

New technologies pharmacists and patients

The November issue of this journal carried a report from the 29th symposium of the European Society of Clinical Pharmacy held in Basel from October 11–14. In this second report, Christine Clark writes about sessions that were devoted to the assessment of outcomes at the level of patients, services and populations

There were serious gaps in the ways in which researchers had been assessing patient outcomes, according to Dr LISA BERO (department of clinical pharmacy and institute for health policy studies, University of California, San Francisco). Patient outcomes were important when it came to answering policy questions such as “Should I have a pharmacist to provide some services currently provided by physicians?” and “Should community pharmacists be reimbursed for counselling patients about drugs and healthy lifestyles?” she said. The answer to the first question was “maybe”, because there had only been one study that looked at this question and that was in 1974. She was confident that the answer to the second question was “yes”.

Dr Bero had participated in a Cochrane review designed to ask “Does the delivery of services by ambulatory care pharmacists (not in hospital) decrease the use and cost of health care services and improve patient outcomes, compared to delivery by other health care professionals?” A second question compared pharmacist-delivered services with no care or standard care.¹

The review had focused on primary data analyses concerned with patient outcomes. It included randomised, controlled trials and controlled before-and-after studies. The outcomes used were health service utilisation, costs (if available), including costs of delivery of intervention as well as costs saved, and professional practice or process outcomes.

Thirty-three studies had been found that matched the inclusion criteria. Eight of these studies had been excluded — three because they had used no eligible outcome measures. Of the remaining 25 studies, 17 involved interventions targeted towards the patient and 11 concerned interventions targeted towards health care professionals (some had both). Patient-targeted interventions included patient education (five), prescribing by a pharmacist (one), drug monitoring and follow-up education (10) and home visits (one). The studies most commonly involved patients with diabetes or hypertension, but patients with hyper-cholesterolaemia and those taking “high risk” drugs had also been studied. The types of patient and intervention should logically predict the type of outcomes that might be measured, said Dr Bero. For example, a patient education programme might be evaluated by measuring patients’ knowledge of their medication.

Only studies with objective outcome measures were eligible for inclusion in the review. Many studies that had used patient satisfac-

tion scores had been excluded because the scores had been collected in a subjective way. Usually in such cases, the scoring instrument had been both designed and administered by the investigator, said Dr Bero. Another important criterion was that original, interpretable data had to be reported.

Both process outcomes and patient outcomes were measured by the studies in the review. Process outcomes included appointments kept, clinic visits and emergency department visits. Often these data had been culled from secondary sources such as computerised records. Other types of process measure were the number of drugs per prescription or appropriateness of prescriptions. A potential weakness here was that prescriptions were monitored but not what was actually dispensed. Patient outcomes were usually clinical measures such as blood pressure, blood glucose, drug levels or clinical assessments. These were objective measurements made by different people from those involved in the intervention, said Dr Bero.

Six of the studies had measured quality of life but none found any difference attributable to the intervention. Only one study looked at adverse drug events. In 10 studies only patient outcomes were measured and in another 11 only process outcomes were measured. Only four studies measured both outcomes. It would have been nice to know whether the process influenced the outcome, commented Dr Bero. Returning to the original questions posed by the review, Dr Bero said that only one study had compared pharmacist-run services with services provided by other practitioners. This had involved patients with hypertension and diabetes who were managed by pharmacists. The results showed very small differences in blood pressure and blood glucose when managed by pharmacists compared to other practitioners.

PHARMACIST-PROVIDED SERVICES

There were 16 studies concerned with pharmacist-provided services versus usual care. Four had measured quality of life using the SF36 and failed to show any differences. One study had shown that the cost of the intervention exceeded the savings in drug costs but this did not take into account the possibility of later savings as a result of reduced health care utilisation, pointed out Dr Bero.

