DRUG TREATMENT: MAXIMISING BENEFIT AND MINIMISING RISK*

B Ofori, Health Services Research Training Fellow, Medicines Monitoring Unit, Department of Clinical Pharmacology, Ninewells Hospital, Dundee

Drug treatment is central to the delivery of healthcare and practice of medicine. Nonetheless, the use of medicines carries with it certain dangers, and a need exists for the dissemination of more information about the intended and unintended effects of medicine in clinical practice. The ever-increasing usage of newer medicinal drugs of greater complexity and sophistication requires urgently a better understanding of the public health implications and consequences of drug treatment, to obtain maximum benefits from drug use whilst minimising the risks. The aim of the symposium was to review the tools required to assess benefits and risks of drug treatment, and to manage such risks in the real world.

SESSION 1

HOW TO DEVELOP THE ASSESSMENT TOOLS

Chaired by Professor TM MacDonald, President of ISPE

Assessing risk – when can epidemiology help, given the limitations of trials and spontaneous reports?

Professor S Evans, London School of Hygiene and Tropical Medicine

Randomised controlled trials (RCTs) provide important information on the benefits and risks of drug treatment at the time of licensing. The interpretation of such data carries important limitations. The trials are generally too small to find important risks and frequently the benefits reported are based on the mean effects of surrogate markers studied in large numbers of people. Different approaches are taken in the way benefits and risks are assessed. Subgroups vulnerable to the adverse effects of drugs are frequently excluded because such trials are primarily designed to demonstrate efficacy rather than safety.

Some of these problems could be addressed by improving the quality and quantity of epidemiological information promulgated about pre-licensing trials. Better information is required about the participants of the trial; the number randomised; duration of treatment; length of study follow-up; completeness of follow-up; and the type of participants included. Ideally such data should be displayed as Kaplan–Meier plots of all those at risk from the beginning of the trial, with the failure event being either cessation of treatment or follow-up; ideally they should be displayed as two separate plots stratified by age and gender. Such an approach would clarify the limitations of knowledge with respect to certain aspects of the trial, such as making evident the lack of women, children or the very old in the study.

Caution is equally required with other study designs used to collect information on adverse events. Spontaneous reports of adverse events are often masqueraded as epidemiological studies, which clearly they are not, and, worse still, are often used to calculate relative risks of events using the number of prescriptions issued for the drug as the denominator value. Spontaneous reporting is, however, of great value as an early warning system for potential problems by signalling such a possibility and raising the suspicion of an adverse drug reaction (ADR). In this context, it is important to appreciate that what such information captures is often data about 'events' related to the use of that drug, and not ADRs. The distinction is that an adverse event is any event associated with the use of the drug, whether or not it is considered product-related. Spontaneous reports generated very soon after drug exposure are strongly suggestive of adverse events but not of ADRs. A well-recognised tendency is to over-report in the short term and under-report in the long term. This reporting characteristic is evident with vaccine-related events, which are strongly suggestive of non-causal drug events.

Spontaneous reporting should therefore never be used to estimate the true risk of a drug's use. Its purpose is to generate signals in order to detect *new* ADRs. The time and effort required to collect such data is wholly misplaced if it is used solely to create huge databases of identical multiple reports. Furthermore, trying to assess causality on the basis of single case reports generated from spontaneous reporting can have enormous resource implications and may be of limited benefit. Such studies should not be a hard-and-fast requirement of drug licensing bodies.

