Women's Human Rights and Health Equality in Clinical Trials in Canada

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Le principe des droits de la personne sur la transparence et l'équité doivent servir de guides aux politiques et activités des compagnies pharmaceutiques. Cet article examine la transparence du processus d'approbation des drogues et de l'égalité des sexes dans les essais cliniques. Les auteurs ont révélé un manque de transparence dans les approches de Santé Canada dans les décisions de régulation des médicaments et une sous-représentation des femmes dans les recherches cliniques importantes.

Clinical trials are crucial when it comes to determining the benefits and risks of pharmaceutical treatments. The human rights principles of transparency and equality are intended to guide pharmaceutical companies and government agencies in the development of policies pertaining to the release of drug information and establishment of equal opportunities for men and women to partake in trials. Representation of both sexes is necessary so that research outcomes can be analyzed and attributed accordingly. Thus, preventing harm and improving patient care. This paper examines the transparency of the drug approval process and gender equality in clinical research since the implementation of Canadian policies. A feminist social justice perspective is used to highlight current industry practices around access to health care information and women's involvement in trials. A content literature review is used to gather information about the research in this paper. Our findings reveal a continual lack of transparency behind Health Canada's approaches to drug regulatory decisions and an ongoing underrepresentation of women in important clinical research. This disturbing pattern reveals both ethical and justice concerns.

Introduction

Human rights are concerned with the attainment of the highest standard of physical and mental health for all people. According to the Human Rights framework,

Two key human rights principles, transparency and equality, are meant to guide policies and actions of health care systems (UNPFA). In relation to pharmaceutical companies, the adoption of these principles to policies and mission statements should influence the development and release of drugs (Khosla and Hunt). This paper examines the transparency of the drug approval process as well as gender equality in clinical trials. The right to health cannot be fully realized without access to unbiased information from pharmaceutical companies and government agencies. Without knowledge, healthcare professionals are unable to make evidence-based decisions regarding prescriptions for their patients, putting them at risk for adverse health events. Furthermore, drug outcomes must be properly analyzed and attributed to the correct population in order to determine safety and effectiveness.

This paper will examine Health Canada's documents and policies, including the Summary Basis of Decision (SBD) documents, the *Guidance Document on the Inclusion of Women in Clinical Trials* (1997), and its revision in 2013, and the *Health Portfolio Sex and Gender-Based Analysis Policy* (2009). With reference to the scholarly literature these documents will be analyzed to determine whether policy and policy implementation in all these areas has improved.

Methodology

This paper will use a feminist social justice lens to examine the frameworks that endeavour to elucidate women's underrepresentation in clinical research. The feminist ethics framework analyzes the norms and assumptions that govern research through a perspective that allows us to understand how research practices involving and affecting women have undervalued and harmed them. Contemporary feminist frameworks have illuminated past theories in order to bring about present views. Simone de Beauvoir has had significant influence on feminist theory by explaining the Hegelian concept of "the Other," which refers to what is unfamiliar and deviating from the norm (cited in Mitchinson). The process of "othering" is a type of oppression, which is endorsed by those who have knowledge as well as power and who use these two elements to achieve a particular political agenda in its goal of domination (Hall). Stemming from this concept of "othering," Susan Sherwin, a contemporary feminist ethics scholar, appeals to Iris Young's social justice theory, which identifies oppression as a form of injustice. Young's notion of social justice recognizes that oppression on the basis of gender translates into injustices in the form of marginalization and leads to inequitable health care for women (cited in Sherwin).

Human Rights and Pharmaceutical Transparency

The International Covenant on Economic, Social and Cultural Rights (UN Economic and Social Council) describes health as a fundamental human right. It provides examples of state parties' obligations to adopting health as a right and defines the principles of accessibility, availability, acceptability, accountability, quality, non-discrimination, transparency, and participation. In the context of pharmaceuticals, access to pharmaceutical information regarding the safety and efficacy of tested drugs can be linked to the principle of transparency (Khosla and Hunt). By all accounts, transparency means that governments must be open about all information and decision-making processes related to rights. People must be able to know and understand how major decisions affecting rights are made and how public institutions, such as hospitals and schools, which are needed to protect rights, are managed and run (NESRI). Unfortunately, mandating this principle to clinical trial registration and access to outcome information has been a challenge.