She identified several major gaps in this field. Why use the SF36 to measure quality of life in this type of study when it was not the best measure? Adverse drug reactions were an area where pharmacists could really impact on patient outcomes and yet this had rarely been measured. In outcomes assessment, there was not enough checking what had already been done. If there was an instrument available that

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had been published, that had known validity and reliability, it was really important to think about using that first, recommended Dr Bero.

The next step in research design was to think about the type of patient. For example, specific quality of life instruments had been developed for some patient groups — these were likely to be more sensitive than standard instruments in these groups, she said. How the data was collected also had to be considered. For example, postal questionnaires yielded very different answers from face-to-face interviews. Finally, it was important to check whether the chosen instrument was a “living” document that was regularly used by researchers in the field (and whose designers the researcher might be able to contact) rather than one that was buried in a library.

Answering a question from Professor ROGER WALKER (Wales), Dr Bero said that no studies had shown negative outcomes associated with interventions by pharmacists although there had been a number of “non-effects”.

PHARMACY PRACTICE RESEARCH

Pharmacy practice research had not embraced social science theoretical perspectives, and this had implications for the quality and acceptability of research, said Dr RACHEL ELLIOTT (school of pharmacy, University of Manchester). Describing the tools available for evaluation of pharmaceutical services, she warned that practising pharmacists should beware of the lure of solving practice problems at the expense of doing any deeper analysis. There were, she said, many published studies that were poorly designed and were not analytical, interpretative or critical.

Evaluation was defined as “the critical assessment, on as objective a basis as possible, of the degree to which entire services or their components fulfil the stated goal.” Research, practice research and audit were all covered by this definition.

Guides to research design recommended that the objectives were defined first and then the outcome measures selected. In practice, said Dr Elliott, the outcomes often turned out to be over-ambitious and so the objectives were modified. This process was repeated until an achievable design was reached.

The randomised, controlled trial (RCT) was the gold standard for research design because it ensured that the only differences between two groups were due to the intervention. However, RCTs used highly-selected samples of the population and tended to be relatively short. Both of these factors made it difficult to generalise the results, said Dr Elliott. The challenge, she said, was to maintain the high internal validity of the RCT while obtaining as much external validity as possible.

Conducting blind trials was a problem in some studies. For example, it was virtually impossible to blind patients to the fact that they were receiving counselling, explained Dr Elliott. Sometimes an active drug was obvious to patients either by virtue of its effect or from its taste. Nicotine chewing gum was a good example of this. The inability to blind a service-related study was not a criticism so much as part of a more general problem.

The placebo effect was difficult to mimic in service evaluation, said Dr Elliott. In one study, patients over 65 years of age were sent letters inviting them to enrol for ‘flu vaccination. In order to mimic the “caring” effect of the letter, subjects in the control group were sent letters inviting them to dispose of unwanted medicines.²

There were many situations where it was completely impossible to evaluate services by means of a randomised controlled trial and so quasi-experimental methods had to be used. Non-randomised designs inevitably led to a loss of internal validity because of the presence of confounding factors that could influence the outcome. The way to deal with this pragmatically was to address the potential criticisms in the study design. For example, patients could be matched (eg, by age, sex, pathology, number of medications) to ensure equivalence. Statistical techniques could also be used to examine the effects of confounders, but these had to be used with caution,

warned Dr Elliott.

Another area where problems were met was in outcome measurement. From an economist’s perspective, a health care process represented input costs and the outcomes were the benefits. It was generally assumed that if the structure and process were correct then the desired outcomes would inevitably follow. This assumed link was rarely supported by any evidence, said Dr Elliott. The other assumption was that process indicators such as prescribing analyses predicted good patient outcomes. Only now were these types of assumptions being called into question.

