

Women's Participation in Clinical Trials

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Does Australia need to catch up with American policy initiatives?

Excluding women from participating in clinical drug trials might seem like a good thing. It may seem like a good way to protect women from the risks of being research subjects and a way to prevent foetal harm. However, the exclusion or inadequate representation of women in clinical trials may actually cause harm. What is more, excluding women from clinical trials does not rule out the possibility of damage to offspring, nor does it guarantee researchers or institutions freedom from legal liability. The issue of women's exclusion has received a lot of attention in the USA but very little in Australia.

Gender differences lead to harm

Differences in the way men and women respond to some treatments mean that studies carried out on male subjects are not reliably or safely generalisable to women. Women are exposed to risk if drugs and treatments have not been tested for safety in women. Examples of gender differences have been found in diverse areas where no obvious differences have been expected. For instance, a study into recovery times from general anaesthesia found that women woke from anaesthesia almost twice as fast as men: women took an average of seven minutes; men took thirteen minutes. This finding was independent of differences in body weight. It seems that men and women metabolise drugs differently.¹

Another finding is that responsiveness to antidepressants differs. Women experience a much greater incidence of depression, they are the main users of antidepressants and they are more likely to be prescribed antidepressants than men experiencing depression. But, women have been excluded from early trials of antidepressant drugs.² In another study, a particular class of painkillers seemed to work twice as well for women as for men. Earlier studies carried out on men suggested that these painkillers were relatively ineffective. A later study found that gender may be a factor when choosing pain relieving drugs.³

The findings demonstrate how clinical studies which do not include women can lead to results which have little value and can put women at risk. Although women may be excluded from research because of the potential for foetal harm, they are not excluded when drugs come onto the market and are prescribed. Prescribing drugs to women in which the safety and efficacy have not been tested in women amounts to post-marketing experimentation. Alternatively, women may experience reduced access to new treatments because physicians are reluctant to prescribe them medications that have not been tested for safety in women of childbearing potential.

Shifting harm

Excluding women from clinical drug trials does not prevent harm, it simply shifts the point at which harm may occur, from the research setting to the community. The exclusion of women who are pregnant or capable of becoming pregnant might reduce the risk of damage through research, but, it is an approach that can lead to 'random disaster' in



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which more individuals are actually damaged.⁴ The commentary in the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* states that:

thalidomide caused much more extensive damage than it would have if its first administration to [women who are biologically capable of becoming pregnant] had been in the context of a formal, carefully-monitored clinical trial.

Exclusion means that non-consenting women are being exposed to risk rather than those who have consented after consideration of the risk-benefit assessment.

The emphasis on protection

Historically the main concern has been with protection and the primary role of institutional research ethics committees is to protect research subjects. Review by committee originated in the United States of America partly as a response to revelations about abuses in human experimentation in that country. In 1966, details of 22 cases of widespread disregard for human subjects were documented by Henry Beecher in *The New England Journal of Medicine* and more scandals continued into the early 1970s.

These revelations played a significant part in the establishment of a National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. Its focus was the identification of ethical principles that should underlie the conduct of research and also the ethical issues arising from the use of vulnerable subjects such as young children, people with mental disabilities and special populations such as prisoners.

Historically, therefore, there has been a perception that the interests of special populations, minorities and vulnerable subjects as well as research subjects in general, are best viewed in terms of protection from exploitation and from the risks of research participation. This conservative stance was entrenched by the thalidomide tragedy and the experience of Diethylstilbestrol (DES) (even though injuries from both did not occur in the research setting). Because of the emphasis on protection, the equitable selection of subjects has been seen more in terms of the freedom to decline. Since the AIDS epidemic, however, serving as a research subject is increasingly seen in terms of benefits and the underrepresentation of some groups of subjects is increasingly seen as discriminatory.

Arguments for women's inclusion

One rationale for the exclusion of women is the claim that most treatment effects and most diseases do not differ significantly between men and women. Even if true, this reinforces the justification for the inclusion of women. According to the United States National Institutes of Health (NIH) Committee on the Ethical and Legal Issues Relating to the Inclusion of Women In Clinical Studies, the increased participation of women would advance the goal of justice. The committee concluded that: 'if indeed most treatment effects in the setting of treatment trials do not differ by gender, then it is reasonable for treatment trials to include both genders'.⁵

Scientific considerations also support the inclusion of women. Unless women are included in research, especially in the earlier stages of research, gender differences will not be detected and later trial design will reflect this deficiency. Informed decisions cannot be made when information is knowable but not provided: in other words when information could be provided but it is not provided.

