A Phase 1 Trial Disaster
A phase 1 trial carried out in London in March left 6 men seriously ill. A cardiologist and 2 organisations give opinions on the implications. Page f110

European Meetings Update
Dates, locations, and contact details of forthcoming cardiology conferences in September and October in and around Europe. Page f112

Viewpoint: The Future of Heart Transplantation

John Wallwork, FRCS, FRCP, has stepped down as director of the transplant service at Papworth Hospital, Cambridge, United Kingdom, after 15 years. Mark Nicholls spoke to him about his career and his views on the future of heart transplantation.

Dr Wallwork, who is 60 this month, handed over the job of director of the Transplant Service at Papworth on April 1. But, he stressed, “This is not retirement. I will still be working and very much involved with the research and development of transplantation at Papworth, and continuing in routine surgical practice. I just feel that succession planning is important and that now is the right time to hand over the management side of the service to someone else.”

It was in California, as chief resident at Stanford University Medical School from 1979 to 1981, and while working with heart transplantation pioneer Norman Shumway, MD, PhD, professor of cardiovascular surgery, who died earlier this year, that Dr Wallwork first became involved in heart and lung transplantation. He came to Papworth as a consultant cardiothoracic surgeon in 1981, and played a major role in the development of cardiothoracic transplantation. He carried out Europe’s first successful heart and lung transplant at Papworth in 1984, followed in 1986 by the world’s first heart, lung, and liver transplant.

Dr Wallwork points to the tremendous developments in transplantation since those pioneering operations. “Transplantation has gone from being in the spotlight to being a routine form of surgery, and it is not restricted now by the science, but mainly by donor organs.”

Another key area that needs more work is the issue of chronic rejection. “There are new drugs and treatments for transplant patients, but we still have to crack the issue of long-term chronic rejection in heart and lung transplants,” he explained.

But patients are undoubtedly living longer, and one of the reasons behind this is the robust professional organisation of transplant services and a multidisciplinary approach to care, along with a team of people helping patients live longer and healthier. He added, “One of the cardiologists here is fond of saying that the main cause of death among transplant patients from Papworth is now old age.” The transplant programme at the hospital has become one of the longest established worldwide. Over half of its transplant patients now survive at least 10 years and lead normal lives.

Dr Wallwork said, “There are very few forms of medical surgery where the public is directly involved, and it is important to keep transplant surgery in the public eye. In the early days we created media stars, but now we have to show that transplant patients can lead normal, useful lives, and the public needs to see that.”

Problems with the supply of donor organs remain the critical restriction on the number of transplants rather than funding. This is a significant factor in Dr Wallwork’s decision to dedicate more of his time to the charity Transplants in Mind, based in Bristol, United Kingdom, which aims to raise greater awareness of the need for organ donation.

“The big problem is donor organs, and what we need to get people to understand is that out of tragedy much good can come out of organ donation.” He continued, “Nobody wants well people to die, and fewer people are dying because we have better treatment for hypertension, for example, but there are still hundreds, possibly thousands, of people who die with a healthy organ that we cannot access.”

Doctors and nurses in hospitals across Europe have an important role to play in not only helping identify potential
A Phase 1 Trial Disaster: The Implications for Research

In March, a phase 1 trial of the monoclonal antibody TGN1412 carried out near Northwick Park Hospital in London left 6 men seriously ill. Ingrid Torjesen, BSc, canvassed opinion about the implications.

An investigation was launched by the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom into the TGN1412 monoclonal antibody trial, in which 6 men suffered multiorgan failure, to ascertain whether it had been carried out properly. The final report of the MHRA, published at the end of May, identified several errors of good clinical practice, but found that the adverse incidents were caused by an unexpected pharmacological event. They were not the result of any errors made in the manufacture of TGN1412, its formulation, dilution, or administration to trial participants.

The Department of Health in England has set up a group of international experts to review the TGN1412 case and consider what changes to clinical trials may be required in light of it. This group, chaired by Gordon Duff, PhD, FRCP, FMedSci, director of the division of genomic medicine at Sheffield University, England, and chairman of the UK Commission on Human Medicines, will publish an interim report by autumn. While it may concentrate its recommendations on future trials involving monoclonal antibodies, there could be implications for the future testing of novel compounds in humans and clinical research as a whole.