OUTCOME MEASUREMENT

Outcome measurement needed to use a theoretically robust methodology drawn from the social sciences. This did not necessarily make it any more difficult to collect the data, explained Dr Elliott, and it would almost certainly be easier to analyse. A good, recent example of outcomes research was a study by Duggan and Bates which described the development of a tool to explore patients’ perceptions of their prescribed drugs.³

It was very important to prove the link between process and outcome measurement in order to justify pharmacy services, said Dr Elliott. Managers wanted to see evidence. Compliance was a major issue here and it was important to consider whether compliance always improved health. As patients took greater control of their own health, then patient evaluations of outcomes became more important. Dr Elliott said that she was involved in work to quantify patient preferences. The quantity and quality of publications in this field was increasing. Patient satisfaction surveys were not always reliable, she suggested. If people were asked if they were satisfied with their local pharmacy, the majority would say yes, because they had no particular expectations.

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INFORMATION TECHNOLOGY

Turning to the impact of information technology, Dr Elliott said that the development of electronic patient records brought both opportunities and problems. There were concerns about confidentiality, which might limit the ways in which electronic data could be used, and concerns about quality. In the UK, the British Medical Association had made recommendations for security of electronic patient records. "Information flow" might give rise to problems because access to some information might be tightly controlled. The biggest problem was likely to be "aggregation control". In theory, patients would need to give permission before their data could be combined with that from other patients for evaluation of patient groups and, if they refused, then their data would have to be omitted from a study.

The advantages of computerised systems were that others had already gathered the data and that it was possible to examine trends over time. In practice it was not always so straightforward, said Dr Elliot. For example, one study that had examined the managed entry of donepezil on to the market had intended to use computerised data but the investigators discovered that the authorities had kept no records of usage. Other possible problems were that the data might not be accurate, complete or even up-to-date.

"Do your evaluations well or don't bother to do them at all," was Dr Elliott's concluding advice.

EFFECTIVENESS

There was no legal requirement to study effectiveness, which he defined as efficacy in daily practice, according to Dr ANDRÉ BROEKMANS (executive director, Medicines Evaluation Board [MEB], The Netherlands). This was one of the problems in evaluating the effects of medicines on populations, he said, in a presentation that reviewed the topic from the regulator's viewpoint. The database used to make regulatory decisions comprised material drawn from a variety of sources and included ADR reports, observational studies, systematic reviews, meta-analyses and anecdotal reports, in addition to the "backbone" of industry-sponsored RCTs, he explained.

RCTs were essential in the pre-approval stage and were embedded in the legal framework, said Dr Broekmans. There were guidance documents for RCTs produced by the European Union and by the International Conference on Harmonisation. RCTs were governed by good clinical practice (GCP) which was soon to be formalised as an EU directive.

One critical issue in RCTs was the choice of comparator and whether it was ethical to use placebos at all. Another important consideration was whether a surrogate endpoint was adequately validated and known to be predictive of the desired outcome. Other issues for the regulators were the uncertainty about long-term effects and the characteristics of the study population.

An example of an RCT with inappropriate comparators was a recent study that had compared newer antifungal agents with older products. An intravenously administered product had been compared with an older, oral formulation that was poorly absorbed. Another example was a study of NSAIDs in which the comparators had been given in lower doses than those recommended.

Surrogate endpoints gave cause for concern in cancer chemotherapy, explained Dr Broekmans. The regulatory authorities required survival analyses because a drug that looked promising at Phase 2 did not always fulfil its promise at Phase 3. For this reason they were cautious about attempts to persuade them to accept (short-term) tumour response data as a surrogate for survival.

These kinds of considerations had prompted regulators to recommend that standards for clinical trials should be further upgraded to cover issues such as the choice of comparator and the fairness of the comparison. Dr Broekmans also said that they would like to see trials that demonstrated superior effects and not merely non-inferiority or equivalence.

Observational studies, including case-control studies and cohort studies, were used in the post-approval phase of drug marketing. Unlike RCTs there was no formalised framework for them, but merely informal agreements between epidemiologists and journal editors. The advantages of these types of study were that they could be carried out quickly and cheaply and could embrace a wider group of patients. The drawback was the risk of bias. Causality (was the effect caused by the drug?) and confounding (is it a true effect?) were two major issues concerning the internal validity of observational studies.