Various initiatives have been employed for clinical trial registration, such as the establishment of the International Clinical Trial Registry Platform (ICTRP) by the World Health Organization (WHO). However, due to lax enforcement and limited provision, the implementation of its recommendations and regulations at national/regional levels remains deficient (Lemmens and Telfer). Another concern is that even if clinical trials are registered, government agencies protect the confidentiality of pharmaceutical companies and limit public access to safety and effectiveness data. In Canada, the government introduced the Smart Regulation strategy, which assured a speedy process for drug approval and made the country a very attractive place to conduct trials, most of which are sponsored by the pharmaceutical companies (Lexchin). Equally concerning is the fact that in Canada information regarding outcome data is considered the property of pharmaceutical companies which may take Health Canada to court for disagreements in regulatory plans (Silversides).

In a society with such heavy use of medication, limited knowledge can have disastrous consequences. For example, adverse effects from drugs contribute to both increased emergency room visits and mortality from overconsumption in hospital. Vioxx, a block buster drug manufactured by Merck, the second-largest drug maker in the U.S., was found to have caused over 60,000 deaths after being illegally promoted for the treatment of rheumatoid arthritis (Lyon). Vioxx was recalled in 2004, but the company's illegal promotion of the drug was considered a simple misdemeanour rather than a felony by the courts.

The Women and Health Protection (WHP), an alliance of researchers and groups concerned with the safety of pharmaceutical drugs, warns that Health Canada is placing proprietary and commercial interests ahead of those of the public by withholding open access to key clinical trial information. For women, the right to reproductive health services can only be truly exercised if they have knowledge about possible benefits and risks. Also, women typically oversee health care decisions for their extended families making access to information on drug safety paramount.

In 1998, Health Canada approved Diane-35 for the treatment of severe acne. Alarmingly, the drug had never actually been tested on the population for which it was approved—those suffering from severe acne. Moreover, the drug was being prescribed illegally off-label as a birth control pill (Grigg-Spall). In February 2013, after eleven deaths of reportedly otherwise healthy women, Health Canada undertook a review of the drug. Despite the known risk of Diane-35 causing a potential serious life-threatening blood clot (venous thromboembolism) and knowledge of aggressive illegal prescription, Health Canada chose to allow continued use. The

benefits of the drug were deemed to outweigh its risks. This case is an obvious illustration of Health Canada's responsiveness to commercial interests rather than public interests.

Policy Development Pertaining to Pharmaceutical Transparency

In 2004, Health Canada introduced Phase I of the Summary Basis of Decision (SBD) documents. These documents were meant to improve the transparency of the drug approval process by making clinical trial information available to the public (Habibi and Lexchin). Their information was meant to aid clinicians and patients in making unbiased and informed decisions regarding the prescription of drugs. A recent study found that the SBD documents provide inconsistent and incomplete information with regards to the characteristic of patients (sex and age) on which the drugs were evaluated and little disclosure about the potential risks and benefits. The Auditor General of Canada also concluded that Health Canada did not fulfill long standing promises to increase the transparency of approved clinical trials. This is a cautionary warning that evidence-based information with regards to the safety and effectiveness of recently marketed drugs is still not at the disposal of physicians. Thus, Canadians should be skeptical when taking newly released prescription medication. Phase II of the SBD documents was launched in June of 2012 with revisions, including the restyling of the documents to a user friendly, web-based, as well as question and answer format; a proposed shorter time to publish the documents (twelve weeks instead of twenty); and more information focusing on a risk and benefit analysis for both drugs and medical devices. However, it remains unclear if more information about the results and characteristics of the clinical trials will be published.

