CLINICAL TRIALS GET TOUGH

Britain Adopts More Stringent Rules for Phase I Trials of High-Risk Compounds

By Gunjan Sinha

A
fter a disastrous phase I clinical trial last year that left six volunteers seriously injured, Britain’s Medicines and Healthcare Research Agency (MHRA) has tightened its clinical trial regulations. Now studies of certain classes of drugs that have never before been tested in humans will have to follow new guidelines on a range of topics, including dosing protocols and training for investigators.

“Everyone realized that the first priority is the safety and well-being of subjects,” said Gordon Duff, M.D., Ph.D., professor of molecular medicine at the University of Sheffield. “So most stakeholders were pulling in the same direction.”

Duff led the expert scientific group (ESG)—an independent body of 19 people commissioned by the U.K.’s Secretary of State to investigate details of the TGN1412 trial and to recommend changes to existing procedures. The group consulted various stakeholders—both national, such as the British BioIndustry Association and the Association of the British Pharmaceutical Industry, and international—before drafting their final report, which was published in December.

The report concluded that none of the parties involved in the TGN1412 trial violated current clinical trial regulations. However, it did recommend revamping existing procedures for certain compounds to better protect clinical trial volunteers. It singled out specific classes of “high-risk” drugs that regulators should scrutinize more closely: biological molecules with novel mechanisms in man, new agents that are highly species specific, and new drugs directed toward immune system targets.

ESG’s recommended changes span both clinical trial sponsors and regulatory agencies and cover five specific areas: preclinical research, drug dosing strategy, reviewing clinical trial applications for risky compounds, facilities for first-in-man clinical trials, and training for clinical investigators. While some critics have argued that tighter regulations in Europe might drive clinical trial sponsors to other countries, others see little reason for concern.

“Most of the recommendations aren’t dramatic changes,” said Richard Ley, spokesperson for the Association of the British Pharmaceutical Industry. “Procedures should be reviewed and revised every few years anyway.”

The MHRA has already implemented many of the ESG’s recommendations, spokesperson Stephen Hallworth said. Prompted by the report, the European Medicines Agency has issued similar guidelines for E.U. member countries regarding first-in-man studies to better harmonize regulations across the continent.

The Catastrophic Trial
In March 2006, eight healthy volunteers entered a phase I trial of a monoclonal antibody at Northwick Park Hospital in London. Six men received the compound by the German company TeGenero AG, and two received placebo. Less than an hour later, the six in the drug group began feeling headaches and pain—symptoms that within a few hours progressed to multiorgan failure. Doctors transferred the men to Northwick Park’s intensive care unit. All eventually needed assisted ventilation and blood filtration. Experts later concluded that the drug had overstimulated their immune systems—cytokines had flooded their bloodstream and caused a near-fatal case of cytokine release syndrome (see J Natl Cancer Inst 2006;98:956–8).

While all six survived the trial, they continue to suffer a range of symptoms that include memory blackouts, extreme weakness, and diarrhea. And because the drug damaged their immune systems, they may face a greater risk of contracting cancer and various autoimmune disorders, U.K. newspapers have reported.

Improving Preclinical Research
After the trial, the MHRA not only looked for misconduct but also investigated whether the drug had been contaminated during manufacturing or preparation. They concluded that the volunteers’ severe reactions were most likely caused by the pharmacological effect of the drug itself at the dose given.

The U.K. government then appointed the ESG to review trial details. “The aim was not to criticize the trial,” Duff emphasized, “but to review and generalize what could be learned.”

The result was a list of 22 recommendations that trial sponsors and regulators could implement to cut the risk of another catastrophe. Most of the recommendations concern preclinical safety testing and ways to establish a dosing strategy for drugs first tested in humans.

Even though the company followed existing guidelines for preclinical research, the trial highlighted how poorly animal
Deciding on Dosing

The biggest chunk of the report’s recommendations concern dosing. Not only did animal studies poorly predict a safe starting dose in humans, but the trial’s dosing protocol appeared to have no scientific justification. The six men received the drug intravenously 10 minutes apart, but there was no rationale given for the dosing regimen in the company’s clinical trial application.

“The TGN study was not very well designed but certainly no worse than others that we’ve seen,” said Stephen Senn, Ph.D., professor of statistics at the University of Glasgow and chairman of a working party at the Royal Statistical Society (RSS), which also issued a report on the TGN1412 study.