To derive additional value from RCTs and spontaneous reporting, epidemiological thinking has to be applied to these techniques, particularly in relation to studying, interpreting and placing into a proper context these

*This symposium was jointly sponsored by the Royal College of Physicians of Edinburgh (RCPE), the International Society for Pharmacoepidemiology (ISPE), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 14 April 2003.

adverse outcomes. The limitations of epidemiological research must also be recognised, the well-publicised hormone replacement therapy (HRT) and coronary heart disease (CHD) issue being a case in point.[1–3] A major contributor to this failing was the lack of adequate data about socioeconomic status and lifestyle. To be trustworthy, observational studies need to address several key issues regarding the disease area being investigated; are the risk factors for the disease known? Have they been taken into account? Do they explain the variation in the data? In the matter of HRT, the risk factor of socioeconomic status, which was well-known to be associated with CHD, was not always measured or reported in the observational studies; it was always plausible that the observed association between taking HRT and reduced risk of cardiovascular disease was confounded by socioeconomic status and lifestyle because women who take HRT were likely to be more affluent and health-conscious than women who did not take HRT.

Users of medicines generally tend to be more health-conscious, and this potential confounding factor makes it more difficult to assess beneficial effects than harmful effects of medicines in observational studies. This issue can be addressed through the use of matched cohorts with propensity scores, and the routine use of such tools in epidemiological research avoids errors similar to the HRT and cardiovascular disease association.

Finally, Professor Evans addressed the issue of when researchers should report 'absolute risk' rather than 'relative risk'. The reporting of relative risk from observational studies should continue as it was informative about causality, but absolute risk should also be estimated because this is a key public health measure, which will ultimately inform clinical decision-making.

RISK MANAGEMENT – HOW CAN MULTIPURPOSE DATABASES HELP?

Dr J LeLorier, Faculty of Medicine, University of Montreal

Risk management refers to the prescribing of therapeutic agents, in conditions of general use, that seeks to ensure that the benefits to the patient outweigh the risks. Whilst this endeavour should be applied to all drugs, it must be specifically focused on drugs used in identifiable subpopulations where both clear and tangible benefits are to be gained at the potential cost of well-defined risks. Unfortunately, this information on subpopulation risk is not always available. At the launch of a drug for medicinal use, animal toxicological data might be available, as well as limited information from phase II and III trials that might be indicative of harm, as with QT interval prolongation or liver enzyme elevation.

Many potential biases and confounders should be considered in epidemiological studies, particularly when assessing the benefits of treatment, compared with when assessing the unintended effects. For this reason, databases have a limited value in observational studies as a means to investigate benefits. However, they help to identify subgroups of people who have the potential to benefit, particularly if there are significant differences in the biases that are in operation between the main group and the subgroup.

Benefits are often much easier to communicate but the communication of risk involves complex discrete processes that require considerable interpretation of such measures as probabilities.

Several steps have to be taken in the communication process between doctor and patient, and each of these steps is fraught with the peril of miscommunication. The steps are:

1. What the physician thinks;
2. What the physician tries so say;
3. What he/she thinks he/she has said;
4. What is actually said;
5. What the patient wants to hear;
6. What the patient actually hears;
7. What the patient wants to understand;
8. What the patient thinks they understand;
9. What the patient actually understands.

Unfortunately, at the end of this process each party is still liable to believe that which in the first instance they wanted to believe. Even successfully understanding the risks does not necessarily translate into action. Patient behaviour and physician behaviour should be studied further in this risk management setting.

Well-designed risk management strategies, even for the most harmful drugs, will allow some patients to derive benefit, particularly where it would be too dangerous to expose the whole population. The key issue of any programme is to be able to evaluate the results and large automated databases are extremely helpful as long as the database is effective in capturing the utilisation of the drug.

USING ROUTINE AND LINKED DATA TO ENHANCE THE VALUE OF CLINICAL TRIALS

Professor I Ford, Robertson Centre for Biostatistics, University of Glasgow

Record linkage is the technique of bringing together routinely collected information about individual respondents obtained from discrete sources to form combined individual micro-records for purposes of research and statistical analysis. The principles of using different records to monitor phenomena associated with the normal use of drugs were proposed in 1964 by DJ Finney; only now has the true potential for this technique been realised, largely due to utilisation of information technology.

Data routinely collected in the NHS, such as that from hospital discharge summaries, deaths, cancer registries, neonatal records and psychiatric hospitalisations, can be used to enhance the design, conduct and interpretation of the results of RCTs.

