ing, and behavior. It is expected that study participants will be counseled about the importance of preventing pregnancy during a clinical trial. It is also expected that laboratory screening for pregnancy will be conducted before and at appropriate intervals during the study. As more preclinical information becomes available, it is expected that the sponsor and investigator will provide the relevant information to the study participant. Nonetheless, in so sensitive an area strong, diverse opinions will lead to further debate about differences in practice. In the case of serious and life-threatening diseases, however, the agency remains committed to the inclusion of women in all phases of clinical trials.

In summary, the FDA expects sponsors to study the full range of patients likely to receive a drug, including both genders, and to analyze the data to determine whether responses in various groups are different. This expectation is not new and implementing it is not likely to add significantly to drug development costs. The FDA recognizes, however, that not all aspects of how to analyze data in population groups are settled and that the best way to obtain population pharmacokinetic information is still a matter of debate (*19*). Nevertheless, the FDA believes that the changes outlined in the 1993 guideline, changes that the agency continues to implement and develop, will not only have a positive effect overall in fostering women's health but will improve the ability of physicians and other health providers to prescribe drugs safely and effectively for both men and women.

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The Inclusion of Women in Clinical Trials

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The U.S. National Institutes of Health (NIH) Revitalization Act of 1993 requires in the case of any clinical trial involving treatment of diseases common to both genders that the trial is (*1*, p. 134)

> designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial.

The "valid analysis" mandate came about because of the perception that the clinical research enterprise in the United States is biased in favor of male participants. The perception has come to be an accepted fact by inductive reasoning from specifics to the general. Most arguments intended to establish the perception as true focus on a 1977 guideline from the U.S. Food and Drug Administration that discouraged the participation of women of childbearing potential in phase 1 and 2 drug trials (*2*) and in a few large-scale heart trials, principally, the Physicians' Health Study (*3*) and the Multiple Risk Factor Intervention Trial (*4*).

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New Guidelines

The NIH Revitalization Act has given rise to guidelines from NIH for implementing the valid analysis requirements of the legislation (*5*) and to a new bureaucracy for review of trials in relation to phase 3 trials (NIH has interpreted the Act to pertain exclusively to phase 3 trials; phase 1 and 2 trials have been exempted from the requirements of the Act). The Act has been challenged in a petition from the Society for Clinical Trials (*6*), in a directive from the membership of the Society to the director of NIH (*7*), and by various writers, including myself (*8*).

For a treatment to be of value for general use, it must first be shown to be of value in some limited setting. There is no point in worrying about whether a treatment works the same or differently in men and women until it has been shown to work in someone.

Every trial involves a select, nonrepresentative study population. The requirement of consent alone is sufficient to ensure that fact. Hence, the strength of a trial lies in its internal validity. A comparison of treatment within a trial is valid as long as the demographic composition of the treatment groups is the same. There is no requirement for demographic coverage or representativeness for internal validity. Generalizations from the study population to the broader universe of patients are a matter of judgment and is always open to question, even when the trial involves a demographically heterogeneous population.

A preoccupation with subgrouping leads to a quagmire of confusion and to a mosaic with ever more parts. That the United States is headed in this direction seems apparent by the increasingly strident voices from constituent groups for their place in the mosaic. Each group argues that it is different from all others and, hence, must be represented in sufficient numbers to provide a valid analysis for them.

If we want to know more about the treatments we use in regard to demographics, we have to be prepared to pay the

piper. We will not generate that information by simply subdividing a pie already too small for answering questions having to do with the main effects of treatments, let alone differences by gender or ethnic origin.

The attention given to clinical trials in the halls of the U.S. Congress would be heartening if its mandate sprung from an inherent appreciation of the strength of trials as a basic evaluation tool. It does not. It springs, instead, from parochial interests in who is studied and in the politics of votes. Alas, the mandate itself is but one more example of an unfunded mandate from Congress.