“Clearly, we need better medicines. But as we develop more specific and potent medicines, there may be more risky agents than TGN1412, but there should be no higher risk trials.”

Except for cancer clinical trials, which are rarely conducted on healthy volunteers, phase I dosing protocols are usually poorly detailed, Senn said. “Most just eyeball the preclinical data to establish a starting dose because no one ever thinks that a drug given to healthy volunteers will cause serious side effects.” The goal of any phase I study is to find an upper limit at which people begin to experience mild side effects. So dosing generally begins low. The method has worked thus far. No other trial in known history has caused such severe side effects.

But as companies continue to develop drugs highly specific for human targets, experts agreed that such methods aren’t adequate. For example, the RSS report found that preclinical studies on TGN1412 are detailed in a document filed with the company’s clinical trial application. But while the studies are described qualitatively, there is little quantitative analysis presented, making it difficult to judge the protocol, Senn said.

One suggestion is to use an alternative method to calculate dose where high-risk compounds are involved. The TGN1412 trial used the “no observable effect level” method to calculate dose, which extrapolates from animal studies. “But no adverse effects in animals shouldn’t be seen as a green light,” Senn said. To improve dose calculation, the RSS supports the ESG report’s suggestion that the industry adopt a broader approach. They suggest combining cellular dose–response studies, experience with similar molecules, and other information in a model called the “minimal anticipated biological effect level.” Also, models should use uncertainty factors in their calculations, the RSS report said, which not all models do.

Sponsors should also provide a scientific rationale for a dosing scheme. Staggered dosing over longer periods to observe each volunteer during the TGN trial instead of dosing each volunteer sequentially at 10-minute intervals, for example, might have spared at least a few volunteers.

“We’re not saying that for every single first-in-man study you need to dose at intervals,” Senn added. “But we are saying that if you choose not to do that, you should have to say why.”

Boosting Regulatory Oversight

In addition to requiring clinical trial sponsors to submit more detailed information, the ESG report also recommended that the MHRA beef up its own ranks. The suggestions included consulting outside experts about clinical trials of high-risk drugs, issuing a special certification for clinical trial investigators, and designating certified “specialist centers” to conduct clinical trials of risky compounds.

The MHRA has already appointed an advisory group to scrutinize trial applications for high-risk substances, Hallworth said. As for training, MHRA is discussing the practicality of principal investigator certification programs with all relevant stakeholders. The agency is also exploring how to designate specialist centers and how to ensure that they are appropriately equipped, Hallworth added.

“I am content,” Duff commented. “I think that the MHRA have tried extremely hard to
move from a list of recommendations on paper to things being implemented.” While some of the suggestions, such as information sharing and creating databases, are long-term goals, “the U.K has already implemented what could be done quickly,” he added.

Prompted by the report, the European Medicines Agency has also issued a draft of new guidelines regarding high-risk compounds. The agency worked with the heads of regulatory agencies of all E.U. member countries to establish them, said spokesperson Monika Benstetter, but most mirror those suggested by the ESG. The draft is intended for public comment and will be finalized by the end of this year.

While other non-E.U. country regulators sat in on ESG meetings, whether they will adopt similar regulations is unclear. The U.S. Food and Drug Administration, for one, has decided not to change U.S. guidelines regarding first-in-man studies.

“We reviewed our existing procedures and polices and concluded that additional new guidance was not needed since existing guidance and policies already address these situations,” said Karen Riley, at FDA’s public affairs office.

The discrepancy between the EU and other countries has raised concerns about competitiveness. The British BioIndustry Association, for example, is worried that the MHRA’s addition of an expert group to examine applications sequentially and not in parallel with the existing process will delay the process to a minimum of 11 weeks, compared with 30 days in the U.S.—delays that might drive more trials to the U.S.

Some sponsors have also expressed concern about the European Medicines Agency’s definition of high risk. “The current guidance could, in theory, apply to all new drugs aimed at a new target,” Riley said, which would also make European countries less hospitable to clinical trials than other countries would be.

But not everyone shares the same concern. “There was only a need to change practices where this group of compounds is concerned—they make up perhaps a half a dozen applications a year,” Ley emphasized.

“Clearly, we need better medicines,” Duff said. “But as we develop more specific and potent medicines, there may be more risky agents than TGN1412, but there should be no higher-risk trials,” he added.

“The risk assessment and risk management measures we are suggesting should bring the safety of all trials to the same high level.”