These data have been used extensively over the last 15 years in work conducted on the West of Scotland Coronary Prevention Study (WOSCOPS) and more recently for work being conducted on cluster randomised trials in Scotland. There is significant value to be added to the traditional type of follow-up from RCTs by using such data, but they may also be used to enhance economic evaluations and studies of long-term safety long after the studies themselves have been completed.

The WOSCOPS trial[4] was a randomised double-blind placebo-controlled trial of pravastatin taken at a dose of 40 mg daily in middle-aged men with no history of myocardial infarction (MI). The results of this trial are well-known: a clear reduction in the primary endpoints of CHD, non-fatal MI and cardiovascular mortality. The trial used standard methods for ascertainment of adverse events through patient attendance at trial clinics and patient recall of events. To answer the question of whether record linkage could add value, or even substitute for this traditional style of follow-up in long-term clinical trials, an alternative data collection technique was used alongside the main study. Searches were run on the Scottish Morbidity Record to identify those patients in the trial who had suffered serious adverse events (i.e. hospitalisation or death). A direct comparison could then be made between the traditional trial-based approach for follow-up and the computerised record-linkage approach. Probabilistic matching techniques were used to match the two records, which were then compared.[5] A small number of events (66) were detected in the conventional follow-up that were not identified in the record-linkage system. One explanation was that whilst deaths, including those occurring outside Scotland, were picked up by the record linkage system, non-fatal events were not. Similarly, events occurring within the private healthcare system would not be picked up by record linkage. Several events (137) were picked up by the record linkage system but were either missed or mis-classified by traditional follow-up. The record-linkage system was also able to detect a number of events that occurred in patients after the formal trial follow-up had ceased.

These results demonstrate the added value of using record linkage in study follow-up. Despite the slight discrepancies between the two systems, the conclusions of this study would not have been different had either system been used exclusively. One of the main merits of the record-linkage system, however, was that it allowed long-term post-trial follow-up. The WOS2000 study showed a 15% relative risk reduction in all-cause mortality at ten years after randomisation in patients who were in the pravastatin group, even though only about one-third of them continued to receive pravastatin at the end of the trial (five years after randomisation) and about one-third of the placebo group were started on statins after the trial ended.

The potential for using record linkage to determine life-years gained by drug treatment was illustrated by an economic evaluation based on the WOSCOPS trial.[6] The life expectancy of patients who had experienced a first non-fatal cardiovascular event was established through prospective follow-up of their clinical events using these automated databases to create age/sex-specific survival curves. The life-years gained by avoiding a first non-fatal cardiovascular event could then be estimated.

In conclusion, the use of record linkage in trial design can give improved follow-up of serious adverse events. It makes an important contribution to economic evaluation, can be resourced cheaply for long-term post-trial follow-up, can provide epidemiological follow-up for unique cohorts screened in clinical trials, and permits the evaluation of the properties of non-standard designs such as cluster RCTs. It is technically possible to design RCTs that rely entirely on record linkage for follow-up of events. However, there are important issues about obtaining consent for record-linkage-based follow-up, and particularly follow-up of patients who have formally dropped out of a trial. Another important issue is the imminent European Trial Directive and its potential impact on restricting record-linkage-based research. It would be a tragedy if the greatest threat to risk management and patient safety turned out to be litigation that limits our ability to perform pharmaco-epidemiological research.

SESSION TWO

THE SIR STANLEY DAVIDSON LECTURE

Chaired by Dr NDC Finlayson OBE, President, Royal College of Physicians of Edinburgh

Rigorous modelling of risk, clinical benefit and cost

Professor MC Weinstein, Henry J Kaiser Professor of Health Policy and Management, Harvard School of Public Health, Boston

Models are analytic methods with specific purposes, intended to assist decision-makers in health and medicine, both at the clinical and public health level.

