CASE STUDIES

CASE STUDY 2

Background

THE ADVANCE STUDY (ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MR CONTROLLED EVALUATION)

A study called ADVANCE will provide new evidence about widely practical treatment strategies for the prevention of the vascular complications of diabetes. It will determine the effects of intensive blood pressure lowering and glucose control on the risks of complications in patients with type 2 diabetes. The study has another 4 years to run.

It will recruit participants from 215 clinical centres in 20 countries in Australasia, Asia, Europe and North America. About one-third of the participants are from high-income countries; participants also come from China (>3000 participants), India, Malaysia, Philippines and a number of central European countries. The coordinating centres are based in Beijing, London, Melbourne, Montreal and Utrecht.

ADVANCE's underlying hypotheses are, first that *routine* lowering of blood pressure, regardless of initial blood pressure levels, will reduce vascular disease in high-risk patients with type 2 diabetes; and second, that more intensive glucose lowering than recommended in current guidelines will produce similar benefits in these patients.

The study will evaluate whether lowering blood pressure on top of any existing therapy will produce benefits. Approximately 75% of participants (including those from developing countries) were already taking blood pressure lowering medications at baseline, and continue to do so. Similarly, for the glucose intervention, the study addresses the balance of risks and benefits of lowering glucose levels below those currently recommended in guidelines. Local physicians are charged with determining how glucose lowering is achieved, usually dependent on the local costs and availability of drugs.

The study is a factorial, multicentre, randomised controlled trial. 11,140 participants with type 2 (non-insulin-dependent) diabetes and at high risk of vascular disease have been recruited and randomised to either:

a fixed low-dose perindopril-indapamide combination (an angiotensin converting enzyme inhibitor and a diuretic) + intensive glucose control (gliclazide-MR based, aiming for a HbA1c level of ≤6.5%)

a fixed low-dose perindopril-indapamide combination + standard glucose control (local guidelines-based targets)

placebo + intensive glucose control

placebo + standard glucose control

Follow-up will be for an average of 4.5 years. Those assigned the intensive glucose control regimen will be seen every 3 months; those assigned the standard glucose control regimen will be seen every 6 months. Study recruitment was completed in September 2002 and follow-up will continue until December 2006.

The project is complemented by the establishment of major sub-studies examining eye disease and cardiac function.

The primary outcomes will be major macrovascular complications (stroke and heart attack) and major microvascular complications (eye and renal disease).

The study is sponsored by the University of Sydney George Institute of International Health http://www.iih.usyd.edu.au/research/heart-and-vascular/heart-and-vascular_home.cfm - ongoing.

Issues to consider

The ADVANCE project addresses a non-communicable disease, and is a very large multi-centre trial involving developed and developing countries. The types of interventions studied in the project would be needed for long-term, perhaps life-long use by patients if they are deemed successful. This may provide a challenge in terms of post-trial access in settings where the drugs are not widely available.

Is there an obligation to provide post-trial access to the interventions used in the study (if the interventions are proven to be successful)? What would happen if the interventions are not proven to be successful, but that standard guidelines-based therapy was effective and not all trial participants had access to this treatment?

Who should be assured post-trial access? Should there be an agreed minimum level of post-trial access for participants throughout the study, or should this be decided on a country-by-country basis? Should post-trial access be given for all complications, or just acute complications such as stroke or heart attack?

Given the possibility of the need for long-term post-trial access to successful interventions, whose obligation is it to provide this access (sponsors, investigators, funders)? For how long? (for the follow-up period, longer?)

Are there mechanisms that could be set up during the trial that might help this process?
When is the research over? The investigators have established a follow-up period of 4.5 years. What should determine the duration of post-trial access – the life expectancy of the participants, or other factors?

What should happen in the future before any similar study gets under way? Whose responsibility is it to ensure this happens (it may not be the same agency with responsibility to provide post-trial access)?

Further information

The George Institute website offers the following background information to the ADVANCE study: "In 2000, stroke and heart attack represented the two leading causes of death worldwide, responsible for more than 10 million deaths annually. The burden of ill health caused by vascular diseases will rise sharply in the next few decades, particularly in developing countries.

By 2020, the toll in lower-income countries will outweigh that in higher-income countries by a factor of four. The requirement for major new initiatives addressing cardiovascular health in developing countries has been clearly identified as a global health priority.

The 2002 World Health Report emphasises the potential benefits of more effective vascular disease prevention strategies. The leading risk factors for stroke and heart attack are blood pressure, tobacco, cholesterol and being overweight. Each of these factors is among the top ten causes of the global disease burden and, collectively, these risk factors account for more than half the entire disease burden in developing countries.

Population interventions that seek to reduce levels of blood pressure and cholesterol and individualised interventions targeting high-risk patients have been identified as particularly promising strategies for cost-effective disease prevention.

During 2001/2002, our heart and vascular research had a major focus on the initiation of new projects in middle and lower-income countries of the Asia-Pacific region. There have been several important successes in this regard, culminating in the establishment of new collaborating research centres in China, India, Malaysia and The Philippines.

Furthermore, substantial expansion of the Heart and Vascular Division in the region is anticipated over the coming years with the planned extension of the recently completed InterASIA (International Collaborative Study of Cardiovascular Disease in Asia) risk factor survey in Thailand into an implementation phase, and the commencement of a major new initiative in the rural Godavari region of Andhra Pradesh, India.

We have also recently commenced recruitment of participants into SHARP (or, Study of Heart and Renal Protection), a large new study that will define the role of cholesterol lowering treatments in patients with chronic kidney disease. This study has evolved from a major new collaboration established with the Australia New Zealand Society of Nephrology."
The Mission Statement of the George Institute is to "help reduce the global burden of non-communicable diseases and injuries through health research, policy development and capacity building. Populations of the Asian and Western Pacific regions are a major focus of Institute activities." The Institute was established in 1999 as an independent charitable institution, the activities of which are overseen by a Board of Directors. In addition, an independent Research and Development Advisory Committee (RADAC) reviews and provides advice on the Institute's activities

.

Collaborators with the George Institute include: University of Sydney, Johns Hopkins School of Public Health, Central Sydney Area Health Service, Peking University Health Science Centre, University of Melbourne; Curtin University; the National Heart Foundation of Australia; the University of Auckland; the University of Otago; the University of Oxford; Tulane University Medical Centre; Mahidol University; the Byrraju Foundation (India).

Acknowledgments:

Bella Starling, Senior Project Manager, Biomedical Ethics, The Wellcome Trust

Anushka Patel, Deputy Director, Heart & Vascular Division, The George Institute for International Health