Possible Consequences

The tendency of funders to gravitate to quotas to fix perceived imbalances or as a means of fending off attack from the underrepresented is short-sighted and fraught with peril. Quotas carry political risks and raise serious ethical issues, especially in the case of treatment trials. Turning away some patients in need of treatment while continuing to enroll others simply to achieve specified demographic recruitment quotas is likely to be viewed as discriminatory and unfair by ethics committees and institutional review boards. It can be argued that they have a responsibility to challenge all demographically based selections or exclusions and to accept only those that can be justified on practical or scientific grounds.

Even in the absence of objection on ethical grounds, there are reasons to steer clear of quotas on practical grounds. Recruiting to quotas to achieve a stated total sample size is invariably more costly and time consuming than recruiting to that total with a floating economy of patients.

As envisioned by Congress and implemented by NIH, the reward for trying to mount a phase 3 trial is added expenditure of time and effort merely to satisfy review requirements. The investigator-initiated, large-scale, multicentered trial is already endangered (*9*). The mandate and the resulting guidelines add to its endangerment and may well serve to move researchers involved in clinical trials away from phase 3 trials to other less politically risky undertakings. If so, the mandate will help no one.

Clearly, in an ideal world, treatments for diseases affecting men and women should be tested on men and women. But what if that is not practical, for example, as in the Veterans Administration Hospital system where the population is predominantly male? Should we forego doing a trial or should we live with a less-than-ideal study population? The answer is obvious. Information is information, and some, even if imperfect, is better than none at all.

Indications are that trials, before any intervention by Congress, provide a broader and more balanced coverage of diseases and demographics than is perceived by Congress. The fact is that most trials published in the medical literature involve men and women (*10*). It is true across most disease areas, including the one where the perception of a male gender bias is strongest—heart disease.

Better Practice

The way to better, more robust trials is not by legislation and recruitment quotas, but rather by making them larger and more inclusive. Indeed, if treatments that work work more or less the same across demographic boundaries, then we should be designing trials for all people having the condition or disease of interest with as few enrollment restrictions as possible. To move in that direction we need to educate those who fund and do trials to devalue demographic selectivity in favor of demographic diversity.

The experimental scientist is taught to value selectivity as a vehicle for variance control and to hold fixed all variables other than the experimental variable. Hence, the laboratory scientist is taught to select animals of the same genetic strain and sex and to house and feed them in identical fashion.

Clinical researchers, dealing with free-living beings, seek to homogenize the populations they study by selection and exclusion. They are obliged to exclude those who are not suitable for treatment as well as those who cannot be assigned to receive one or more of the study treatments. They are not obliged to exclude on the basis of demographics, except where treatment is contraindicated in specified demographic subgroups. They may legitimately choose to exclude on the basis of demographic characteristics in order to enroll a population considered suitable for finding a treatment difference, as in the case of the Multiple Risk Factor Intervention Trial (*11*). They may choose, as well, to select or exclude on the basis of specified demographic characteristics if there is reason to believe that the nature of the treatment effect observed will differ by gender, age, or ethnic origin. Demographically based inclusions or exclusions should not be imposed because others have done so in the past or as an act of conservatism in the absence of scientific rationale to justify the exclusions or inclusions.

There are advantages to being a minimalist when it comes to using demographic characteristics for selection into or exclusion from clinical trials. First, the fewer the restrictions, the easier it is to recruit. Second, the more unconstrained the flow of participants into a trial, the more likely it is that those enrolled will be reflective of the general population of people eligible for treatment. Third, the demographic heterogeneity allows for subgroup analyses otherwise precluded. Such analyses in regard to demographically based subgroups are informative, even if the resulting subgroups are not large enough to provide definitive answers to treatment questions within those subgroups. It is apparent in retrospect that everyone would have been better served by a Physicians' Health Study that had enrolled women physicians, even though their number was not adequate to provide a definitive answer as to the value of aspirin as a preventative for myocardial infarction in women. We would have been better off with some information on the question than none at all.

The goal should be to create a climate aimed at encouraging researchers to move toward demographic heterogeneity in the trials they perform. The fear is that the Congress's mandate, as written and implemented, will continue the tradition of demographic selectivity and exclusivity in the absence of scientific justification. We should be moving toward unconstrained heterogeneity not controlled representativeness through demographic selection and exclusion.

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