Clinical Trials: Values and Limitations

Lately clinical trials have been criticized—for example, ethical questions have been raised. Are these criticisms valid?

Dr. Fisher: Allow me to first establish that the prospective, randomized clinical trial is, in my opinion, one of the great scientific advances of our time. It represents an enormous breakthrough in medical research and in many cases is the only way to approach treatment questions.

The major problem is not one of ethics or of faulty conceptualization. At the root of the trouble with clinical trials is the fact that physicians generally are not sufficiently schooled in the scientific method. The clinical trial, when properly designed and conducted, is defined as the application of the scientific method to clinical problem-solving. For some reason—despite claims to the contrary—the scientific method is not taught in our medical schools and so we have studies that are poorly designed, loosely conducted and whose data are improperly or inadequately analyzed. The scientific method should be ingrained in our doctors, so that when they have finished their training they can apply it to their practices. I cannot overemphasize the importance of this.

Editor: How does this alleged lack of training affect the interpretation of clinical trials by the primary physician?

Dr. Fisher: For one thing, there's so much medical literature published these days, comprised not only of clinical trials but also of
Editor: Are physicians' attitudes toward participating in clinical trials the result of inexperience with methodology?

Dr. Fisher: This is indeed true, and it is unfortunate. Misconceptions about the purposes of clinical trials, and a failure to appreciate their value, often prevent primary physicians from getting involved. There are other, more subtle reasons as well: the most influential of these is a fear of patients' reactions. Primary care physicians—general practitioners and family practitioners in particular—are assigned fatherly roles in their communities and many of them worry that if they place their patients in therapeutic trials they will appear less than infallible in their patients' eyes. It is a realistic concern, because we are still living in an era when patients expect their doctors to have all the answers. Patient education is the key to overcoming this problem.

Another common misconception that inhibits involvement is the notion that in order to participate in a clinical trial, one's affiliate institution must also endorse the study and participate fully. This is not so; in fact, when a medical center is referred to as a "participating center," it very often means that only one or two doctors are actually involved in the trial.

Another major difficulty concerns physician compliance. A doctor participating in a clinical study may attend a meeting...
somewhere and hear a presentation about some new, promising treatment. He returns from the meeting, pulls all of his patients out of the trial and puts them on the new treatment. The study goes down the drain. This has happened again and again, and it reflects a lack of understanding of what clinical trials are all about, and an underestimate of their value.

**Editor:**

*Are we making progress?*

**Dr. Fisher:**

Overall we have made tremendous progress, especially since World War II; and as it was after the war that the prospective, randomized clinical trial first appeared, I believe it is fair to say that clinical trials have contributed immensely to improved medical treatment in this country.

In addition to leading to the improved management of many diseases, clinical trials have made a large contribution to the general upgrading of medical care, and this is often overlooked. It has come about because the protocols specify that every patient must have this or that test as part of the diagnostic workup, or as part of the preoperative procedure and so forth. This aspect of clinical research has had a strong educational impact and a very positive effect on the quality of medical care.

In other areas, I am very disappointed. Many questions that were being asked and investigated when I was in medical school remain unanswered today. This has been particularly true in surgery; for example, there has long been controversy regarding the best treatment for peptic ulcer, but to this day there has never been a properly designed clinical trial to comparatively evaluate the modalities in use. To me, this is utterly fantastic.

We have tended to drift in and out of therapeutic modes almost as if by chance, or for reasons that have been difficult to ascertain. Promulgation of certain treatments may have been related to the prominence or charisma of their proponents, for instance. In any case, the day of the “Great Professor” is gone and we can no longer afford the luxury of a haphazard approach to medical research. And that is why we need trained laboratory and clinical researchers who are able to systematically define and study the problems confronting us.

**Editor:**

*How will the growing health oriented consumer movement affect the future of clinical trials?*

**Dr. Fisher:**

At present the challenges are still scientific, rather than social or political. However, consumer activities and the ensuing political involvement have certainly had an impact on clinical research. The main concerns center on ethical considerations, and no reasonable person would argue with such tenets as the patient's right to be fully informed about all aspects of his or her illness and its treatment. I heartily defend the doctor-patient dialogue.
However, I feel there is definitely a danger that the issue of clinical research may become over-politicized; if our research efforts are regulated to a significantly greater extent than they are already, the United States will lose its eminence in clinical research. There are very capable people who are conducting clinical trials in other countries, where such strict regulation does not exist, and we will lose our prominence to them.

Editor: 

Isn't it likely that our government will become much more, rather than less, involved in patient care and the practice of medicine?

Dr. Fisher: 

Yes, but again the solution lies in education. There are gross misconceptions about clinical trials in the public and political sectors. Probably the most common and damaging of these is the belief that participating in a clinical trial is tantamount to sacrificing oneself to medical research—that these trials are highly experimental and assignment to one or another protocol is completely random. Of course, this is not true: a patient is placed in a trial when, based on our best judgment and all that we know from previous studies, it is equally probable that the patient will benefit from either of two modalities that are being evaluated. It's a flip-of-the-coin situation, and the purpose of the study is to determine whether one of the treatments is in fact superior to the other.

