New Data on Clinical Trials Directive in Europe Show Few Favorable Outcomes

Early predictions that the European Union Clinical Trials Directive would have a damaging effect on academic research seem to be coming true, Patrick Therasse, M.D., from the European Organization for Research and Treatment of Cancer in Brussels, Belgium, told the European Cancer Conference in Paris last fall.

The directive, a pan-European law that must be implemented in national legislation in all 25 European Union member states, was intended to simplify and harmonize clinical trials throughout Europe. Among the directive’s requirements are the obligation that one sponsor take total legal and financial responsibility for a trial, be it national or pan-European, industry or academic. Many charities and academic groups have found that they cannot afford the financial burden that this stipulation imposes or the increased administrative burden that has resulted from compliance with other directive requirements.

The intentions were honorable—to protect patients and to improve the quality of research through international harmonization. But long before the directive’s implementation, academic researchers had been raising concerns. There were few data available to back up these concerns, but more than a year into the operation of the directive, some hard evidence of its effect on European clinical trials is now available.

High among the concerns was that the directive would greatly increase the cost of clinical trials. And indeed, costs have risen by about 85%, Therasse said. “This is partly due to the increased cost of insurance and fees to regulatory authorities or ethics committees, but largely because of the massive increase in staffing that has been necessary to deal with managing the complicated procedures that the directive has installed,” he said. “For example, every minor change in a protocol—even something as small as changing the name of the data manager—has to be submitted to regulators and ethics committees. We could be facing situations where investigators may prefer to continue to work with a ‘dirty’ protocol instead of going through the amendment procedure.”

To illustrate how the procedures have bogged down the system, Therasse points to trial activation figures. In 2001, the EORTC activated 38 trials. In 2005, a year after the directive came into force, it was seven. “Numbers began to decrease in 2002,” he said, “when countries starting reviewing their existing legislation in order to be able to fit in with the new directive.”

Insurance requirements are particularly burdensome. Before the directive took effect, most standard hospital doctors’ insurance included coverage of care delivered in clinical trials as long as the trial protocol was strictly adhered to, and malpractice insurance covered them when it was not. Under the directive, there can be only one sponsor of a study, so collaborative academic researchers are therefore required to take out a multicenter-sponsor insurance policy. Such insurance is expensive and sometimes difficult to obtain, particularly where...
some individuals do not have prior clinical research management experience, Therasse said.

Brian Moulton, M.D., of the All-Ireland Cooperative Oncology Research Group in Dublin, argues that despite the intentions of the directive, patients are not better protected. “The vast majority of those engaged in conducting research have for many years already carefully protected their patients. The Clinical Trials Directive has done nothing to change the process of informed consent, for example, and it could even be argued that it has harmed patients by reducing clinical trial activity in Europe and therefore reduced their opportunity to obtain access to research treatments after current best-practice options have been exhausted.”

Unifying the regulatory authorities and ethics committees has also been time-consuming and has led to major delays, Therasse said. “Not only have we seen no added value for patients in oncology but there is no harmonized regulatory framework either,” he said. There have been large variations in submission forms, not just between but sometimes within countries, and language issues were an additional headache. Only one country, France, has a centralized ethics committee system; in other countries, there is often confusion between the roles of central and local ethics committees, which led to large variations in assessments. Given that one of the objectives of the directive was to make European medical research more competitive and to give it a level playing field with the United States, where regulations are more harmonized, the outcome is disappointing, Moulton says.

“European investigators have contributed much to the development of medical science, especially—ironically so—in recent years,” said Moulton. “The directive has undoubtedly reduced the enthusiasm and commitment of the middle-ground investigators, who make up approximately 60% of the research community. Because they are essential to the future of clinical investigation in Europe, the difficulties of the directive need to be addressed as a matter of urgency before this disenchanted group walks away entirely.”

In the end, Therasse is most concerned about the effects of the directive on the patients who may not be able to enroll in clinical trials because of red tape. “What I really cannot accept, and what benefits no one at all, is the decrease in patients’ access to innovative medicines, which will be the final result of the legislation,” he said. “This surely is exactly the opposite of what the European Commission had in mind when introducing the measure, and they should tackle this situation as soon as they possibly can.”

—Mary Rice