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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

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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
donors, but also in caring for them. He acknowledged that in the past there were examples where doctors had been unnecessarily obstructive in obtaining a donor organ, and some organs had been lost in this way, but that is rarely a problem now.

Funding becomes more of an issue when a donor patient needs to be kept in an expensive intensive care unit bed while the organ(s) can be harvested. “Donor management is a very important area, and good donor management ensures we get a good organ,” he said.

Another area that cardiologists and transplant surgeons are looking into is how to extend the life of a donor organ and consequently extend the geographical area in which an organ can be donated. The TransMedics Organ Care System used in May this year in Papworth Hospital is an example of this. Such developments have clear implications for improved pan-European cooperation.

At present, France has its own transplant agency, as does the United Kingdom and Spain, while there is a more coordinated cross-border system in central Europe under the EuroTransplant umbrella. The EuroTransplant International Foundation, based in Leiden, The Netherlands, is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Germany, Luxembourg, the Netherlands, and Slovenia. Within this international collaborative framework, the participants include all transplant hospitals, tissue-typing laboratories, and hospitals where organ donations take place.

Dr Wallwork said, “We do share organs across Europe — there are various different national and international agencies that can use organs and we will offer it to another country in some cases. But most of the time nobody wants the organ because it is not suitable. But there could be a time, for instance, if you have people with blood group AB, but you may not have a patient in your country of that group who needs a transplant, that we will offer it to another country.”

UK cardiologists have also been looking at Spain’s success in obtaining donor organs. “Spain has a much higher strike rate for potential donors, probably twice as high as in the UK. It has protocols for identifying donors that we do not have in this country.” As for greater sharing of donor organs across Europe, Dr Wallwork believes looking at ways to improve organ preservation and transport is the key. “I think if we can look at innovative ways of transporting hearts, then we could cover longer distances,” he said. “We have 4 hours at present, but if we can extend that to 12 hours, we could effectively go anywhere in Europe, even into Eastern Europe.” He concluded, “Achieving this is at an early stage of development, but we are about to go to clinical trials, and if successful, this would make a big difference.”

Dr Wallwork said, “But we are not just here for heart and lung transplants; we need to start looking at novel and innovative therapies for end-stage organ disease. We have to be more interested in mechanical devices for heart failure or transplantation using animal organs, and in time we need to take a broad look at using stem cell therapy to repair and regenerate damaged organs.”

Mark Nicholls is a freelance medical writer.

Reference


The opinions expressed in Circulation: European Perspectives in Cardiology are not necessarily those of the editors or of the American Heart Association.

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
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 volunteers 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 rigorous as possible in the development of any new intervention 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 World Health Organisation International Clinical Trials Registry Platform

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.

Timothy Evans, MD, assistant director general of the Department of Evidence and Information for Policy at WHO

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

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*Editor: Thomas F Lüscher, MD, FRCP, FACC.  
Managing Editor: Keith Barnard, MB, BS, MRCS, LRCP. We welcome your comments. E-mail the managing editor at kbarnard@lw.co.uk*