In brief

Hip replacements riskier in hospitals that do fewer:

Risks: associated with knee and hip replacements are greater at centres that handle fewer cases, a study based on almost 500 000 procedures in England has found (*Journal of Public Health* 2006 Apr 5 (<http://jpubhealth.oxfordjournals.org>) doi: 10.1093/pubmed/fdl003). The odds ratio for in-hospital death within 30 days of hip replacement in trusts doing less than 50 a year is 1.98 (95% confidence interval 1.13 to 3.47) compared with trusts doing 251-500 replacements.

Watching soaps can indicate brain decline:

Older people who often watch television talk shows and soap operas may be predisposed to future cognitive decline (*Southern Medical Journal* 2006;99:226-33). Research on 289 older women showed that those who named talk shows or soap operas as their favourite category of television programme were consistently associated with poorer cognitive scores ($P<0.05$ for both).

Swiss doctors protest at cuts:

Ten thousand GPs in Switzerland took to the streets of the capital, Bern, on Saturday 1 April to protest against spending cuts. Health minister Pascal Couchepin unveiled cuts of €57m (£40m; \$69m) in November 2005, slashing funds for laboratory analyses in particular.

Chinese medical research goes international:

Research published in 34 Chinese science journals, including the *Journal of the Chinese Medical Association*, is being made available to an international audience under a new scheme launched by Elsevier. The publisher will provide access to the English language journals through its online portal ScienceDirect for free in 2006.

Fund distributes mosquito nets:

More than two million mosquito nets have been delivered to mothers of children aged below 5 throughout Nigeria before the country's rainy season, which begins in May. The scheme is financed by the Global Fund to fight AIDS, Tuberculosis, and Malaria.

Inquiry into adverse events in trial blames drug, not study design

Susan Mayor *London*

A preliminary investigation of a UK trial in which six healthy volunteers became critically ill said this was probably due to effects of the drug in humans not predicted by animal studies. But the report stopped short of questioning how the study was carried out.

The investigation into the phase I trial of the monoclonal antibody TGN1412, carried out by the Medicines and Healthcare Products Regulatory Agency (MHRA), the body that approves clinical trials in England, said the trial was run according to the agreed protocol, using the correct dose. It also found no evidence of a manufacturing problem or contamination of the product given to the trial volunteers.

The MHRA's report did not comment on suggestions that it might have been more prudent to have tested the drug in one volunteer at a time, leaving enough time to observe any adverse effects before giving it to another person, rather than giving it to the whole group at once (*BMJ* 2006;332:683, 25 Mar).

The protocol for the trial of TGN1412, which the MHRA released at the same time as its report, says that the drug would be administered intravenously within a two hour period to all participants.

However, a report on testing antibody treatments published last week by a working group of the Academy of Medical Sciences—a group of medical scientists from hospitals, academia, industry, and the public service—argued: "It would be usual prac-

tice to administer a single dose in a single patient, who would then be observed for an appropriate period of time."

In response a spokesperson for the MHRA said: "The protocol specifying that all dosing would take place within two hours appeared to be reasonable, based on the large safety margin allowed for by use of a much lower dose than used in previous animal studies."

The academy's working group, which is chaired by Patrick Vallance, head of the division of medicine at University College London, pointed out that the specificity of antibody action and the relative youth of this field of research "means there is a smaller body of knowledge to draw on when attempting to predict unwanted effects."

The MHRA said that its inquiry indicated that TGN1412 showed "a pharmacological effect in man which was not seen in preclinical tests in animals at much higher doses."

It said that the six men who became ill suffered life threatening incidents of "cytokine release syndrome," in which cytokines released by activated T cells produce a type of systemic inflammatory response.

The inquiry noted that although several monoclonal antibodies are already licensed to treat a range of human diseases, TGN1412 is from a new class that stimulates T cells in the immune system.

"In this case the resulting activity seen in humans was not predicted from apparently ade-

quate preclinical testing," it said. While the trial protocol and the investigators' brochure on TGN1412 noted that a "cytokine burst" or "storm" could theoretically occur within the first few hours after infusion, the patient information sheet mentioned the less alarming possibility of "cytokine release (causing a hives-like allergic reaction)."

On this issue an MHRA spokesman said: "There was no evidence of a cytokine burst shown at any dose given to non-human primates." He said that the inclusion of the warning about this in the trial documents was to remind investigators of the possibility and of the need to be prepared to treat it.

Joe Collier, professor of medicines policy at St George's University of London, said: "It seems to me that the MHRA is covering its back. It is saying that everything was OK in the trial design, when in reality it was clearly not OK."

Professor Collier said that staggering the dosing of the drug by giving it to the volunteers one at a time could have meant that fewer experienced serious adverse effects. "All of us who have been involved in clinical trials know that the unexpected can occur."

The MHRA has said that a group of leading international experts will be set up "to review the evidence from the TGN1412 case and consider what necessary changes to clinical trials may be required."

The group will consider factors that ought to be taken into account in the transition from preclinical to phase I studies as well as the design of trials of biological molecules with novel mechanisms of action, new agents with action that is highly species specific, and agents that target the immune system. The group will provide advice on how future trials should be authorised and will produce an interim report within three months.

Until this expert group has completed its work, the MHRA said that it will take a precautionary approach towards all further applications to it for clinical trials involving phase I trials of any monoclonal antibody.

Professor Kent Woods, chief executive of the MRHA, said the trial was run according to the agreed protocol

A report on the MHRA inquiry is at www.mhra.gov.uk. The Academy of Medical Sciences' report, *Testing Antibody Therapies: Position Paper*, is at www.acmedsci.ac.uk