Dr Watkins said it was important to learn from the incident. “It is for the MHRA and other regulators both in the UK and abroad to see how best those lessons can be learnt and promulgated.” The incident had demonstrated that phase 1 human trials were still the best way of evaluating novel interventions, he said. “Animal experiments are a necessary and essential part of the drug development process, but one does need to do these phase 1 first-in-man...
studies to actually understand unforeseen events. “The fact that this unfortunate incident was so rare in a phase 1 trial is a testament to the processes that are in place before new medicinal products are tested in man.”

The United Kingdom has fairly rigorous regulations and has implemented the EU clinical trials directive. All protocols have to go through ethics committees, and this includes volunteer information sheets and consent forms. However, Dr Watkins said there were issues relating to the risk perception of healthy volunteers and patients that needed to be addressed. He emphasised that it was important that researchers realise that researchers would never know every possible absolute risk associated with an intervention. “Knowledge accrues over time, and there is a continual gaining of knowledge of the effects and side effects of interventions,” he said.

“All researchers are very mindful that their first duty is not to cause harm; they are very conscientious that they are as rigorous as possible in the development of any new intervention. I would not say there needs to be more stringent or less stringent regulations for new compounds.”

John Martin, MD, FRCPI, FESC, professor of cardiovascular medicine at University College, London

In 2004, the World Health Organisation (WHO) set up an International Clinical Trials Registry Platform to recommend international standards for trial registration. These standards would require the following items to be registered: the scientific name of the study, the name of the treatment being tested, how it is funded, in which countries it is taking place, the key contacts, what it is investigating, and what outcomes are expected.

In July 2005, the International Committee of Medical Journal Editors instituted a policy that no papers relating to phase 3 trial results would be published in their journals unless all the items highlighted by WHO had been recorded in a publicly-accessible register from its outset and the trial assigned an identification number. Phase 1 trials are excluded from the policy, and the publication of phase 2 results is at the discretion of each journal’s editor.

In May 2006, WHO’s International Clinical Trials Registry Platform called on all research institutes and companies to register all medical studies that test treatments on humans and provide the specified items of information. Currently there are at least 50 registers of clinical trials worldwide, and WHO has identified those that meet its criteria and plans to launch a website later this year through which anyone can access this information.

Dr Martin agreed with this view. He said that although he did not know a great deal about the TGN1412 incident, he did not think much would change as a result. “I do not think that the regulations will be tightened for nonbiological novel compounds, except that compounds might be administered to one individual in the first instance,” he said.

The World Health Organisation
International Clinical Trials Registry Platform

Moves to tighten up registration of clinical trials were underway internationally before the TGN1412 incident. In 2004, the World Health Organisation (WHO) set up an International Clinical Trials Registry Platform to recommend international standards for trial registration. These standards would require the following items to be registered: the scientific name of the study, the name of the treatment being tested, how it is funded, in which countries it is taking place, the key contacts, what it is investigating, and what outcomes are expected.

In July 2005, the International Committee of Medical Journal Editors instituted a policy that no papers relating to phase 3 trial results would be published in their journals unless all the items highlighted by WHO had been recorded in a publicly-accessible register from its outset and the trial assigned an identification number. Phase 1 trials are excluded from the policy, and the publication of phase 2 results is at the discretion of each journal’s editor.

Dr Evans is assistant director general of the department dealing with evidence and information for policy at WHO. He said he believed that it was important the initiative applied to phase 1 trials and not just later ones. “In phase 1 trials, there are very important ethical issues for the protection of the healthy volunteer, who won’t see a benefit from the drug, but a possible risk from the side-effects,” he said.

At present, the number of clinical trials taking place in the world is unknown. “Many trials are not registered, and many of those that are don’t meet this recommended minimum standard for information disclosed,” Dr Evans said.

