be given to issues of diversity so that the drugs studied meet the needs of a full range of women, including women with disabilities, racialized women and bisexual, lesbian, and transgendered women.* Using the terms “appropriate,” or “adequate” representation of women in guidelines and policy statements is grossly inadequate; specifics about the women (e.g., details about who and how many they are), not generalities, should be required.

*Moreover, choosing the outcome to be used as a measure of “success” of a drug tested in a therapeutic trial must take into account its (clinical) relevance to the women who will be given the drug if it works (e.g., with regard to an increase in survival, an improvement in quality of life, an easier management regime, etc.).* Increasingly, “surrogate” laboratory-based markers are being used to define effectiveness, but too often such things as a decrease in tumour size or in some biochemical measurement does not indicate longer survival or a better quality of life. **If a surrogate marker of “success” is used, it should at the least be shown to be relevant to the women to be studied. And these “patient-oriented/reported” outcomes should be given primary status, and not**

relegated to “side issues.” As well, **in reporting outcomes, it is imperative that absolute, and not merely relative, figures be used.**

Perhaps most important, in view of the pro-trial biases outlined earlier, is ensuring that women who decide *not* to enter a trial are not harmed in any way, including being verbally berated, for not participating. ***Consequently, it is critical to ensure that joining a trial does not lead to queue-jumping and speedier access to appropriate interventions by participants, nor to inferior clinical management by women who decide not to enter a trial.***

Last, but probably most important, ***women (including women’s health advocates) must be included when decisions about what research to do and how to do it are debated.<sup>102</sup> It is not sufficient to include women as research subjects; they must also be included further upstream, helping inform research and funding decisions, and, of course, priorities.*** Involvement of patient and patients’ groups is increasingly accepted, however there is need for vigilance to ensure that these individuals and groups are truly community-based and not speaking for industrial funders. Who is being represented and to whom one is accountable are critical questions to ask, with recent concerns about pharmaceutical funding of the European Patients’ Forum (HAI report) underscoring the need for involving community-based people.<sup>103</sup>

Clinical trials answer specific questions that need to be asked if we are to have safe and efficacious medicines to treat real diseases. It should be apparent, though, that answering the narrow question about what’s being done now with regard to the inclusion of women in clinical trials is simplistic, and that even in discussing the topic we must constantly remember the particular historical place of clinical trials and of gender matters in Canadian biomedicine.

We need to recognize that RCTs are *one* way, but not the only way, to get the information we need about how to respond to women’s health problems. We also need to recognize and apply as study outcomes human risks and benefits that cannot be commodified.<sup>104</sup> In this regard, we need to validate and credit observational and other forms of expertise, and develop health promotion and disease treatment options outside a neomedical model.

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<sup>102</sup> See Mayer, 2005 for a compelling call for “trained evidence-based advocates [to] have a seat and a voice at every table where clinical trails are designed and implemented.....”

<sup>103</sup> In this regard, it is of interest that as of January 1, 2006, the UK has changed its code of practice so that all drug companies must “make public their involvement with patients’ advocacy groups” (Day, 2006).

<sup>104</sup> Hankivsky, 2004

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Web-based directory of clinical trials: [www.controlled-trials.com/isrctn/](http://www.controlled-trials.com/isrctn/)

European directive: [www.wctn.org.uk/downloads/EU\\_Directive/Directive.pdf](http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf)

UK response to European directive: [www.legislation.hmsso.gov.uk/si/si2004/20041031.htm](http://www.legislation.hmsso.gov.uk/si/si2004/20041031.htm)

The dawn of gender-specific drugs by Vivienne Parry, presenter of One Man's Medicine  
<http://news.bbc.co.uk/1/hi/health/3129455.stm>

### USA

#### FDA

FDA: Women's Health: FDA Guidance Documents: [www.fda.gov/womens/guidance.html](http://www.fda.gov/womens/guidance.html)

Participation of Females in Clinical Trials and Gender Analysis of Data in Biologic Product Applications (FDA research project): [www.fda.gov/cber/clinical/femclin.htm](http://www.fda.gov/cber/clinical/femclin.htm)