Legal liability

Excluding women from clinical trials will not avoid foetal harm or legal liability. Men also cause prenatal harm. Studies show that a father's excessive use of alcohol can reduce the IQ of his offspring and defects such as cleft palate and even some cancers have been linked to nicotine use by fathers.⁶

Rather than exclude *all* fertile persons from clinical trials it would be better to inform men and women of the known risks to offspring and the possibility of unknown risks. Excluding women will not prevent legal liability but a proper warning of the known and unknown risks may avoid it. If a trial has a reasonable risk-benefit ratio and if harm does occur, it should be seen as a result of the subject's decision to participate in the trial, not a result of the researcher's conduct.⁷

There are legal dangers relating to omissions as well as positive acts. Researchers and ethics committees should be concerned with comparing the legal hazards of excluding women from their research with the risks of inclusion. Research sponsors are more likely to be legally liable for their failure to conduct pre-marketing testing with women and pregnant subjects.⁸

There is a view that it is morally wrong for women to be allowed to place their foetuses or potential foetuses at risk. The risk to offspring cannot be dismissed but it is discriminatory to require a woman of childbearing potential or a pregnant woman to act on behalf of a potential or future child at the expense of her own health needs. Participating in a clinical trial may benefit some pregnant women and their children. Women with epilepsy, for instance, need to continue medication while pregnant. Children born to women using the older anti-epileptic drugs suffer congenital malformations two to three times greater than children born to women without epilepsy. However, the exclusion of pregnant women from clinical trials means that the potential dangers or advantages of the newer anti-epileptic drugs are unknown.⁹

Excluding women from clinical trials means that others are making the risk-benefit assessment on women's behalf. According to Merton (1996), the arguments used by defenders of foetal welfare to justify women's exclusion from biomedical research are no more than an:

obsession with the risk to potential offspring that continually privileges their theoretical, future well-being over the health and lives of actual, existing women ... the liberty, autonomy, and privacy of pregnant women militates in favour of allowing them, not others, to make choices about their participation in research.

A political issue

Despite compelling reasons to remedy the lack of knowledge about gender differences in health there may be drawbacks in acknowledging them. Studies finding health differences such as those relating to gender or race can be put to different uses. Findings that indicate women may be more prone to depression and emotional disturbances could be cited to suggest that women are unsuitable for certain occupations or roles. Therefore, these findings could be used to promote and perpetuate unjust discrimination. Reluctance to address the issue of women's exclusion may be due to concern with how the findings about gender differences will be used.

Policy initiatives

In the USA there has been much debate about the omission or inadequate representation of women in study populations and there have been significant policy changes in recent years (see box). Public opinion has changed from protection to inclusion. In Australia, our system of universal health cover means that clinical trials do not have the same critical importance as in the US where for some people without health insurance they can be the only means of gaining access to medical treatment. Apart from this difference, the arguments for women's inclusion apply equally to the Australian situation. However, although the participation of women in clinical trials was identified as a major issue in 1995 there has been little debate and policy has not progressed.

The National Health and Medical Research Council (NHMRC) Women's Health Strategy and Implementation Plan (1993) recommended an:

investigation of the legal, financial and ethical implications of measures to ensure the inclusion of women in clinical trials, tests of new drugs, epidemiological studies and the development of guidelines and safeguards.

An introductory background paper was prepared by Leanna Darvall, and the Australian Health Ethics Committee (AHEC) appointed a working group to expand on that work. From this promising beginning, the result to date has been disappointing.

The issue receives no special treatment in the recently released NHMRC *Draft Statement on Ethical Conduct in Research Involving Humans* (1998). Because of the commencement of the revision of the Statement in December 1996, the Women In Clinical Trials document was never finalised and remains in draft form. The essential content of that document, however, has been published as a chapter in a book.¹⁰

AHEC decided that comment on the issue would be sought as part of the revision of the *Statement on Human Experimentation and Supplementary Notes*. Only three submissions out of 129 commented on the issue. AHEC, considered including a section on women in clinical trials, but, 'eventually decided that it would be demeaning and discriminatory to single out women in this regard and so it was not done'.¹¹ The committee 'felt that it was geared more towards protecting the foetus than protecting women per se'. Also, some members 'felt strongly that by identifying women particularly, it suggested that they were incapable of making informed judgements about their inclusion in research and required special attention'. Finally, because the guidelines ensure 'in a general way' that people from particular groups are 'not disadvantaged by non-inclusion' AHEC considered this sufficient to cover the women's participation issue.¹²

This decision does not reflect the issues raised in the background discussion paper which amounted to a compelling argument for inclusion. As we have seen, informed judgements about treatments and the later research phases are not possible if women are excluded from participating in research. What is more, participation in decisions is what counts. Simply acknowledging that women are capable of making informed decisions does not resolve the matter. Women's exclusion and inclusion involves fundamental ethical issues about who should decide, study design integrity and the equitable selection of research subjects.