In 2013 the Harper Government introduced Bill C-17, or Vanessa's law, after a fifteen-year-old girl died from side effects of the prescribed drug, Cisapride, in 2000 (Herder, Gibson, Graham, Lexchin and Mintzes). The bill is meant to improve drug safety by giving Health Canada legislative powers to recall drugs, increase fines, compel companies to do post-market research, and make adverse event reporting mandatory in health care facilities. In theory, the bill should bring about legal change. In practice, however, changing a longstanding culture of protecting the confidentiality of pharmaceutical information will be challenging. According to Health Minister Rona Ambrose, drug manufacturers "may" disclose clinical trial information in order to protect public safety (cited in Herder et al. 289). In other words, "the Health Minister may suspend a manufacturer's license to sell a drug, but he or she cannot require the drug to be recalled from pharmacy shelves, only the manufacturer can do so" (288). Thus, at this time, there are no guarantees. Whether and how this bill will actually be enforced and protect Canadians from unsafe drugs remains to be seen.

Health Equity and Gender Equality in Clinical Trials

Health equity is concerned with the attainment of equal opportunities for good health and high-quality care for all people. It requires continuous social and political effort to address historical and contemporary injustices and eliminate disparities in health care to ensure that everyone is valued equally. The different life experiences and needs of men and women must be taken into consideration when developing programs and policies in society. In all societies socially constructed, gender-based disparities all too frequently exist that disadvantage women, impeding their development. Since 1982, the Canadian Charter of Rights and Freedoms, has asserted the principle of equality allowing affirmative action programs to eradicate disadvantages (Hogg). In spite of years of effort, overall progress in improving women's equality has been inconsistent as women are still underrepresented in all levels of leadership and other decision-making domains. In a traditionally male-dominated labour market, women, especially those with less education, are more likely to occupy lower paying jobs such as cleaning, care work, as well as contract or part-time work. Women also bear the burden of a dual work day, often limiting their ability to participate equally in the labour market as well

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When it comes to pharmaceuticals, health equality requires including women and men equally in drug trials so that safety, effectiveness and tolerance of drugs can be tested and outcomes can be attributed appropriately. Researchers must consider the pharmacokinetic and pharmacodynamics differences between the sexes that stem from variations in body size, composition, and differences in hormones. The higher fat content and smaller average body size of women typically result in higher concentrations of a given drug circulating in their blood as compared to men's for a period of time, leading to varied drug responses (Merkatz, Temple, Sobel, Feiden and Kessler). For example, a study done by Paul Ridker et al. showed that aspirin has different effects on women with regard to primary protection against stroke and heart attacks. Aspirin lowered the risk of stroke but did not affect the risk of myocardial infarction or death when consumed by women as opposed to men. Women can only reap the benefits of pharmaceuticals if they have been included in the testing.

Furthermore, not only biological but socially constructed gender-based differences must be reflected as they likewise account for differences in drug outcomes. Epidemiologically, certain medical conditions are unique to women (Doyal). For example, they are twice more likely to experience depression at some point in life than men (Nolen-Hoeksema). This can be attributed to gender roles which place the additional stresses of work and home responsibilities on women, including caring for children and the elderly. Also, gynaecological exams are generally excluded in studies of AIDS even though infected women most often present with chronic gynaecological problems (DeBruin). Thus, achieving an equitable representation and analysis of both biological and gender-based differences of women in clinical trials is imperative for their welfare.

Historical Context and Policy Development

The history of women's participation in clinical trials can be read in policies and regulations. Policy development in the area of protection of human research participants began in 1949 with the issuance of the Nuremberg Code, which outlined research ethics principles in response to flagrantly offensive human experimentation conducted by the Nazis during World War II (Pauker). This document as well as the related declaration of Helsinski formed the basis for Health Canada and U.S. research regulations (Mandal, Acharya and Parija). In the mid-1900s, health problems caused by the drugs thalidomide and diethylstilbestrol (DES) signified abuse and brought about a public awareness of the need for greater protection for fetuses from hazards in medicine. In response, in the late 1970s, the U.S. Food and Drug Administration (FDA) adopted a policy of exclusion entitled "General Considerations for the Clinical Evaluation of Drugs," recommending that premenopausal women capable of becoming pregnant be excluded from participating in Phase I and early Phase II of drug trials (U.S. Food and Drug Administration). While this policy was supposed to refer only to women of childbearing years and early phases of clinical trials, it quickly led to all women being excluded from all pharmaceutical research for nearly two decades (Lippman).