The purpose of models is to inform clinical and resource allocation decisions. Models are no substitute for judgement but bring together evidence in a structured and logical way that incorporates probabilities as well as values, based on the relative preferences for benefits versus harms. Models cannot determine in any absolute

scientific sense whether a treatment is beneficial, whether benefits outweigh harms or whether the benefits are worth the costs of providing that treatment. Models are not static. The 'truth' may change between the time the model is developed and the decision has to be made, and consequently they need to be constantly revised and updated.

Three examples can be drawn upon to illustrate the use of models in clinical policy decisions. In the treatment of hepatitis C, models may be used to help answer questions that are pressing for physicians and health service agencies such as the NHS; should monotherapy or combination therapy with interferon alpha be made widely available? Should pegylated interferon or standard interferon be used?

In HIV there may be questions over antiretroviral therapy: when to start it, when to use prophylaxis, or whether to perform genotypic resistance testing in advance of therapy, to estimate the likely effectiveness of that therapy.

Cervical cancer screening is a non-drug example where modelling can help resolve issues of uncertainty, for example, what to do with the equivocal cervical smear results, the 'atypical squamous cells of uncertain significance' (ASCUS). Should the smear be repeated at six-monthly intervals, or should colposcopy and biopsy be performed? Should samples be tested for human papilloma virus DNA? Should liquid-based or conventional technology be used for the cervical smear reporting?

Clinical trial evidence on many of these questions is limited. The trials themselves may have limitations that restrict their usefulness. They may be too short, rely on surrogate markers and fail to evaluate all the options of interest. It is often desirable in decision-making to consider multiple data sources, but where study designs are diverse, it is frequently not possible to use meta-analytical techniques to resolve the issues of uncertainty. Furthermore, the measurement of multiple end-points (benefits, risks, costs) is desirable, something that is very difficult to do within the context of a single study.

Nevertheless, clinical trials are necessary to answer questions about treatment efficacy. The question of whether benefits are greater than harms, however, goes beyond the scope of the clinical trial, not least because people in the 'real world' may have different values that they attach to benefits and harms. Also of increasing importance are the questions of value for money and whether the chosen treatment is cost-effective. In this situation, modelling is almost inevitably required, particularly where comparative analyses of different treatments need to be performed.

In hepatitis C viral infection, clinical trial evidence supports the effectiveness of drugs such as interferon alpha or the antiretroviral drugs in preventing progression to more severe liver disease; however the trials are often too short to observe the mortality and morbidity effects associated with disease progression to the endpoints that people care about. In addition, they do not provide quantitative evidence on side-effects and costs to enable risk-benefit or cost-effectiveness evaluation.

Five treatment strategies for chronic hepatitis C were compared using a cohort-type model: no treatment, interferon alpha monotherapy, combined therapy with interferon alpha and ribavirin, peg-interferon alpha monotherapy, and peg-interferon alpha and ribavirin combination therapy. The principal considerations were the effect of each treatment option on the progression of the disease, the effect on mortality and serious liver disease, the side-effects of treatment and the effects on quality of life and costs. Through empirical calibration of the model, the study, as reported by Salomon *et al*.,[7] provided insights into those uncertain aspects of the natural history of hepatitis C and improved the knowledge base for projecting the future course of the epidemic. Ranges of parameter values, such as the probabilities of progression from early to late disease, were obtained through a systematic review of the literature. Model predictions were compared to available epidemiological data on infection prevalence and liver cancer mortality. Various goodness-of-fit criteria were used to identify the range of parameter values that were consistent with these data. To produce a cost-effectiveness analysis, this calibrated natural history model was combined with data from clinical trials on the efficacy of treatment to estimate gains in quality adjusted life expectancy and treatment costs. Modelled estimates of projected mortality over a 20-year period could then support informed decision-making. If the mortality impact due to the disease was likely to be great, the use of the more expensive but effective treatments would most likely be more cost-effective.

