BODY POLITIC **Nigel Hawkes**

How do we get the measure of patient care?

The UK government's latest plan is to try asking the patients rather than the doctors

Death is an end point we can all understand. When reading the latest clinical trial, I always find my eyes drawn to the column that shows mortality. This may be a little morbid, but no other measure has the crisp finality of death.

As a means of assessing the quality of care, however, it has many drawbacks. True, the heart surgeons have submitted to an audit of the number of their patients who die, enabling the public to weigh up the odds before going under the knife. But in most circumstances, mortality—even a run of bad results—tells us little about the quality of care.

In recent months both Papworth Hospital near Cambridge and Glasgow Royal Infirmary stopped their heart transplant programme after a number of deaths—seven out of 20 at Papworth, and four out of 11 at Glasgow. Both resumed after close scrutiny found no common factors behind the deaths.

I would be the last to criticise hospitals for taking precautionary action. It's a lot better than dealing with the fallout if a journalist hears of the deaths and starts to cry cover-up. In public relations terms, what Papworth and Glasgow did was exemplary. But it wasn't rational; even the average punter at next month's Cheltenham Festival could have understood the odds better than that.

Few operations are common enough for mortality statistics to be meaningful. An analysis published in 2004 (*JAMA* 2004;292:847-51) concluded that only for coronary artery bypasses was there a sufficient caseload in any US hospital for a doubling of the mortality rate to be detectable. For other operations, such as hip replacements, repair of abdominal aortic aneurysms, or paediatric heart surgery, the volume of operations or the chances of death was simply too small.

Even if you increased the sample

size by adding five years' results together, heart bypasses were still the only operation for which more than half of US hospitals had a sufficient caseload for statistics to be useful. The study did not include heart transplants, but the sample is obviously far too small for the deaths reported by Papworth or Glasgow to mean anything at all.

If we cannot judge our surgeons by the number of patients who die, how can we judge them? Some clinicians argue that "outcome measures," now so popular among makers of health policy, are a pipe dream. Professor Richard Lilford from the University of Birmingham, for example, argued in the *BMJ* that it is impossible to adjust the data so as to take into account all the possible variables that determine how well a patient does (*BMJ* 2007;335:648-50).

If outcomes are a poor measure even at a hospital level, they are even worse at the level of the individual clinician. Professor Lilford's answer is not to measure outcomes at all, but to measure process. If a hospital or a doctor follows proved tenets of clinical care, and can show it, then outcomes will be better. Rather than trying to measure outcomes, we should measure the adherence to processes known to produce better outcomes.

Turning the issue around, how about asking the patients rather than the doctors? This is the plan hatched by the Department of Health and slipped out before Christmas with such a total absence of publicity that only the alert Nick Timmins of the *Financial Times* even spotted it.

A diligent search among the many documents outlining the 2008-9 operating framework will tell you that in April the NHS plans to introduce the routine collection of Patient Reported Outcome Measures (PROMs). To start with, these will cover hip and knee replacements, hernias, and varicose veins. The national introduction

“The danger is that PROMs [patient reported outcome measures] will add to the noise without contributing much to the signal”

follows a pilot programme run by Professor Nick Black of the London School of Hygiene and Tropical Medicine with 2400 patients in 24 sites.

The system involves asking patients a series of questions on the day of admission, using forms they fill in themselves, and following up with a second form three months later for hernias and varicose veins and six months later for hips. The forms are called EQ-5D; they have been proved to be an accurate way of assessing if patients feel any better, and the administrative cost works out at about £5 per patient.

The NHS already gathers reams of information, not all of it of obvious relevance. Yet it still has some odd gaps. It has always puzzled me, for example, that having pioneered hip implants the NHS did nothing to monitor how well they worked. This has now been put right and the National Joint Registry is beginning to produce useful results—better late than never.

PROMs are probably a good idea. But if the data are to be valid, at least 80% of patients will have to fill in the forms before they are treated, and 80% of those will have to complete the final forms. The guidance that was issued in December admits that some patients may be incapable of filling in their PROMs, and that it will be up to clerking staff to spot them.

And what about the follow-up forms? Statistics show high non-attendance rates for follow-up appointments (19% for men aged 15 to 44), so the 80% target looks pretty ambitious. Real patients—except those who feel terrible—may simply treat the follow-up forms as another bit of junk mail. The danger is that PROMs will add to the noise without contributing much to the signal.

Nigel Hawkes is health editor, the Times nigel.hawkes@thetimes.co.uk

OPEN LETTER

European regulatory agencies should employ full time statisticians

We would like to draw attention to what we believe is a major deficiency in European regulatory agencies that are responsible for reviewing applications to market new medicines across the whole of the European Union. Only agencies in the UK, Germany, Sweden, and Austria employ several full time statisticians, and a few others employ a single statistician. Some agencies that have a major role in the European regulatory process, such as those of Italy and Spain, do not employ any full time statisticians—instead they rely on external consultants.

Statistics is central to the design of clinical trials and to the interpretation of their results. Key regulatory guidelines such as ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) E3, E9, and E10 carry this clear message, as do numerous disease specific, clinical guidelines from CHMP (Committee for Medicinal Products for Human Use). The clinical trial component of regulatory submissions can be made up of the accumulated data from several thousand patients enrolled in several clinical trials. Evaluation of the data requires consideration of the impact of complex statistical issues relating to design of the trial and analysis of the data, such as bias in trial design, use of multiple end points, missing data, interim

Statistical review should be conducted by those who are professionally expert in the area, not by medical assessors with some knowledge of statistics

analysis, subgroup analyses, analytical technique, and selection of statistical model.

