(fewer than one-fifth) express some misgivings about their work. "As a researcher in the field of HIV vaccine development, I am placed in a very awkward position regarding the use of non-human primates," said one immunologist. "I personally feel uncomfortable with primate research yet I realize that without primate data, vaccine candidates are rarely forwarded to human trial."

Fear is clearly a significant factor in excluding the voices of ordinary researchers from public discussion of these issues. No scientist should have to risk life and limb in order to speak about perfectly lawful work. Welcome steps have been taken by governments in both Britain and the United States to pass laws that will protect scientists under the law. And there is some evidence, in both countries, that public support for animal research has actually increased in response to animal-rights extremism.

Our survey also suggests that research agencies, universities and other institutions could do more to ensure that scientists feel free to talk about their work. There are also some indications that peer pressure is not always conducive to open communication with the public about animal research. "I am more concerned that the scientific community, rather than the animal-rights movement, makes it difficult to voice a nuanced opinion on animal research," said one neuroscientist, whose research involves using imaging to study the brains of human patients.

It is essential that researchers feel free to speak out, both within the community and beyond it, on this issue. If, as seems to be the case, scientists have made some headway in persuading the public of the value of animal research, then this is an opportune moment for them to engage in a full and open debate about the options that lie ahead — including improvements to research practice and the development of alternative approaches. ■

The elephant in the room

A biotech trial that went awry.

Sooner or later during the life of any drug candidate, there comes the time when it must be administered to humans. Phase I clinical trials, or 'first in man' trials, will always carry an inherent risk; the critical thing is how to manage the risk to the paid participants who volunteer as test subjects.

This is the question that a panel convened in Britain has sought to answer in the wake of the trial of TGN1412 — an antibody aimed at treating autoimmune diseases such as rheumatoid arthritis — that put six men in intensive care at London's Northwick Park Hospital in March this year (see *Nature* **440,** 388–389; 2006). The panel was brought together to advise the Medicines and Healthcare Products Regulatory Agency (MHRA), which governs British clinical trials, on how to minimize the risks of such an event recurring.

Implicit in the list of 22 recommendations released by the panel on 7 December is an acceptance of the inherent dangers posed by some drug candidates — particularly those that target the immune system. The group's final report describes such compounds as "high-risk drugs", but makes no recommendations about when the MHRA should refuse to authorize a trial on the basis of unknown risk. Instead, the report leans towards learning as much as possible about such molecules before they are administered to people.

The panel recommends, for example, that the MHRA should consult external experts with specific knowledge of the area in question, such as a particular group of compounds. It also advocates creating a database of animal data, which might flag up adverse reactions observed previously that could otherwise be missed by regulators.

The proposals depart from the British regulator's prior practice of approving clinical trials through a process that amounted to ticking a series of boxes, towards a more subjective consideration of how drug candidates actually work. It will no longer be enough simply to demonstrate that a compound is non-toxic in an animal model.

This is to be applauded. But the fact remains that many of the drugs now being readied for clinical trials, for all their enticing potential benefits, carry risks that can never be eliminated. TGN1412, for example, was intended to bypass one of the cellular checks blocking the activation of a certain class of T cell. The problem was that, in humans, its activation was more widespread than expected among the different types of T cell, inducing a storm of inflammatory molecules that led to widespread inflammation and organ failure.

Preclinical trials in monkeys had shown no such adverse reaction, despite the fact that they share an almost identical receptor for the antibody. As part of the investigation that led to the report, immunologist Stephen Inglis of the National Institute for Biological Standards and Control near London and his colleagues developed an *in vitro* test using human blood cells that recreated the behaviour of the trial volunteers' cells.

Inglis and the rest of the advisory panel now advocate including such tests in future preclinical evaluations of antibody drug candidates. But this test was retrospective — a team of immunologists took months to recreate something that bitter experience had shown to be possible. Using similar methods to spot dangerous compounds before they go to trial will always be an exercise in guesswork.

"It will no longer be enough simply to demonstrate that a compound is non-toxic in an animal model."

The panel's advice included several recommendations that should be simple common sense. Volunteers should be dosed one by one, rather than simultaneously; doctors performing the tests should have specialist, rather than general, expertise; and trials should be carried out in dedicated centres within existing hospitals, with 24-hour emergency facilities.

All this represents necessary progress. Less satisfactory is the government's failure so far to hold anybody accountable for the Northwick Park incident. The MHRA, in a subsequent investigation, exonerated both itself and Parexel, the company that administered the trial; TeGenero, the German firm that developed the drug, has gone bust. The victims have been appallingly maimed, suffering from amputations and with bleak health prospects. They are well represented legally and will doubtless now look to the courts, rather than the regulator, to determine where responsibility for their condition lies. ■