Modelling techniques were also used to assist decision-making over the issue of whether highly active antiretroviral therapy (HAART) was cost-effective and whether patients should get resistance testing before initiating or changing therapy. This cost-effectiveness of preventing AIDS complications (CEPAC) model was based on a Monte Carlo simulation in which each patient was drawn randomly from an initial distribution of characteristics including age, gender, CD4 count and HIV-RNA counts. In this model, every month the individual could change health state or develop various clinical events, and they could move in and out of various clinical states such as opportunistic infection. The data for this model came from a variety of sources including

clinical trials and meta-analyses. The advantage of modelling over the use of purely clinical trial data was its ability to handle the discordance between variables and clinical outcomes often seen in trials, e.g. between natural history, treatment, immunologic response or viral response and clinical response. The model could explore the different interpretations of any such inconsistent data and test the implications of such discordance using sensitivity analysis and uncertainty analysis, or simulate different kinds of intervention such as antiretroviral prophylaxsis or the consequences of altered adherance or adverse effects. Such an experiment was used to determine the cost-effectiveness of resistance testing after treatment failure and in treatment-naïve patients. The results, as reported by Weinstein *et al*.,[8] showed very reasonable cost-effectiveness ratios.

The third example of the application of modelling was an illustration of guiding clinical decisions on cervical cancer screening, how to screen, how often to screen and how to manage the equivocal findings in cervical smears. The model[9] addressed three different options, immediate colposcopy, two repeat smears at six-month intervals or HPV-DNA testing. This model included the various stages of cervical lesion and progression all the way to invasive cancer. With respect to the management of ASCUS, the model predicted that by screening every year there was little difference in the percentage reduction of cancer incidences between the three different management strategies. The less often one screened, however, the more value there was in using the more aggressive strategy such as immediate colposcopy. A significant finding was that even at five-yearly screening HPV testing did almost as well as colposcopy. The cost-effectiveness analysis showed that the strategy of doing repeat cervical smears was more expensive than the strategy of doing HPV testing but the incremental benefit of doing colposcopy rather than HPV testing for follow-up of ASCUS findings was very small. These results were largely responsible for a new policy regarding the availability of HPV testing for all women with ASCUS.

Standardised methods are required to validate and evaluate models. Three criteria were suggested:

1. Validation (predictive validity) – can the model predict what will actually happen?
2. Verification (face validity) – does the model, at the time it is built, produce results that make sense?
3. Corroboration (convergent validity) – do different investigators produce the same results?

There is the potential for models to help people make better decisions, and models can almost certainly help clinicians feel more confident about the decisions they make.

SESSION 3

ASSESSING AND MANAGING RISK IN THE REAL WORLD

Chaired by Dr K Beard, Consultant Physician, Glasgow

Assessing and managing risks of drugs in the final patient population using field and automated health information

Dr S Perez Gutthann, Head Global Epidemiology, Pharmacia, Barcelona

In 1999 a report to the US Food and Drug Administration (FDA) commissioner outlined the risk management framework:[10]

1. Risk assessment/measurement: estimation and valuation of risk.
2. Risk confrontation: determining acceptable levels of risk.
3. Risk intervention: risk-centred action.
4. Risk communication: interactive exchange of risk information.
5. Risk management evaluation: evaluating effectiveness of activities.

This report resulted in the legislative document 'Prescription Drug User Fee Amendments of 2002' (PDUFA 3) in which specific recommendations were made on the way drugs are developed, including specific inclusion of information in submission documents on the limitations of planned clinical trials, disease epidemiology and risk management tools, such as labelling, medication guides and restricted distribution. Further to this, at the beginning of March 2003, the FDA published three concept guidance papers on pre-marketing risk assessment, risk management programmes and risk assessment of observational data.[11] Similar initiatives have also been taking place in the European Union, with the publication in January 2003 of a summary document by the *ad hoc* working group on risk management with a specific chapter dedicated to pharmacovigilance management plans.