Decisions to approve or deny potentially important new medicines will be based on the assessment of these dossiers. Unless the design and statistical analysis of a trial are appropriate, results cannot be considered reliable and no confidence can be placed in the subsequent clinical interpretation. These issues have been recognised by major medical journals, which routinely provide a statistical review of submitted papers.

Another important role of regulatory agencies is to provide scientific advice on proposed clinical development programmes and general guidance on statistical issues. Companies seeking regulatory advice want to be confident that the advice they receive is based on considerable experience of regulatory work and knowledge of acceptable methodology. Without permanent statisticians, agencies are at risk of giving incomplete advice. In particular, innovation may be stifled if novel methods that are presented are methodologically sound but are disregarded because they are poorly understood by regulatory advisers.

Statistical review should be conducted by those who are professionally expert in the area, not by medical assessors with some knowledge of statistics. Part time academic consultants, regardless of their level of expertise and experience, are unlikely to be able to devote the time required to carry out a thorough assessment of a regulatory dossier and of the individual clinical trials contained in it. Work of this nature must be carried out in an organised and timely fashion by experts interacting regularly and in detail with experts from other disciplines. Knowledge and experience must be carried over from assessment to assessment. When necessary, assessors must be able to devote sufficient time to an assessment to allow them to explore issues concerning statistical methods and data in real depth.

We believe the current situation is unacceptable. These same concerns were raised in the 1990s by a working party from the Royal Statistical Society (*J Royal Stat Soc (A)* 1991;154:413-9) and were subsequently addressed by the UK regulatory agency. All agencies who undertake review of applications should employ full time statisticians to enable competent licensing and labelling decisions. We call on the heads of the regulatory agencies in the EU that do not have full time statisticians in their organisations to rectify this as a matter of urgency.

Sara Hughes, chair of PSI (professional UK body of statisticians in the pharmaceutical industry) and director of statistics, GlaxoSmithKline chair@psiweb.org

This letter is also signed by:

Oliver Keene, PSI regulatory subcommittee chair and director of statistics, GlaxoSmithKline, UK;
 Nigel Howitt, EFSPi president (European Federation of Statisticians in the Pharmaceutical Industry) and director of analysis and reporting, PRA International;
 Kit Roes, EFSPi vice president and vice president, Global Clinical Information, Organon Schering-Plough;
 Deborah Ashby, professor of medical statistics, Queen Mary, University of London, UK;
 Mohan Beltangady, vice president and global head statistics, Pfizer;
 Professor Sheila M Bird, vice president, Royal Statistical Society and Medical Research Council's Biostatistics Unit, Cambridge, UK;
 Catherine Burton, global head and vice president clinical information sciences, Novartis;
 Marc Buyse, executive director, International Drug Development Institute, and associate professor of biostatistics, Hasselt University, Belgium;
 Simon Day, statistical expert, Roche Products Ltd, UK;
 Peter van Ewijk, senior director Biometrics Europe, Genzyme;
 Chrissie Fletcher, director and head of international biostatistics, Amgen;
 Andrew P Grieve, professor of medical statistics, King's College London, UK;
 Christiane Guinot, president of the French Society of Statistics and for the Biopharmacy and Health Group, France;
 David J Hand, president of the Royal Statistical Society and professor of statistics, Imperial College London;
 Rob Hemmings, statistics unit manager, MHRA, UK;
 Professor D Holt, immediate past president of the Royal Statistical Society, UK;
 Ludwig Hothorn, president German region of International Biostatistical Society and professor of biostatistics, Leibniz University Hannover, Germany;
 Peter Jagers, outgoing president of Bernoulli Society and professor of mathematical statistics, Chalmers University of Technology and Gothenberg University, Sweden;
 Niels Keiding, outgoing president of International Statistical Institute and professor of biostatistics, University of Copenhagen, Denmark;
 Pasi Korhonen, SSL chair (Statisticians in the Finnish Pharmaceutical Industry) and chief executive officer of StatFinn Oy, Finland;
 Emmanuel Lesaffre, president of International Society of Clinical Biostatistics and professor of biostatistics, Leuven University, Belgium;
 John A Lewis, visiting professor of statistics, University of Newcastle upon Tyne, UK;
 Geert Molenberghs, professor of biostatistics, Hasselt University, Belgium;
 Norbert Neumann, president of BBS (Basel Biometric Section of International Biometric Society) and head of biostatistics, Basel Roche;
 Klaus Juel Olsen, president of Danish Society for Biopharmaceutical Statistics, Denmark;
 Gonnie van Osta, EFSPi Council and chair of working group, Pharmaceutical Statistics and Data Management, Netherlands;
 Stuart Pocock, professor of medical statistics, London School of Hygiene and Tropical Medicine, UK;
 Frank Rockhold, senior vice president drug development sciences, GlaxoSmithKline;
 Andrea Rossi, secretary of the co-ordination committees of BIAS (Biometristi dell'Industria Farmaceutica) and head of statistics and medical Writing, Eli Lilly Italy;
 Stephen Senn, professor of statistics, University of Glasgow, UK;
 Theo Stijnen, professor of medical statistics, University of Leiden, Netherlands;
 Michael Væth, professor of biostatistics, University of Aarhus, Denmark;
 Stig Johan Wiklund, president of the Swedish Society for Medical Statistics, Sweden;
 Josephine Wolfram, associate director of biostatistics, Astellas Pharma Europe
 Responses to this letter are invited via the *BMJ* or via email to chair@psiweb.org