Fault or no-fault: Clinical trial insurance needs an overhaul

Following the recent events at a Phase I unit in the UK where six volunteers suffered serious adverse events during a first-in-man study, **Linda Horton** and **Camilla Buchanan** consider the liability implications for companies running clinical trials, and whether no-fault compensation should be available for subjects injured during the course of studies

Clinical trial insurance has recently surfaced as a major issue as a result of the calamitous Phase I study of the monoclonal antibody TGN 1412 conducted in March this year.[1] The sponsor, TeGenero, had engaged PAREXEL International to conduct the study and the CRO sought permission to conduct a Phase I clinical trial in both the UK and Germany. The UK clinical trial authorisation came through first and the Northwick Park episode soon followed. The trial resulted in the hospitalisation of six volunteers due to unexpected severe swelling of their heads and upper bodies. At least four of them suffered major organ failure.

According to reports in the press, TeGenero has accepted responsibility for paying the volunteers compensation and has offered them interim payments of £5,000, provided they agree not to sue.[2] The volunteers have reportedly instructed their lawyers to reject this offer, and believe that a £5,000 lump sum seems somewhat insulting considering what the men went through, and all the more so for the least fortunate who, it is reported, may lose his fingers and toes to gangrene.

Therefore, aside from the investigation into what went wrong and why, this case raises important questions regarding liability and insurance. To help shed some light on these issues, this article will discuss the insurance obligations under Article 3 of the EU Clinical Trials Directive.

Legal requirements

At EU level, clinical trials are regulated by the EU Clinical Trials Directive (2001/20/EC) which came into force on 1 May, 2004. The Directive is transposed into the national laws of the EU member states and its implementation varies across the EU. In the UK, it is transposed into law by the Medicines for Human Use (Clinical Trials) Regulations, 2004. These UK regulations replaced the clinical trial provisions of the Medicines Act 1968 and its secondary legislation. The Directive specifies that it is without prejudice to the civil and criminal liability of the sponsor or investigator under national law. The major changes to previous UK practice are that:

- The sponsor and investigator are required to be insured or indemnified for their liabilities
- Pharmacology studies in healthy human volunteers (Phase I studies) require authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA), whereas previously they needed only a favourable opinion of an ethics committee
- Investigational medicinal products must be manufactured to GMP standards and the manufacturer must have a manufacturing licence
- Each trial must have an identified sponsor who takes responsibility for its initiation, management and conduct.

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Insurance requirements

When deciding whether to allow a clinical study to commence, the ethics committee and competent regulatory authority, will take into account, among other considerations, any insurance or indemnity to cover the liability of the investigator and sponsor. The Directive does not require no-fault compensation. The insurance requirement is meant to provide coverage for liability, such as liability for negligence. The Association of the British Pharmaceutical Industry, however, recommends that sponsors offer no-fault compensation. Under the Directive, it is for the ethics committee to assess whether it is acceptable to seek consent without no-fault compensation, given the risks for the particular trial in question.

The above points raise two important questions. First, what do the liabilities of the investigator and sponsor include: for example, liability for the behaviour of the qualified person; for the manufacture of the drug; and/or for the carrying out of the trial? Second, what should be the level of insurance? Regarding the former question, the Directive is not clear but it can be deduced that the situation would be influenced by whether there is a direct causal link between the sponsor or the investigator and the injury.

In the case of the TGN 1412 Phase I trial, the five key players were the investigators, the institutions, PAREXEL International (the CRO), TeGenero (the sponsor), Boehringer-Ingelheim (the contract manufacturer), and, of course, the subjects.

An investigation of the case by the authorities was initiated to find out if the reaction seen was due to contamination of the dose, an incorrect dose being administered, or an inherent flaw in the drug. A further concern is the short timeframe within which the doses were administered. According to a report in *The Times*, one of the volunteers who received a placebo reported that the subjects had been given the drug at intervals of around two minutes between each patient, with allergic reactions starting five minutes later.[3] However, it appears that the protocol the MHRA had approved for the trial involved

the doses being given within two hours.

