

# Will drug trials ever be the same again?

Six young men were admitted to intensive care last week during a trial of a new monoclonal antibody, and two were still in a critical condition as *The Journal* went to press, Tom Moberly looks at the impact the events at Northwick Park Hospital, north London, may have on future drug trials

Paraxel's aborted trial of the monoclonal antibody TGN1412 has dramatically brought the issue of how medicines are developed and tested to the public's attention. However, rather than causing people to shy away from the risks involved in developing new treatments, the events at Northwick Park, north London, appear to have led to a surge in interest in clinical trials.

"The numbers of people expressing interest in trials have, paradoxically, increased," Trevor Smart, Schild professor of pharmacology at University College London, says.

The Medical Research Council says that although its Clinical Trials Unit usually receives a few queries a month, they received more than a dozen towards the end of last week. And Hammersmith Medicines Research, a contract research organisation in London that specialises in phase 1 and 2 studies (see Panel 1), has also seen a general increase in interest, Malcolm Boyce, managing director, says.

He does not believe that this is simply because people did not know that there was money to be made, but there were many other more altruistic reasons that people might want to take part in trials, or they may simply want more information.

This interest is likely to be a result of an increase in awareness, Professor Smart believes. "Members of the public probably knew about phase 2 and 3 trials, but they may not have been aware of phase 1 trials, so this

will certainly have highlighted those to them," he says.

Nirmala Bhogal, science manager at the Fund for the Replacement of Animals in Medical Experiments, agrees. "This will have brought the issue of the testing of medicines to people's attention and they may have become much more aware of the testing medicines undergo in other species," she says. Such tests in non-human animals must be carried out before the first tests in humans — phase I trials — can be carried out. Phase I trials are regulated in the UK by Regulations incorporated the EU Clinical Trials Directive into UK law in May 2004 (see Panel 2).

These Regulations require sponsors of clinical trials to have a clinical trial authorisation from the MHRA for phase 1 trials — previously such trials only needed a favourable opinion of an ethics committee. It was this clinical trial authorisation for the study at Northwick Park that the MHRA withdrew last week.

Professor Smart believes that this present level of interest may be sustained in the long term. "I think the numbers will probably remain higher than before for standard trials of conventional drugs, but for trials of biologicals there may be a problem, particularly if a trial is for an agonist monoclonal antibody like the drug used in this trial," he says.

However, Dr Bhogal argues that people will now be more demanding about the data they are given before they take part in trials.

"Healthy people will probably now be unwilling to volunteer unless they are given more information," she says. "Perhaps volunteers should be shown all the available data and allowed to make their own judgements," she adds.

The events at Northwick Park are likely to affect not just volunteers for clinical trials, but also to raise issues of the appropriateness of conventional clinical trials to assess modern biological therapies, Dr Bhogal believes. "For a traditional medicine, animal studies would normally be used to find out the highest tolerable dose, but monoclonal antibodies may not have an upper tolerable limit so the trial also raises questions about whether present clinical trials guidelines are suited to antibody-based therapeutics," she says. "We may then have to ask whether we are now trying to fit new therapeutics into an old testing scheme."

Saah Shakir, head of the Drug Safety Research Unit in Southampton, agrees that current testing methods may no longer be appropriate for the new therapeutics being developed. "I think we need to have a real think about the trials that are done to test monoclonal antibodies and whether the types of tests used for conventional medicines are suitable for drugs like these," he says. "That certainly raises a lot of questions and will be an issue for long-term scientific enquiries. There may also be changes to the regulatory processes, but those will take time to come through.

"One of the most important things we can learn now, though, is that [as a result of the six men being given the treatment at almost the same time] we need to look at dosing patients sequentially rather than simultaneously. That may involve a change of regulations," he adds.

However, the impact of the events at Northwick Park will, in the end, depend on what exactly went wrong, Professor Smart argues. "There could be implications for how one assesses in future what tests are used prior to phase 1 to ensure safety of biologicals, and how the results are analysed."

## Panel 1: Pre-clinical testing and clinical trial phases

Before testing in humans begins, unpromising compounds are sifted out and candidate compounds selected for development. Non-clinical and pre-clinical bench and animal tests are then run before the drugs are tested in humans. The types of pre-clinical tests that have to be conducted on animals vary from medicine to medicine, depending on the characteristics of the active ingredient, a spokesman for the Association of the British Pharmaceutical Industry explains. "Typically, studies will need to be carried out on at least two species. Around 80 per cent of tests are carried out in rats or mice and then on a larger species," he says. "The larger species used will again depend on the medicine being tested but are normally a larger rodent. Other animals such as dogs, cats or pigs are sometimes used because of the similarities between some of their organs and humans'. And any drug for a neurological condition, or involving the brain, will usually have to be tested in non-human primates first, before phase 1 trials can begin."

Clinical trials assessing the safety and efficacy of medicines in humans are then divided into four phases:

- Phase 1 or healthy volunteers trials are small studies and the first test of a drug in humans. They are designed to establish safe or tolerable levels of the drug and the route by which it should be taken. The trial at Northwick Park Hospital was a phase I study.
- Phase 2 trials involve groups of 100–200 patients suffering from the disease which the drug is being developed to treat. They provide more evidence about activity and safety and are also used to define the dosage and regimen for the medicine.
- Phase 3 trials are larger scale controlled trials designed to assess the risks and benefits of the treatment. Such trials involve 1,000–3,000 patients, sometimes many more, and compare the treatment under assessment with either a placebo or a comparator drug.
- Phase 4 trials are those initiated after a medicine has been launched and are designed to identify any undocumented adverse effects.

## Panel 2: Trial regulations

The Medicines for Human Use (Clinical Trials) Regulations 2004, which implemented the EU Clinical Trials Directive (Directive 2001/20/EC) into UK law, came into force on 1 May 2004. These Regulations replaced the clinical trial provisions of the Medicines Act 1968 and were designed to provide a statutory basis for the standardisation of clinical trial procedures.

Robin Harman's two-part series on international harmonisation of clinical trials explains the regulatory environment in more detail (*PJ* 14 August 2004, p224 and 21 August 2004, p260).