USA Policy Initiatives

- In 1994 the USA National Institutes of Health (NIH) introduced guidelines on the inclusion of women and minorities as subjects in clinical research stating that these groups are to be included in research unless a clear and compelling reason for exclusion can be justified. Justification for exclusion cannot be based on the cost of conducting clinical research. Researchers will be required to examine different gender effects and to this end, more attention to gender is needed in the earlier stages of research so that trial design allows for proper informed decision making in phase three trials.
- The US Federal Food and Drug Administration (FDA) has also published guidelines. The *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* 1993 was a response to growing concerns that the drug development process did not give adequate information to women about effects of drugs and there was a general consensus that women should be able to decide for themselves about participating in early clinical trials. The guideline encourages the participation of women of childbearing potential in Phase 1 and early Phase 2 trials. It also underscores the importance of collecting gender-related data at the earlier phases so that relevant study designs can be developed for later trials.
- In late 1997 the FDA published a proposed rule intended to ensure that women with life-threatening diseases are not excluded from clinical drug trials on the grounds of their reproductive potential. The proposed rule would allow the FDA to place a 'clinical hold' (an order to delay or suspend a trial) if the exclusion is because of potential reproductive or developmental toxic effects. According to the US Associate Commissioner for Health Affairs, the proposal represents 'the evolution in the views of the scientific community and the public at large on ethical issues such as fairness and an individual informed patient's ability to participate in decisions that involve personal risk'.
- The FDA has also created an Office of Women's Health with a core mission of encouraging the inclusion of women in clinical trials. Other ways in which the agency advances this agenda include sponsoring major scientific conferences, proposing new regulations, frequently speaking on the topic and sponsoring a pilot tracking system to monitor the enrolment of women in trials.

Conclusion

Australia needs to catch up with American policy initiatives in this matter. AHEC has stifled debate by not referring specifically to the issue of women's participation in its draft Statement. Many people including researchers and members of ethics committees are unaware of the issues involved when women are excluded or underrepresented in research. This is supported by the fact that only three submissions relating to the issue of women's participation were received in

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victim of abuse by the clergy, health practitioners or other professional groups.

There have been critics of gender-based justifications for sanctions on professional-client sex. The emphasis on the vulnerability of women clients may simply reinforce Victorian-era notions of women being inherently fragile and asexual. Women may freely and knowingly choose to lust after even the most domineering and power-hungry male.

Even allowing for such criticisms, the relative immunity of lawyers who engage in sexual activity with their clients may not last too much longer. There are now at least three States in the US which specifically ban 'attorney-client sex'. More jurisdictions are sure to follow. The depressing fact is that the law does not solve the problem of lawyer-client sex any more than it does for abuse by health professionals. A review of California's 'sex ban' laws for lawyers, carried out one year after the legislation was passed, revealed that most cases were still in the 'investigatory' stage, many were dropped due to insufficient evidence and others could not even be investigated because the complaints were mounted by third parties.⁶ It seems likely, therefore, that sexual exploitation by professionals, whatever their discipline

will continue to produce many more victims, for a long time to come.

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the first stage of public consultation. Given that AHEC has the responsibility of co-ordinating and assisting institutional ethics committees in reviewing research, and its functions involve promoting community debate and monitoring international developments in health and ethical issues, it is reasonable to expect that the issue of women in clinical trials would at least be debated. To date, AHEC's decision in this matter seems to be at odds with its role and its functions.

These issues may yet be addressed in the final revised statement or in the operating manual for institutional ethics committees. The NHMRC is currently preparing an operating manual for institutional ethics committees which should be available in late 1998. It is being developed by a consultant in consultation with AHEC and 'key stakeholders'. With regard to the *Statement on Human Experimentation*, there has been a second stage of public consultation and submissions on the *Draft Statement* were received up until 14 August 1998. The new statement should be released in the new year.

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