Pharmacoepidemiology is the study of patterns of disease and treatment outcomes in human populations, and the factors that modify risk and benefit. Epidemiology has had its most dramatic impact in the improvement of public health conditions classic examples being cholera, lung cancer and more recently the AIDS epidemic. However, a close relationship also exists between epidemiology and therapeutic research and development, where epidemiological activities have helped to document early safety issues with drugs as well as to direct research and development activities to address unmet medical needs. If epidemiology is the science of public health research and evaluation, then it must also become the underlying science for risk ascertainment and risk management evaluation. Therapeutic safety risk management is a multidisciplinary activity requiring the integration of

different fields including pharmacovigilance, regulatory, legal, communication, market research, basic sciences, clinical research and project management. It relies heavily on epidemiologically-based research taken from the public health perspective.

For the industry, risk management spans the lifetime of the drug. For the regulatory bodies, there is the responsibility to manage risks during the licensing stages and to make predictive assessments on how drugs will be used after approval. In addition, compliance activities are essential, such as those carried out by the Centre for Drug Evaluation and Research (CDER), which focus on addressing the greatest public health risks and develop communication strategies aimed at better informing the public towards a goal of safer drug use.

Risk assessment procedures involving COX-2 inhibitors were based on an epidemiological portfolio compiled to document the important safety end-points in the target consumer population, primarily gastrointestinal toxicity and cardio-renal safety. Another important area of focus was to accumulate knowledge on how the drugs were being prescribed and how patients were using them.[12, 13] The risk assessment of timolol was used to illustrate the use of modelling and simulation of the impact of this drug on patients with varying prevalences of respiratory conditions. Other risk management strategies were described, such as restricted distribution of clozapine and population safety studies and label change for HRT.

In conclusion, the risk management process is not something that can be tackled only post-approval or exclusively by the industry or academics. It must involve an integrated and collaborative effort to be initiated as early as possible in the life cycle of a drug and should include the process of signal detection, benefit–risk assessment and risk management plans.

Cost of ADR-related hospital admission

Professor A Avery, Department of General Practice, University of Nottingham

There is considerable inconsistency in the literature over how outcomes are reported, particularly in the distinction between ADRs versus adverse drug events. Outcome events are frequently based on the judgement of individuals who come to a decision over whether a hospital admission is related to a drug or not; in many situations the drug is not the sole factor responsible for the admission but may be one of several contributory factors. The extent to which these drug-related admissions are preventable is an equally important consideration. Whilst it is acknowledged that certain adverse events are inevitable, such as those associated with cancer chemotherapy, the study of the preventability of other such reactions is key to determining the solution to such problems.

Several systematic reviews have been published on the subject. Lazarou *et al*. 1998[14] examined 39 prospective studies from the US, published between 1966 and 1996. They reported an incidence of ADR admissions of 4·7% and a fatality incidence of 0·13%. The estimated number of fatalities per year from ADRs in the US was 43,000, rising to 100,000 if in-patient events were also included, making it the fourth leading cause of death in the US. Similar figures have also been published for the UK. Drug classes most commonly implicated included antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemics and non-steroidal anti-inflammatory drugs. The mean bed-days associated with ADRs ranged from 6–14 days suggesting that patients admitted for ADRs tended to spend longer in hospital than controls admitted for other reasons.

Important gaps in our knowledge exist concerning the benefits that were derived from using the drugs that resulted in the ADR and a scarcity of information on the true costs of the problem, including litigation costs. Studies that have costed ADRs have varied considerably in their estimates. This is in part due to the underlying assumptions made about the incidence of ADRs: whether reactions or events are measured; and whether the measurements are based on emergency department attendance alone or hospitalisations requiring in-patient care. Many published studies focus on means of reducing these costs, such as secondary-care-base 'gate keeping' and 'policing' strategies involving pharmacists, nurses or other methods such as computerised prescribing. Very few, however, have addressed interventions in primary care, or the study of prescribing patterns and monitoring strategies to prevent drug-related admissions.