Dr Broekmans gave some examples of problems arising from observational studies. First was the case of ibopamine, a dopamine agonist used for mild heart failure. After registration, a long-term RCT had shown an increased risk of mortality in patients with severe heart failure (NYHA classes III and IV) and as a result the indication had been restricted to patients with mild disease. Soon after, an observational study had suggested that patients with mild heart failure (NYHA classes I and II) were also at risk, but in this case the evidence was not strong enough to justify any additional restrictions on use.

A different example was oestrogens, where several observational studies had suggested a protective effect against coronary heart disease. The MEB had not been convinced. Later on, an RCT, with a follow-up period of more than four years, had failed to show a reduction in the rate of CHD with oestrogen treatment.

Another reason for the reluctance to use data from observational studies had been the publication of conflicting results about the risk of fractures associated with the use of statins, said Dr Broekmans. Two groups of investigators had used the UK general practice research database to investigate this question. One had concluded that there was decreased risk of fractures (odds ratio 0.55 [95 per cent CI 0.44–0.69]) and the other a small increase (odds ratio 1.17 [95 per cent CI 1.03–1.33]). These situations were very difficult for regulators, he said. There were also positive aspects of this, said Dr Broekmans, as shown by the case of glafenine, an antipyretic analgesic. When it was first marketed there were many anecdotal reports of serious reactions including anaphylaxis, hepatotoxicity and nephrotoxicity, but there was not enough evidence to take action. The MEB itself undertook a case-cohort study to determine the risk of hospital admission for anaphylaxis with analgesics. They found that the relative risk for glafenine versus other analgesics was 20.6. As a result the marketing authorisation was revoked.

Dr Broekmans said that the MEB now considered that observational studies had a legitimate place in regulatory decisions. Recent publications supported this decision. In particular, other trialists had concluded that "estimates of treatment effects in observational studies [were] neither consistently larger or qualitatively different from those obtained in RCTs,"⁴ and that the results of observational studies did not systematically overestimate effect sizes compared with RCTs.⁵ The MEB had agreed a list of situations in which observational studies were appropriate (see Panel).

In closing, Dr Broekmans made a plea for good governance in clinical trials and re-emphasised the need for the establishment of "good epidemiological practice".

POSTERS

More than 100 posters were displayed at the symposium, many concerned with practice research topics. Bench-marking and

Panel: Indications for observational studies

The study of long term effects — both safety and effectiveness
The study of effects in specific populations, eg, the elderly
Comparisons with other types of intervention, eg, surgery
When ethical reasons preclude the use of RCT both for patients and for investigators

descriptive studies figured prominently in the programme. XAVIER POURRAT and colleagues (Tours, France) have carried out a prospective study of medication errors in the intensive care unit. They found an administration error rate of 17 per cent and 1 per cent of the recorded errors were in the serious (non-fatal) category. ANNE-CHRISTINE JOLY and colleagues (Paris, France) have carried out a nationwide survey of cytotoxic reconstitution. They found that among 275 establishments with oncology practices, 55 per cent had centralised reconstitution units (CRUs) for the preparation of cytotoxics. Of the 151 CRUs, 59 per cent had hoods, 38 per cent isolators and 3 per cent had both. CRUs were being considered in 92 establishments.

SAM SALEK and colleagues (Cardiff, UK) have conducted a prospective, cross-sectional study of patients' knowledge of their medications in an outpatient Parkinson's disease clinic. When asked to state the name, dose and regimen for their medicines, 41 per cent were able to do so correctly using a list but this fell to 21 per cent for those who did it from memory. Of the group, 4 per cent said they would contact their community pharmacist if they had a query about their treatment whereas 64 per cent would contact the consultant, nurse or clinic and 22 per cent the GP. The authors concluded that patients' knowledge of their medication was poor and that pharmacists were rarely their first choice for information in spite of their ready availability.

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