“We are starting to see more clinical trials registered, but I think we are still on the early part of the curve relative to the total number of clinical trials that are out there.”

The Clinical Trials Registry Platform and the International Committee of Medical Journal Editors initiatives were developed to resolve this information deficit, and because of specific concerns relating to trials of TGN1412, the Cox-2 inhibitor rofecoxib, and the antidepressant paroxetine.

“Using TGN1412 as an example,” he said, “if that trial had been registered with its scientific name, so people knew what the pharmacologic entity was, and knew the intent of its registration and the population that it was being studied in, then another company considering a similar phase 1 trial may be able to get this information rather than advance blindly on their own not knowing what has happened.”

Dr Evans said that although compliance with this standard was voluntary, it would be hard to justify noncompliance. “I think this will become an expectation for good practice and the de facto standard,” he said. “Register as soon as you enter phase 1 trials, and register the minimum data set so that you can be fully accountable to the public. I think that position is particularly important at this stage in terms of the public’s trust in the clinical trials process.”

Although the International Committee of Medical Journal Editors had only agreed not to publish unregistered phase 3 trials, Dr Evans expects them to go further. “They have not met since we established this standard, and they may in fact come back to that decision and extend that publication incentive to meeting or conforming with the standard suggested,” he said.
“I think that would be immensely helpful. Journal editors have the same interests in securing the public trust, as do academic organisations, biotech companies, and multilateral institutions.”

It seems that it is not a question of whether or not there will be a change to clinical trial regulations, but how that transformation will take place. The public is demanding more openness regarding clinical trials, so those conducting them may find themselves obliged to be more transparent if they are not willing to comply voluntarily.

Ingrid Torjesen is a freelance medical writer.

European Meetings Update

September and October 2006

2–6 September
World Congress of Cardiology 2006: Joint Congress of the European Society of Cardiology and the World Heart Federation
Barcelona, Spain
For more information, contact congress@escardio.org

19–21 September
UK Heart Rhythm Congress 2006
Birmingham, United Kingdom
For more information, contact aa@stars.org.uk

20 September
Annual Meeting of the Moldavian Society of Cardiology
Chisinau, Republic of Moldova
For more information, contact sc_moldova@yahoo.com

21–23 September
Xth International Congress of the Polish Cardiac Society
Gdansk, Poland
For more information, contact kongres2006@amg.gda.pl

23–26 September
45th National Congress of the Romanian Society of Cardiology
Poiana, Brasov, Romania
For more information, contact rscardio@rscardio.ro

25–27 September
5th Advanced Symposium on Congenital Heart Disease in the Adult
London, United Kingdom
For more information, contact m.gatzoulis@rbht.nhs.uk

5–7 October
Annual Meeting of the Slovak Society of Cardiology
Bratislava, Slovak Republic
For more information, contact ssc@susch.sk

6–7 October
Annual General Meeting of the Irish Cardiac Society
Killarney, Co. Kerry, Ireland
For more information, contact secretary@irishcardiacsociety.org

7–10 October
2nd Fall Brainstorming Meeting
Heraklion, Crete Greece
For more information, contact vassiliadis@hellasnet.gr

10–12 October
Annual Congress of the Society of Cardiology of the Russian Federation
Moscow, Russian Federation
For more information, contact info@cardiosite.ru

11–13 October
Autumn Meeting of the Finnish Cardiac Society
Helsinki, Finland
For more information, contact fcs@fincardio.fi

12–13 October
Arrhythmias, from neonate to adult
Groningen, Netherlands
For more information, contact info@medconeurope.com

15–18 October
The 8th International Dead Sea Symposium (IDSS)
Tel-Aviv, Israel
For more information, contact team1@congress.co.il

18–21 October
Annual Meeting of the Spanish Society of Cardiology
Malaga, Spain
For more information, contact agarcia@cardiologiacongresos.org

19–21 October
10th World Congress of Echocardiography and Cardiovascular Imaging
Rome, Italy
For more information, contact susanna.sciomer@uniroma.it
European Perspectives

Circulation. 2006;114:f109-f112
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/114/3/f109.citation