European Commission Considers Revisions to Clinical Trials Directive

By Emma Mason

The cancer community is hoping for important revisions to how clinical trials are run in Europe as the European Commission (EC) sets about overhauling the much-criticized Clinical Trials Directive.

Adopted in 2001 and implemented by all EU member states in 2004, the directive aimed to create a harmonized framework for clinical research, as well as to improve patient safety and procedures for ethics review and data recording. But from the beginning, clinicians, scientists, and patient groups have criticized the directive, saying that it negatively affects clinical trials—particularly international, non-commercial trials run under the auspices of hospitals, institutions, and cancer networks.

“While the aims of the directive were laudable—to harmonize clinical trials across Europe and improve patient safety—the reality has turned out to be quite different,” said Michael Baumann, M.D., Ph.D., president of the European Cancer Organization and a professor at the University of Technology in Dresden. “It is generally acknowledged that the Clinical Trials Directive has had a catastrophic effect on the independent evaluation and comparison of drugs and other therapies by academic clinical researchers.”

Critics cite a huge increase in bureaucratic procedures and costs, leading to a reduction in the number of investigator-led trials, particularly multinational trials, and a slowdown in the delivery of cutting-edge clinical care to patients.

In 2007, the EC held a conference to address these problems, and in 2008, it launched a longitudinal study to assess the directive’s effect on the number, size, and nature of clinical trials, as well as on the workload, required resources, performance, and costs (see Stat Bite). Then, last fall, the EC launched a “public consultation paper” asking for answers to specific questions on the functioning of the directive. The deadline for submissions was January 8, and the EC is now reviewing responses. It is expected to draft either amendments or a new regulation to replace the directive, probably sometime in the summer.

Major cancer organizations in Europe responded to the consultation paper, saying that the directive has caused particular problems for international trials, substantially reduced the amount of academic clinical cancer research in Europe for all types of treatments (surgery, radiotherapy, and systemic drugs), and hit certain groups of patients particularly hard. These groups include children, patients with rare cancers, patients who would benefit from trials that improve existing treatments (and which, therefore, do not attract commercial funding), and elderly patients with other health problems, including secondary cancers due to earlier treatments.

Disharmony and Paperwork

One major problem, according to respondents, is the different ways that member states interpret the directive.

“The directive was transposed in a heterogeneous manner by member states,” said Françoise Meunier, M.D., Ph.D., director general of the European Organization for Research and Treatment of Cancer (EORTC). “Requirements and regulatory procedures vary from one member state to another.” This disparity has resulted in a lot of duplicated paperwork, she said, wasting resources and time for the sponsors of international clinical studies.

Similar bureaucratic problems exist for obtaining ethical approval and insurance for the clinical trials, for monitoring patients, and for reporting adverse reactions. The EORTC proposes that adverse reactions be reported to a central authority, such as the European Medicines Agency, that would be responsible for transmitting them to the authorities of countries concerned, Meunier said.

The EORTC also recommended that levels of regulation, monitoring, insurance and pharmaco-vigilance (drug safety assessment) for trials should be adjusted depending on the risks associated with the type of trial, rather than having a one-size-fits-all approach; that submission and approval of amendments should be simplified, with a
single authority coordinating evaluation and approvals; that the roles and responsibilities of ethics committees should be clarified and organized so that there is a single opinion per country rather than the several opinions that can be given at present; and that funding be increased for international academic clinical trials by the EU and member states.

The directive presents some specific problems to those carrying out clinical research in children’s cancers, according to Kathy Pritchard-Jones, Ph.D., past president of the European Society for Paediatric Oncology and a professor at the Institute of Cancer Research and Royal Marsden Hospital in London. Many studies investigating new treatments for children’s cancers use drugs already licensed to treat cancer patients, but because they have not been fully tested in children, and therefore don’t have a marketing authorization for use in children, the directive classifies them as investigational medicinal products (IMPs). Any childhood cancer study using these drugs then falls under the directive, even though they may have been used for years to treat childhood cancers and are considered the current best standard of care. Pritchard-Jones advocates changing the definitions of IMPs and of clinical trials to reflect this.

“Unless they can find a way of making exceptions for anticancer drugs that are well tried and tested in children with cancer [so that they do not have to be] called IMPs, an awful lot of extra safety reporting, pharmaco-vigilance . . . is imposed upon the pediatric academic community because the drugs are not licensed for use in children,” she said. “A lot of the proposed solutions do not take this into account.”
Multinational Trial Issues

Another difficulty with the directive involves the role of trial sponsors in international studies. Currently the directive requires a clinical trial to have one sponsor that has overall responsibility. Although this is not necessarily a problem for trials of new drugs that commercial companies organize and fund, it is a problem for noncommercial, multinational trials that a hospital, institution, or network might oversee. Such organizations are reluctant to assume responsibility for patients and insurance in other countries. An increasing number of trials are multinational, particularly for trials investigating treatments for children’s and other rare cancers, where recruiting the required number of patients in one country is difficult.

“The directive was based on the assumption that the study sponsor and the owner of the drug are the same legal entity,” Meunier said. “This does not reflect the reality of academic studies. The sponsor of these kinds of studies is often an academic organization independent from the owner of the drug. Therefore, some obligations of the sponsor cannot be achieved by an independent academic organization.”

A separate, but connected, issue is that sponsors of international trials must wait for each country’s national competent authority (NCA) to assess the proposed trials. This requirement leads to further delays and inconsistent approaches to assessments. Also, some NCAs may lack the required expertise.

Pritchard-Jones suggested that a way to simplify this would be for one NCA to oversee and coordinate this process for international trials, by acting as a “reference” NCA. “The reference NCA would review the study, highlight the issues, ask if the other countries’ NCAs wish to comment, and then once it’s been approved by the reference NCA, it should be a simple tick box exercise for it to be approved in all the participating countries.”

Such cooperation between member states has already begun to happen to a limited extent, without EC involvement, for medicines without marketing authorization under the Voluntary Harmonized Procedure. Pritchard-Jones pointed out that a similar arrangement could allow different NCAs to develop expertise in different kinds of trials.

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“Each trial doesn’t always go to the same place, and it could well be that particular member states’ NCAs might want to develop expertise in pediatrics or cancer trials, for example,” she said. “I think you do need to have some knowledge to make proper assessments of trials for rare indications or populations.”

Risk Levels and Insurance

The way the level of risk in a trial is calculated and issues around trial insurance are other key problems for the pediatric oncology community, said Pritchard-Jones. Since implementation of the directive, insurance costs for pediatric trials have increased 100-fold despite there being no increase in the actual risk.

The standard care for children with life-threatening diseases such as cancer already consists of toxic treatments, with acute and long-term side effects, Pritchard-Jones argues. Therefore, the insurance for taking part in a trial shouldn’t have to cover the expected potential side effects of the currently available standard treatment regimens. These are considered ‘best practice’ and would be used regardless of whether the patient is enrolled in a clinical trial or not.

“If insurance is mandated, it should only need to cover any potential additional risk of being a trial participant,” she said.

Pritchard-Jones said that for pediatric oncology there is no evidence that children with cancer are better protected than previously and plenty of evidence to show that the number of phase III clinical trials available for children has declined. “We now face periods of sometimes several years where there is no frontline phase III trial open for certain diagnostic groups,” she said.

The European Cancer Patient Coalition echoes this view. “The number of trials, the number of trial sites, and the number of patients enrolled in studies have gone down [substantially], in comparison to the time before the directive was implemented,” said Jan Geissler, director of the Coalition. “We see a trend towards a focus of oligocentric, industry-driven research instead of a healthy competition between academic and commercial research.”