In the 1980s, AIDS activists working to promote entry to trials for AIDS therapies were successful in receiving access to experimental drugs used to treat the serious and life-threatening illness (Mastroianni, Faden and Federman). Women's advocacy continued with the recognition that clinical outcomes of medications given to women and men were only evaluated in men. Concerns over the lack of research on breast and reproductive cancers amplified lobbying for the inclusion of women in clinical trials and in 1997 led to the development of the *Canadian Guidance Document on the Inclusion of Women in Clinical Trials* (Lippman). The policy recommended that women should be included in all phases of clinical trials in an appropriate sample size that would allow for adequate effects of drug treatment to be evaluated. This was intended to lead to safer prescriptions and decreased adverse health consequences in women. Inclusion criteria was directed to all women of childbearing and post-menopausal years and researchers were encouraged to include both genders as well as to analyze outcomes of treatment by sex-related differences. Drug manufactures were to guarantee that those drugs seeking market approval included women at all stages of the drug development process, ensuring that the full spectrum of risks and benefits were captured throughout the clinical trial. In 2013, *The Guidance Document, Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences*, was released to supersede the 1997 document.

In 2000, another initiative, Health Canada's Gender-Based Analysis Policy, unveiled its support for a gender-based analysis (Fuller). The policy goals were to address health differences between men and women as they pertained to sex and gender as well as to understand experiences with health and illness and interaction with the health care system. This was to be accomplished by "identifying gender equality issues and proposing remedies to inequality in the areas of

policy and program development or implementation, research, funding, data collection, surveillance, and regulatory activities" (10).

Results of Policies and Status of Women in Clinical Trials

A review of the 1997 *Canadian Guidance Document on the Inclusion of Women in Clinical Trials* noted that the policy guidelines for researchers served merely as recommendations with no mandatory requirement to conform (Lippman). While The Women's Health Strategy of Health Canada promised to monitor the inclusion of women in clinical trials this endeavour was never mandated or put into practice. In comparison, guidelines from the National Institutes of Health (NIH) in the U.S. made it a requirement for researchers to include women in clinical trials if they were to be funded. However, despite the prerequisite of the established guidelines, various investigators, including the General Accounting Office in the U.S., found a continuing under-representation of women in clinical trials in the country. Considering that the U.S. National Institute of Health failed to bring about change despite having an actual requirement for inclusion, it should not be a surprise that Canada, with recommended guidelines only, has also failed. In fact, neither the U.S. nor Canadian policies enforced monitoring provisions for the strategies.

A study conducted by Saumyadwip Bandyopadhyay, Anthony Bayer, and Sinead O'Mahoney reviewed nineteen trials between 1990-1999, looking at the effects of statin drugs on lowering cholesterol and decreasing the risk of heart attacks and strokes. They found that only ten percent of the participants were women and none were over the age of seventy-five. Statistically, the fastest growing infected population from AIDS is women (Dresser). Yet from 2000 to 2008, HIV-infected women accounted for only 20 percent of participants in antiretroviral therapy clinical trials in the U.S. (Soon et al.). Reshma Jagsi et al. reviewed 661 cancer research studies for seven non-sex specific types of cancers. They found a lower percentage of women were included in the research than were being diagnosed with the particular cancer in the general population. In 2010, the Institutional Review Board (IRB) and other researchers concluded that pregnant women continue to be excluded in clinical trials despite policy changes (Levin). The Gender Based Analysis Policy (GBAP) makes no mention that gender and sex based differences must be analyzed separately for their impact on the experiences of women taking medication to be known. A study conducted at the University of British Columbia's Centre for Health Services and Policy Research found that GBAP was neither adopted nor implemented in pharmaceutical policy and lacked translation into research practice (Greyson, Becu and Morgan). Likewise, Marion Doull, Vivien Runnels, Sari Tudiver, and Madeline Boscoe investigated the use of GBA in thirty-eight Cochrane systematic reviews of cardiovascular health, finding that GBA was largely lacking in the examined literature.

