The involvement of women of childbearing potential in research has been discussed extensively in this journal and elsewhere. At the heart of the discussion is balancing the potential benefits to female research participants of childbearing potential (and to similarly situated female patients in the future) against the potential risks to hypothetical fetuses. Various approaches have been proposed to deal with this tension, and each is subject to the criticism about the extent to which the balance is maintained.

In this paper we describe the outcome of an institutional review board’s (IRB’s) review process for a drug study in which even the most minimal of requirements for including female participants of childbearing potential was unacceptable to the commercial sponsor, leading to the sponsor’s withdrawal of the study at our site. Presumably, the study is being conducted at other sites with no requirement that women of childbearing potential be included.

The trial consisted of a 12-week, phase II placebo-controlled study of the efficacy and safety of an oral agent for the treatment of a serious chronic disease. The drug had previously been shown to cause fetal malformations in animals and was classified by the Food and Drug Administration (FDA) as Use-in-Pregnancy category C. There were a number of aims for the study; however, the major objective was investigation of the dose response curve for the medication. Thus, it was clear that there was an expectation of direct benefit to study participants since “responders” would clearly be benefitting directly from the agent. This was reinforced in the sponsor’s application for IRB review that listed clinical benefits to participants as part of the relevant considerations for risk-benefit analysis. This is particularly important because, although there are numerous reasons for including women in research studies, fair access to a potential benefit for the prospective participant is among the most immediate.

An exclusion criterion for the study was being a woman of childbearing potential. In the first IRB submission, the rationale for excluding these women was that the project was not intended to study the drug in women of childbearing potential. The IRB tabled the proposal in part because its policy forbids the arbitrary exclusion of women. This policy derives from the guidelines of the National Institutes of Health (NIH) for the inclusion in research of understudied groups, including women and ethnic minorities. Although the NIH policy does not specify which women should be included, we note that excluding those of childbearing potential has the result of excluding a large majority of women from the ages of 15 to 55. Thus, the exclusion of women of childbearing potential excludes most women, thereby depriving women of potential direct benefit from the study drug. In addition, such exclusions place additional risks on all women between the ages of 15 and 55 as future consumers of a drug not previously tested on women in their age range. Given significant physiological differences, it is certainly likely that at least some drugs react differently in women in this age range than in men or other women. Thus, by not testing drugs in this population of women, we subject them to significant unknown risk.

The IRB also noted that it would be acceptable for the investigators to propose contraception requirements appropriate to a reasonable expectation of the magnitude of risk to a potential fetus as a way of addressing this concern. In fact, the IRB policy requires the use of appropriate contraception for category C drugs. This would typically involve one or two forms of effective contraception depending on the proposed risk of the study drug. We note that even in the case of
drugs with known teratogenic effects, the IRB policy does not allow exclusion of women or women of childbearing potential. The policy exists specifically to allow for the minimization of fetal risk while still obtaining the benefits of the inclusion of women in research. There are methods of pregnancy prevention (an intrauterine device or implant) that lower the risk of conception to < 1% per year when used alone. Used in combination with another form of contraception, they reduce the risk even further, making the risks of unknown teratogenic effects on a hypothetical fetus very small indeed. Given that the proposed study was only 12 weeks in duration and thus requiring only two or three cycles of contraception, the magnitude of risk could be significantly decreased. Thus, in our analysis, the additional risk of including women of childbearing potential was near zero. If the risk-benefit ratio was acceptable for other participants, it was acceptable for women who could become pregnant but did not intend to become pregnant. At the very least, this potential additional risk is so small that a reasonable person should be allowed to bear this risk if she wishes. Upon resubmission to the IRB, the investigator replied to our concern by saying that the sponsor declined to revise the inclusion and exclusion criteria and noted that this sort of exclusion was often the sponsor’s policy. The IRB again tabled the study.

On a third submission, the investigator again noted that the drug had unknown teratogenic effects, that there were preclinical data suggesting the potential of teratogenic effects, and that the effects of the molecule were not fully understood. The sponsor did not believe that the risk-benefit ratio for women of childbearing potential was acceptable. The company officials asserted that they would reassess the exclusion of women for the phase III study.

Our IRB again had extensive discussions of this issue. Ultimately, the IRB’s position was that if the sponsor’s exclusion was allowed, this would set a precedent for excluding women of childbearing potential from any study involving drugs known to be teratogens or with unknown teratogenic effects. Given that this is by far the greatest number of agents, the result is a virtual exclusion of women from clinical trials. This would fundamentally nullify federal policies on the inclusion of women in research and be a clear violation of the principle of justice: women would be deprived equality of access and would lose the ability to decide for themselves which benefits and burdens are appropriate for them. Therefore, for the third time, the IRB tabled the proposal, and the sponsor ultimately withdrew it.

We believe that three issues arise from this case. First, although we rarely see studies that propose excluding women as a group (presumably because of NIH and other guidance), excluding women of childbearing potential serves much the same end and denies potential benefits to women in much the same way as a blanket exclusion. Thus, exclusions of women who might get pregnant require much the same justifications as excluding women as a group. Second, it appears that this is a case of “protection creep,” where arguments previously used (perhaps appropriately) to exclude pregnant women from study participation are now being employed in order to justify the exclusion of “potentially pregnant” women (that is, virtually all premenopausal women). Finally, this case illustrates the practical difficulty of enforcing guidelines that encourage the inclusion of women in research studies.

There are, of course, many studies in which the decision of whether to include women turns on subtle, value-laden judgments of risks and benefits to women and their potential offspring. Our IRB has often struggled with these cases and found that the exclusion was justified. However, here we find a case in which many women who could benefit from a trial if the study drug is effective are excluded because of what they could do (become pregnant) in the future. It is our
concern that if exclusions such as this are permitted, there will be virtually no therapeutic trial that would be required to enroll women.

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References


3. To preserve the confidentiality of the study, the nature of the “chronic disease” is not disclosed. Otherwise, the characteristics of the drug and the study are unchanged.

4. Please note that pregnant or breast feeding women were also, appropriately, excluded. Our concern was the exclusion of women who might become pregnant.


7. Although we acknowledge that such requirements present a barrier to full participation in research by women, we require appropriate contraception, but no more than is appropriate, as a means of balancing risks to potential fetuses with a woman’s right to participate. For a full discussion, see ref. 2, Schonfeld et al. 2010.