Another issue is whether the company should have known the drug would provoke this reaction in humans. An immunologist contacted by *New Scientist,* who wished to be anonymous, commented, 'You don't need to be a rocket scientist to work out what will happen if you non-specifically activate every T cell in the body.'[4] While the drug had appeared to be safe in animal models, researchers noted that there are reasons why these models may not be indicative of the response in humans, particularly with respect to this type of drug. Experiments with another drug affecting the CD28 receptor (but to a lesser extent than TGN 1412) had also shown side-effects in human trials.[5]

Interim findings

On 5 April, the MHRA issued an interim report on the TGN 1412 trial. It found no deficiencies in TeGenero's preclinical work; there was no evidence of undisclosed studies. PAREXEL's records and processes appeared in order (including dose measurement and administration) and the MHRA felt that the CRO's actions did not contribute to the serious adverse events. Nor were there any deficiencies in the animal work; results accurately reflected raw data.

German regulatory authorities inspected the production of the material by Boehringer Ingelheim, looking at the manufacture, testing, storage and distribution of the TGN 1412. No deficiencies were identified which could have contributed to the serious adverse effects. Although tests are ongoing on the actual material used, the MHRA stated that tests are consistent with the TGN 1412 being up to specification at the moment.

The MHRA concluded that the most likely cause of the reaction in trial subjects was an unpredicted biological action of the drug in humans. The interim report recognises that important scientific and medical questions about the risks of testing these agents in human subjects have been raised. To that end, the UK Secretary of State for Health has agreed to establish a group of leading international experts to consider those issues, and to provide a report on the future authorisation of such trials (with an interim report at three months).

Until the expert group has reported, all further UK clinical trial applications involving first-in-humans trials of any monoclonal antibody or other novel molecules targeting the immune system will not be authorised without additional expert opinion on whether the effects seen in the TGN 1412 may be repeated. There will be a fuller report on the TGN 1412 trial in the future, but the expert group will run concurrently.

Insurance claim

As noted above, a clinical trial may not be approved unless provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor. Approval for the trial is given by the national regulatory authority, and a positive opinion of an ethics committee is also required. Therefore the legislative scheme implies that the national regulatory authority and ethics committee carry some responsibility for assessing the extent of liability which the trial could potentially incur.

It is questionable whether they are equipped to carry out this task. As this case illustrates, the extent of liability which may be incurred when a trial goes wrong is huge. TeGenero reportedly only has insurance of £2 million (US$3.7 million), which might be viewed by some as inadequate to cover damages due to the injured subjects. The insurance coverage of the CRO, the investigator and the institutions is unknown.

The investigation of the TeGenero trial may or may not uncover whether any of the players involved are legally culpable. However, questions will linger over whether society as a whole should offer a no-fault compensation system to cover risks incurred by those who, on behalf of us all, agree to participate in clinical trials of new therapies. Incidents, such as the one at Northwick Park, raise a host of questions deserving full debate on clinical trial insurance. GCP

References

1 J Law. 'TGN 1412: More questions than answers?', *Good Clinical Practice Journal*, 13(5), pp12–15, 2006.

2 F Gibb. 'Drug company offers £5,000 if victims of trial agree not to sue', *The Times*, 19 April, 2006 (www.timesonline.co.uk/article/0,,8122-2140946,00.html).

3 S Lister, L Smith. 'Doctors seek international help in treating victims', *The Times*, 17 March, 2006 (www.timesonline.co.uk/article/0,,8122-2090146,00.html).

4 S Bhattacharya, A Coghlan. 'Catastrophic immune response may have caused drug trial horror', *New Scientist*, 17 March, 2006 (www.newscientist.com/article/dn8863-catastrophic-immune-response-may-have-caused-drug-trial-horror.html).

5 H Pearson. 'Tragic drug trial spotlights potent molecule', *Nature*, 17 March, 2006 (www.nature.com/news/2006/060313/full/060313-17.html).

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