All of the above findings have serious medical implications for women and have led the Canadian Research Ethics Boards (REBs) examiners to review the various assumptions or rationales researchers voice as justification for the underrepresentation or exclusion of women in their clinical trials (Giacomini and Baylis). Common rationales for these practices, include the notions that women a) are similar to men biologically and results can be generalized to them; b) are privileged to avoid potential hazardous outcomes in research; c) introduce too much variability and confusion for result interpretation; d) are hard to recruit and retain; e) add expense due to increased sample size; and f) pose a liability risk if pregnant. In March 2013, Health Canada released its updated version of the *Guidance Document for Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex*. The document acknowledged that women's partaking in clinical research had increased but underrepresentation continued to be visible especially in the early phases of trials. Furthermore, pregnant and breastfeeding women continue to be excluded leading to misinformation and safety concerns about the effects of treatments. However, as was noted in the 1997 review, the guideline continues to serve merely as a recommendation to drug sponsors. It

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has still not been made mandatory to include women and there is no clear indication as to how or if monitoring provisions will be enforced.

A more recent study examined the reporting of sex and gender in randomized controlled trials (RCT) across Canada during the period of January 2013 – July 2014. The results demonstrated poor analysis of sex and gender in all of the reviewed research (Welch et al.). Another study suggests that while the overall representation of women in clinical trials has indeed improved, the routine exclusion of pregnant women remains a concern (Baylis and Kaposy). Despite the fact that during pregnancy two to three out of five women use four or five medications, there are only a few drugs that are labelled for-use during pregnancy. Data on dosage and safety for most medications on the market remains insufficient. In light of these findings, the authors suggest a mandatory shift towards a justification model for excluding pregnant women from important clinical research. In other words, pregnant women should be included in research unless there is reasonable justification that the tested drug will produce harm to either the mother or the fetus.

Conclusion

This paper examined the transparency of the drug approval process and gender equality in clinical research since the implementation of Canadian policies. The right to health documented by WHO as the right to the highest attainable standard of physical and mental health cannot be fully realized without access to unbiased information from pharmaceutical companies. In theory, drug regulatory agencies should be responsible and accountable for the safety of the public as opposed to serving commercial interests. This is currently not the case when it comes to Health Canada's approaches to the drug regulatory process. Although there have been some policy developments in the area of drug transparency with the passing of the SBD documents and Bill-17, it remains to be determined whether recommendations will be enforced to protect Canadians from unsafe drugs.

Furthermore, Health Canada still does not require the inclusion in trials of specific populations with less than optimal potential to demonstrate a drug's effectiveness. At this time, Health Canada guidelines recommending for women, including those who are pregnant to be equally included in clinical trials and federal government commitments to Gender Based Analysis in research is not being effectively implemented. Women, especially those who are pregnant, continue to be underrepresented or excluded from important clinical research resulting in a lack of information regarding vital health outcomes. The literature suggests that cultural biases continue to shape medical research and unethical and oppressive practices are still present.

Drug transparency and the inclusion of women in research is ethically imperative as it advances justice by preventing harm and improving the quality of research where the goal is to ensure safe and equitable health outcomes for women and men. At this time, the human rights principles of transparency and equality are not being mandated in the pharmaceutical industry by the Canadian government.

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Singing His Name

The key turning in the lock
Never sure
What I'll find.
Not dangerous, they said, never meeting my eye.
A metallic clunk as the tumblers slide, and I snake
My arm into the widening crevice and knock lightly on the inside of
The peeling grey door, like they said to do.

Ease myself into the room, and on impulse, begin gently
Singing his name.

Damp, felt-wrapped silence, the light
Dim and filtered as I adjust and make my way to the drapes,
drawn back,
Startling dust and random particles in the sudden sunlight.
Softer now, low and lilting, my voice singing his name and filling
That empty space like a caress.

The big mahogany clock ticks down the hall, it's face stark and
White, distorted numerals twisted on the dial when I hear
A slight whimpering and the hair on my
Neck prickling as I slowly become aware…
where…. (my eyes darting)
Where are you…

Images and fears shatter my thoughts, and then a grip,
A sudden pull, the loud crack of my bones
and as my eyes open,
I can smell him, dark, under the bed, still holding my leg, a
sickening loosening in my gut, I can't scream, his dilated pupils
and shoulders trembling and shuddering and
shock, *self-injury*, *illness,* I'm still assessing the patient
when I see the shining, red
gleaming drops,
and then a perfect,
velvet
silence
wrapping itself about me
like an
anesthetic
shroud.

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