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EDITOR'S PAGE

The Exportation of Clinical Research

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We recently held an international conference on cardiovascular translational research and cell therapy at the University of California, San Diego. As I sat through the presentations of very novel therapies I was struck by the frequency with which the initial clinical trials were being performed outside of the U.S. In fact, I was somewhat stunned, not only that nearly every initial trial was being performed overseas, but also by the "matter of fact" manner with which this was stated. As investigators and industrial representatives discussed stem cell preparations and percutaneous valve devices, they identified the non-U.S. sites of early studies as if this was standard procedure and to be expected. It stimulated me to give some thought to this issue and to discuss it with some of the individuals involved, including Food and Drug Administration (FDA) representatives.

The increasing role of the international medical community in large-scale, multicenter clinical trials has been recognized and critiqued for several years (1). Over the past decade, dramatic growth has occurred in the number of non-U.S. FDA-regulated investigators, many coming from less industrialized and less wealthy nations. Although the potential scientific and social benefits of the interaction of the worldwide medical community have been acknowledged, several concerns have arisen as well. While the increasing participation of overseas physicians and institutions in multicenter clinical trials raises a number of issues, the exportation of initial phase clinical investigation of very novel and hitherto untested biologicals and devices adds additional considerations. Such initial studies are often single centered, and sometimes lead to approval for clinical use in other countries prior to the U.S. They clearly raise a question as to whether we in America are exploiting the rest of the world to prematurely test potentially hazardous therapies, or conversely, whether our regulatory and financial environment is stifling access to important new innovations for patients and investigators.

Conducting a clinical investigation of any type outside of the sponsor's country imposes a number of disadvantages. There are obvious logistical problems such as language differences and the necessity of shipping supplies and personnel to a distant location. Monitoring of such sites is often more difficult, particularly in less wealthy countries. The apparatus needed for clinical research may be less developed and the investigators less experienced. The nature of the patients enrolled may differ significantly from those in the U.S. and other countries likely to use the agents. The disease etiologies may differ (e.g., ischemic vs. nonischemic heart failure), the underlying optimal care may differ, and significant genetic or genomic conditions may be present. All of these issues present possible obstacles to acceptance by the FDA of data generated overseas.

The foregoing difficulties may be offset by the large number of advantages to performing clinical research in other countries. The cost of conducting studies is less in most other countries, and much less in the developing world. The ability to rapidly acquire patients is a major advantage for exported studies. In most of the rest of the world, regionalization of health care facilities concentrates patients, and the lesser prevalence of

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private practice may facilitate referral of patients for clinical trials. Enrollment in trials often provides patients with access to care that would not otherwise be available, and the financial incentives inherent in participating in research are usually greater for both patients and investigators. There is a sense that institutional review boards are usually less stringent, the process of informed consent is sometimes less vigorous, and the authority figure of the physician is a bit more prominent outside than inside of the U.S. It is not surprising, therefore, that sponsors are often attracted to overseas sites for placement of studies. However, it should also be recognized that these factors could contribute to obtaining less robust data, and raise ethical concerns with the research as well.

Discussions with those involved in cutting edge innovations such as stem cells and percutaneous valve devices reveal additional factors that make exportation of clinical research attractive. The European equivalent of FDA approval, the CE mark, has a high degree of credibility. Nevertheless, there is an almost universal feeling that the regulatory bar for approval of new therapies is set higher in the U.S. even as compared with Western Europe. This is particularly true for devices in terms of standards for durability and fatigue, biocompatibility, Good Manufacturing Processes, and packaging and sterility. Indemnification issues are also more stringent. As opposed to an advisory board meeting for the FDA, the written submission for a CE mark may be sent to only 2 or 3 reviewers. Accordingly, the pathway to achieve a CE mark seems less onerous, and may be possible with fewer patients in a single-arm study. Moreover, relatively prompt achievement of a CE mark may be of critical value to a startup company by providing funds flow as well as representing an important accomplishment upon which to base the raising of additional capital. Given these extraordinary advantages of exporting early-phase clinical investigation, one can only wonder if much of this research will ever return to the U.S.

If you are a clinical investigator in the U.S., the loss of the opportunity to participate in early-stage clinical investigation can only be viewed as a negative. Several questions regarding the exportation of research come to mind. Are we exploiting the populace of less wealthy or vigilant nations by exposing them to research with products that have not been adequately evaluated for safety and that will predominantly be used in wealthy countries like our own? The recent emergence of several "first in man" trials from sites not previously recognized for major clinical research raises such a possibility. The FDA can point to therapies such as transmyocardial laser revascularization that were initially approved overseas and subsequently found to be ineffective in larger clinical trials. Conversely, are we in the U.S. confronted with unnecessary barriers to clinical investigation that render us not competitive to serve as trial sites and that deprive our patients of prompt access to beneficial therapies? Do FDA standards have to be so stringent; do university costs and overhead have to be so high; and can't all patients who are candidates for clinical trials be centralized? If exploitation exists, this clearly raises important ethical issues that should be addressed immediately. If barriers are too great, then steps should be taken to remove or lessen them. If, as is likely the case, the exportation of clinical investigation is related to both the advantages of overseas sites and issues with the research enterprise in the U.S., steps should be taken at both venues to ensure the optimal conditions for clinical trials everywhere.

The exportation of clinical trials from the U.S. and elsewhere in the industrialized world has many positive aspects. Participation in clinical research provides intellectual involvement for physicians, potential benefits to patients, and the opportunity for industry to evaluate products in multiple populations and clinical settings. However, it is important that the exportation of clinical trials not be the result of inappropriate or unacceptable conditions either in the U.S. or abroad. Ultimately, clinical trials are meant to provide all physicians with therapies by which to benefit all patients. They should be conducted at the best sites by the best qualified investigators to achieve this goal.

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