In summary, ADR-related hospital admissions have important costs, both financially and in terms of patient morbidity. Whilst it may be difficult to give accurate estimates of cost, ADR admissions are probably associated with over 4% of healthcare costs. The majority of these are avoidable. Pharmacist interventions and educational outreach programmes are two strategies that may reduce drug-related admissions and the associated costs.

Ensuring quality and minimising drug-related risk in the NHS in Scotland

Dr M Armstrong, Chief Medical Officer for Scotland

The most important issue in managing the problem of drug-related risk in the 'real world' is communicating risk and benefit, both to the individual patient and to the public and politicians. Medicine is practised in a societal context. The advent of consumerism, the information revolution and advances in internet technology pose challenges to the way we practise and work. Patient safety has become a high-profile issue. The Wanless report was produced to provide guidance to the UK

Treasury on costing healthcare in 2020.[15]

The report estimated that there are around 850,000 adverse events in the NHS per year, half of which are avoidable, and costing £2 billion in additional bed-days. Litigation costs for clinical negligence amount to a further £400 million a year in England. Legislation can have an effect in reducing risk. The introduction of childproof containers 20 years ago and, more recently, the reduction in pack sizes of paracetamol and iron tablets have reduced the risks from accidental self-poisoning in children. There is an on-going effort to improve awareness of the dangers surrounding medicines and driving and the control, regulation and standardisation of herbal remedies.

An area of increasing importance in the study of drug error is in the administration of intravenous drugs where a recent investigation by Taxis *et al.*[16] showed that there were drug errors in almost half of 430 episodes of intravenous drug administration including three potentially fatal errors; 73% of the errors were associated with the administration of bolus injections that were given too quickly.

The public expects healthcare systems to be safe and they expect the risks to be properly managed. Making things better means changing the NHS culture to allow us to learn from errors, and making risk management an integral part of clinical governance. The outcomes achieved, whether good or bad, are a product of the system that produced them. Poor systems of care will inevitably produce certain levels of harm. Currently, those levels are not acceptable. Two recently published documents, 'Organisation with a memory' (England)[17] and 'Learning from Experience' (Scotland)[18] have paved the way for setting new standards in patient safety.

To reduce risk and maximise benefit to patients in the NHS, risk-assessment systems and tools need to be in place within a no-blame practice that analyses all incidents, ensures that lessons are learnt and disseminated back to staff, and that practice actually changes.

SESSION 4

Chaired by Professor PG Davey, President of ISPOR

DEBATE: POST-MARKETING ECONOMIC EVALUATION OF MEDICINES IS A BARRIER TO GOOD PATIENT CARE

For: Mr K Tolley, Health Economist, Ortho Biotech

Given fixed and limited budgets, economic evaluations help to maximise beneficial outcomes in a population, through the use of analytical techniques such as cost-effectiveness and cost-benefit analysis. Economic evaluations, contrary to some opinions, do not result in rationing, and in the past have not had a significant impact on prescribing or decision-making at the doctor-patient interface, with criteria such as patient age or locality playing a larger role. However, bodies such as the National Institute for Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC) have fostered a clearer role for economic evaluations today. These pose a 'fourth hurdle' to patients' access to medicines, but may increase access as they are prepared to recommend drugs that cost more but improve patient health outcomes (value-for-money drugs). A policy of cost-containment implemented at the local Health Authority level poses a greater threat to good patient care if not married to an adequate consideration of the benefits of new but more expensive pharmaceuticals.

It was suggested that from the perspective of risk management there are risks associated with 'at launch' economic evaluations in correctly judging a new drug as cost-ineffective. Hence there could be a premature denial of access to the drug before evidence is gathered on cost-effectiveness in actual clinical practice (through post-marketing economic evaluations). At launch, economic evaluations are important, but often the data are insufficient to make definitive decisions on cost-effectiveness in actual practice in the medium to long term. Also, care must be taken in the economic evaluation of new drugs to take account of the level of unmet need where there may not be any other therapeutic option on the market.