Another unfortunate fact, relative to public support of clinical trials, is that as we attain additional knowledge, everything becomes more complicated, to the point where we often seem to get further from solving the problem, rather than closer. This is dramatically illustrated in the case of breast cancer: for so many years it was considered one disease with one treatment, the Halsted radical mastectomy. Now we are finding that breast cancer is a heterogeneous group of diseases that very likely respond to different therapeutic strategies. The picture has become very complex and there is vehement controversy. When we actually knew little about the disease, there was little to be controversial about.

This is very difficult for politicians to understand—they have allocated huge sums of money for research and they expect definitive answers. The frustration is overwhelming, and nowhere is this truer than in cancer research. Our politicians must be educated to appreciate that with new knowledge and progress, medical research becomes more complex.

Editor: 

How about the 90,000 women who will get breast cancer this year?

Dr. Fisher: 

The only way we're going to obtain firm data on treating these women is by conducting clinical trials. Therefore, we'd better work hard at removing the obstacles to performing these trials. Education is the only way to do it.
Editor: Is the nature of the clinical trial still evolving?

Dr. Fisher: Each new trial or group of trials brings added refinements. The first clinical trials were a step better than the retrospective studies that preceded them; our present studies show improvements over the earlier clinical trials, and future ones will be still better. Clinical research is a continuum wherein one phase is built upon the previous one, according to what's been learned and what new questions need to be answered. Anyone can criticize out of the temporal context and make earlier clinical trials look ridiculous, but that, of course, is inappropriate. Conversely, it would be dangerous to regard any trial as the definitive clinical study; I suspect that our studies will never be definitive. Everything is provisional and subject to re-evaluation and revision. What one attempts to do is to seek information that is firm enough to enable one to take a stand, even though that position may one day have to be altered. That is exactly where we are with our current NSABP protocol—based upon previous clinical trials of total versus radical mastectomy, we have taken the stand that the Halsted radical mastectomy is not the only answer for patients with breast cancer. Our present study will teach us a little more about alternative therapies, and we will have a new hypothesis to test, and so on.

Editor: How much time is needed to get statistically significant results?

Dr. Fisher: I'm very glad that you asked that question—it brings to mind a feature that is absolutely crucial to the success of a clinical research continuum: once a trial is designed, it must be carried out and ended as quickly as possible. Of course the design itself is terribly important—it has to be impeccable and very, very simple. One of the worst mistakes made in setting up any kind of research is attempting to answer too many questions. However, once the design is complete, the study should be ended as quickly as possible.

Editor: It sounds as though you are refuting the value of long-term studies.

Dr. Fisher: Not exactly; it's difficult to dispute the worth of long-term data accumulation, and as a matter of fact, once a patient is in a clinical trial she should literally be followed for the rest of her life. However, one can easily debate the relative merits of doing 10 two-year studies versus one 20-year study. To some extent, of course, the length of a trial depends on the situation and on the data that one is obtaining. But in general we cannot afford the luxury of waiting until one trial is complete before starting the next one. Using preliminary conclusions one moves on to the next study; this is the continuum I mentioned. In a context of meaningful research, clinical trials do not represent isolated, discrete efforts at problem-solving.
Of course this entails some risk-taking, but it is minimal and also it is unavoidable. We're dealing in probabilities. For instance, 75 percent of treatment failures in breast cancer patients occur within two-and-one-half years of the beginning of therapy. Therefore, we take this into account when we design our protocols. It is possible that wrong decisions may on occasion be made relative to the design of successive protocols. But in the end more benefit will accrue than from the apathy and stalemate of no decision.

The rationale for ending the studies quickly is that if a trial is prolonged, there's a danger of its falling apart. Patients move away and are very difficult to follow; new therapeutic modalities emerge and render the trial anachronistic—or participating physicians get discouraged and uneasy and pull out of the study. A lot of circumstances mitigate against keeping a trial together, and the faster one can wind it up, the less the chances that it will collapse. Rapid patient accrual is an important component of a tight design.

Editor: How do you achieve a fast research pace?

Dr. Fisher: Now we're back to a very crucial point that we discussed earlier: the only way that we can fulfill the great potential of clinical trials is by having as many patients and doctors as possible participating. Again, it's a matter of educating people, physicians and laypersons alike. We must have an organized strategy at the national level so that competition for funds and patients does not exist. Such competition may be self-defeating. If physicians' fear and lack of understanding are so great that they effectively block their participation, we might as well give up. However, I believe we can be successful and I am fairly optimistic that we will succeed because so much depends on it.

Editor: Thank you, Dr. Fisher.