Editorial Comment

Extension of Clinical Trials

10½ Year Follow-up of the Multiple Risk Factor Intervention Trial

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The randomized controlled clinical trial to resolve major issues in clinical medicine is a method well accepted in the scientific community. Because progress in treatment of chronic diseases is more likely to develop in small increments than in large steps, clinicians have had to design large trials, often with thousands of patients enrolled in the test groups and with long-term follow-ups. The costs of such trials have increased in a dramatic way, so that few organizations have been able to fund trials aimed at discovery of small-to-moderate intervention effects.

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One way to reduce costs is to look for end points other than mortality and morbidity. In cardiovascular clinical medicine, various indexes of atherosclerosis development have increased in use; for example, changes in the lumen of the femoral artery, the maximal diameter in coronary arteries, and the number of coronary arteries with progression/regression of lesions. Trials with such end points have produced significant and important findings during short-term observation. However, atherosclerosis and disease are not always the same and extrapolation might be misleading.

Another way to obtain additional information is to prolong clinical trials beyond the time set in the test protocol. This is often done by continuing observation with a markedly simplified protocol, collecting information on cause-specific mortality. There are several reasons for doing so. First, a trial finding for a certain period of time may be questioned due to short follow-up. Second, subgroup findings that the trial was not designed to detect can be addressed with a larger data set (although in the same patients). Third, the level of risk in the included patient population could be less than anticipated, resulting in inadequate statistical power.

In this issue of Circulation, the investigators of the Multiple Risk Factor Intervention Trial (MRFIT) present mortality results for an extended, 10.5-year follow-up for the subgroup of patients who were hypertensive at baseline. These important data indicate the risk reduction of special intervention on CHD mortality to be 15% as compared with usual care, an improvement from 4% at the end of the original trial. The result is close to global estimates from overview analysis of hypertension trials. However, it is still somewhat less than was achieved in the other large US hypertension study, the Hypertension Detection and Follow Up Program, but not significantly so.

The original MRFIT trial results indicated that a certain subgroup of hypertensive patients with certain uncharacteristic ECG changes at baseline could be harmed by the antihypertensive drugs used (especially hydrochlorothiazide). The investigators address this question once more with the extended data set and still find an excess risk of CHD mortality in these subgroups. The finding in the original trial that hypertensive patients treated with diuretics were at excess risk is now changed, and patients are observed to experience a reduced risk consistent in time with the switch in drugs from hydrochlorothiazide to chlorothalidone.

Although this explanation seems reasonable with the given data, a certain scepticism should be exercised. The hypothesis of excess CHD risk in these patients was based on characteristics in the same patients as were subjected to extended follow-up, and the findings have not been strongly supported by other trial results. Moreover, the possible development of concomitant CHD risk factors like smoking and elevated cholesterol are not controlled in the extended follow-up period. One could argue, merely on the basis of the differences between special-care and usual-care patients in smoking and cholesterol at the end of the original trial, that one should expect a long-term CHD mortality difference of almost the same magnitude as that observed in the total extended follow-up period.

The persistent finding that hypertensive patients with resting ECG abnormalities at baseline behaved differently from those without seems to be an important message to the clinician and especially so if
diastolic blood pressure is below 100 mm Hg at baseline. This finding is consistent with the observation that mild hypertensives with CVD at baseline were at excess risk if blood pressure fell below 85 mm Hg, the decrease possibly due to a reduced reserve of blood flow.

One of the problems with extended follow-up is that in most cases investigators do not continue to collect the same amount of data as in the trial itself because of cost considerations. Moreover, some patients will refuse to participate in the extension or they may change medications in uncontrollable ways. The practice of extended follow-up in trials raises numerous questions about scientific validity. One could ask when and on what grounds decisions are made to extend follow-up. Also, the rationale behind a decision to stop the extension at a certain time may be obscure. If the expected results emerged at the end of follow-up as planned, an extension might not be performed even though prolonged observation might lead to a different result. Thus, one may wonder whether we most often get only the good news.

It is hard to believe that planned extensions actually completed will not be reported due to "unfavorable" results. However, in many places, for instance in the Scandinavian countries, automatic and informal yearly mortality follow-up can easily be arranged through national registers; decisions of whether to publish extension data could be contingent on such monitoring information, and the decision to stop a trial might be taken just when statistical significance occurred. As long as the main protocol of a trial does not contain precise descriptions of how to deal with the question of extended follow-up, a bias in the literature could easily develop.

How, then, should results from extended follow-up be interpreted? Should the results be treated with the same degree of scientific credibility as the data for the main trial? If so, should meta-analyses of all trials be done on all available end point information, irrespective of all possible criticisms of extensions? One example demonstrating such difficulties stems from the extension of a trial called the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY) trial, involving a subpopulation of the Swedish Heart Attack Primary Prevention in Hypertension (HAPPHY) trial. In the MAPHY trial, a subgroup of hypertensive patients treated with metoprolol or diuretics were subjected to 14 months of extended follow-up. However, the rest of the patients, treated with atenolol or diuretics (and with metoprolol at four other centers), were not subjected to follow-up, and separate results were not reported until much later for those patients in either trial. Should the much-criticized MAPHY be regarded as a new trial, an extended follow-up of the HAPPHY trial, or an extension of the subgroup of metoprolol-treated patients who were willing to continue? How should meta-analyses be done to include independent trials in the overview covering all patients?

The scientific community should address the issue of extended follow-up in the context of clinical trial methodology and guidance, and recommendations should be given as to when extension data should be accepted as having the same credibility as the original protocol data. One way of dealing with this problem would be to provide that protocols of randomized clinical trials include certain statements about possible extended follow-up. Such statements should include criteria for inclusion/exclusion of patients for continuation, end point evaluations, and statistical power considerations as well as methods of statistical analysis. The criteria for deciding when to publish various extensions and when to stop should also be included in the primary trial protocol.

If this is found too restrictive, authors should distinguish clearly between results obtained in the original trial and those in an extension. Discussions and conclusions, however, would probably be complicated in such situations.

References
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