Women's Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement: <http://frwebgate.access.gpo.gov/cgi-bin/useftg.cgi?IPaddress=162.140.64.21&filename=d01754.txt&directory=/diskb/wais/data/gao>

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Prescription for Success: [www.nurseweek.com/features/98-2/meds.html](http://www.nurseweek.com/features/98-2/meds.html)

Women's Health Research Registry™:  
[www.csmc.edu/5823.html](http://www.csmc.edu/5823.html)  
[www.csmc.edu/pdf/WomensHealthResearchRegistry.pdf](http://www.csmc.edu/pdf/WomensHealthResearchRegistry.pdf)

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Society for Women's Health Research: [www.womenshealthresearch.org/policy](http://www.womenshealthresearch.org/policy) , downloaded 28 January 2005.

Facts and Figures. National Cancer Institute: [www.nci.nih.gov/clinicaltrials/facts-and-figures](http://www.nci.nih.gov/clinicaltrials/facts-and-figures)

A US Clinical Trials listings service: [www.centerwatch.com/](http://www.centerwatch.com/)

Campaign launched by the Society for Women's Health Research: [www.womancando.com/](http://www.womancando.com/)

Trials specifically for women: [www.veritasmc.com/webmd/studiesforwomen.cfm](http://www.veritasmc.com/webmd/studiesforwomen.cfm)

Isis fund for Sex-based biology research: [www.womens-health.org/rf/isis.htm](http://www.womens-health.org/rf/isis.htm)

Background on clinical trials legislation in the US: [www.womens-health.org/policy/issues\\_clin\\_bg.htm](http://www.womens-health.org/policy/issues_clin_bg.htm)

A comprehensive list of clinical trials databases in the US:  
[www.healthcyclopedia.com/biotechnology-and-pharmaceuticals/pharmaceuticals/clinical-trials.html](http://www.healthcyclopedia.com/biotechnology-and-pharmaceuticals/pharmaceuticals/clinical-trials.html)

## **CANADA HEALTH CANADA**

Therapeutic Products Programme Guidelines: Inclusion of Women in Clinical Trials: [www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/wominct\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/wominct_e.pdf)

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Guidance for Industry, Statistical Principles for Clinical Trials, ICH Topic E9: [www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/e9\\_e.pdf](http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/e9_e.pdf)

A list of clinical trials in Canada for which researchers pay to list a trial, maintained by a private company:  
[www.myhealthcanada.com/index2.html](http://www.myhealthcanada.com/index2.html)

Health Canada's Gender-based Analysis Policy: [www.hc-sc.gc.ca/english/pdf/womens/gba.pdf](http://www.hc-sc.gc.ca/english/pdf/womens/gba.pdf)

Health Canada Women's Health Strategy: [www.hc-sc.gc.ca/english/women/womenstrat.htm](http://www.hc-sc.gc.ca/english/women/womenstrat.htm)

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Ontario Cancer Trials Registry info (allows search for current trials): [www.ontariocancertrials.ca/](http://www.ontariocancertrials.ca/)

National Cancer Institute of Canada, Statistics:  
[www.ncic.cancer.ca/vgn/images/portal/cit\\_86751114/14/35/195991821ncic\\_stats2004\\_en.pdf](http://www.ncic.cancer.ca/vgn/images/portal/cit_86751114/14/35/195991821ncic_stats2004_en.pdf)

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## Acknowledgements

Many colleagues and friends contributed in different ways to this report, and some deserve special recognition. (Of course, I take full blame for any errors or omissions.) First, many thanks to Elizabeth Turner for her careful and thoughtful assistance in helping to get this project started and kept going. Thanks, too, to Cassy Robinson-Cohen and to Stephanie Lloyd for their cheerful help in bringing it to an end. Throughout, Diane Saibil and Anne Rochon-Ford were all one could wish for as sources of support and editorial ideas, and I am most grateful for their patience and good humour. Thanks, too, to those members of the WHP Steering Committee who, as always, shared their expertise generously. Finally, a big thank you to the translators: Margot Lacroix et Dominique Joly.

Copies of this publication can be downloaded from [www.whp-apsf.ca/en/index.html](http://www.whp-apsf.ca/en/index.html) or ordered free from:

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