Against: Professor J Raftery, Director, Health Economics Facility, University of Birmingham

Following thalidomide, post-marketing evaluation of medicines is inevitable. Moreover, the number of medicines withdrawn from the market after launch is increasing. The FDA withdrew 11 medicines between 1997 and 2000, compared with only 12 in the preceding 20 years. Post-marketing economic evaluations are highly desirable because of the importance society gives to cost. Without such evaluations decision-making that is guided by economics would have to be based on RCT data, which are unreliable for this purpose. In the UK, NICE has moved economic evaluation from academic journals to NHS guidance, and has specified economic evaluation as a key contributor to its decision-making. Nonetheless, NICE evaluations are limited by the lack of long-term data about outcomes. Key recent examples include evaluation of new treatments for multiple sclerosis (Guidance Number 32) and Crohn's disease (Guidance Number 40). Prohibition of post-marketing studies would exacerbate these problems. It would increase reliance on short-term RCT data in modelling, leading to longer more pragmatic and expensive RCTs. The key issue is the optimal collection of post-launch data. Necessary steps include improving quality assessment of models and addressing key missing elements ('real-world' pathways of patient care and assessments of the impact of treatment on quality of

life). Industry must accept the inevitability of 'post-launch' data and work with government and healthcare providers to design post-launch databases to be of greatest value.

REFERENCES

1 Grodstein F, Stampfer MJ, Manson JE *et al.* Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996; **335:**453–61.

2 Grodstein F, Manson JE, Colditz GA *et al.* A prospective observational study of postmenopausal hormone replacement therapy and primary prevention of cardiovascular disease. *Ann Intern Med* 2000; **133:**933–41.

3 Baber RJ, O'Hara JL, Boyle FM. Hormone replacement therapy: to use or not to use? *Med J Aust* 2003; **178:**630–3.

4 Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998; **97:**1440–5.

5 Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. The West of Scotland Coronary Prevention Study Group. *J Clin Epidemiol* 1995; **48:**1441–52.

6 Caro J, Klittich W, McGuire A *et al.* The West of Scotland coronary prevention study: economic benefit analysis of primary prevention with pravastatin. *BMJ* 1997; **315:**1577–82.

7 Salomon JA, Weinstein MC, Hammitt JK *et al.* Empirically calibrated model of hepatitis C virus infection in the United States. *Am J Epidemiol* 2002; **156:**761–73.

8 Weinstein MC, Goldie SJ, Losina E *et al.* Use of genotypic resistance testing to guide HIV therapy: clinical impact and cost-effectiveness. *Ann Intern Med* 2001; **134:**440–50.

9 Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA* 2002; **287:**2382–90.

10 (http://www.fda.gov/oc/tfrm/riskmanagement.pdf)

11 (http://www.fda.gov/cder/meeting/riskmanagement)

12 Sonnenblick EH. Cardiorenal differences among NSAIDs and coxibs: real-world experience. *Am J Manag Care* 2002; **8:**S369–70.

13 Prescription Medicines Data File Documentation. *Third National Health and Nutrition Examination Survey (NHANES III), 1988–94.* Series 11, No. 2A. 1998.

14 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998; **279:**1200–5.

15 (http://www.hm-treasury.gov.uk/Consultations_and_Legislation/wanless/consult_wanless_final.cfm)

16 Taxis K, Barber N. Ethnographic study of incidence and severity of intravenous drug errors. *BMJ* 2003; **326:**684.

17 DOH. An organisation with a memory. Norwich: The Stationery Office; 2000. (http://www.doh.gov.uk/cmo/progress/patientsafety/patientsafety2.htm)

18 Scottish Executive Health Department. Learning from experience. How to improve safety for patients in Scotland. 2002. (http://www.cdc.gov/nchs/data/nhanes/nhanes3/PUPREMED-acc.pdf)