Editorial

Patient Confidence in Clinical Trials

Over 5 years ago the Arthritis Research Campaign (ARC), the principal charity for funding arthritis research in the UK, followed the lead of other specialist charities, notably those funding oncology and cardiovascular studies, and entered a collaboration with the Medical Research Council (MRC) (the conduit for government funding of medical research in the UK) and the British Society for Rheumatology (BSR). A proportion of funds were put aside for the establishment of a formal trial network and a secretariat was established. Applications were invited and clinical trials were set up.

It was anticipated that applications, which were subject to intense competitive peer review, would be slanted to answering fundamental therapeutic questions in rheumatology in which the pharmaceutical industry would not be interested. This has proved to be the case. It was also anticipated that many of the trials funded would be multicenter, with the benefit of larger sample size, faster results (before scientific interest in the treatment is lost), wider dissemination of results, and perhaps most important, a wider range of relatively unselected patients such that results might be applicable not only to patients with more severe disease seen in hospital practice but also to patients with milder disease seen in general practice. Funded trials have included the use of steroids in early inflammatory arthritis, bisphosphonates in ankylosing spondylitis, methotrexate in psoriatic arthritis, and prophylaxis for patients with antiphospholipid antibodies, as well as trials of physiotherapy in the community. The majority of trials have been placebo controlled[1] but the BSR has also taken the initiative in longterm cohort studies[2] (notably the biological register), which perhaps better represent real life experience.

Overall, this initiative has been judged a success, both by those involved and by external reviewers. Protocols have often drawn on large groups of patients, avoiding the bias that so often creeps into studies for pharmaceutical companies performed in specialist centers with rarefied populations where, for example, elderly patients who will form the majority of the population finally taking the drug are often excluded from the study protocol[3]. The collaboration also has the potential to accumulate large databases. However, an increasing concern, almost universal across a wide variety of studies, has been one of inadequate or delayed recruitment, some studies taking twice as long as anticipated to complete. This has caused concern to trial steering committees, data monitoring committees, and ethical committees alike. There is an anxiety that consistency of measurement may be lost if personnel change with time and, although recruitment can sometimes be rejuvenated in a small number of enthusiastic centers, this causes statistical concern if the study population ends up less homogeneous than originally conceived. With studies half completed and the dye already cast, funding bodies have little alternative but to continue their investment beyond the timescale originally conceived in order to guarantee a result. In turn, new projects in the queue have to be placed on hold.

Some problems associated with poor recruitment are perhaps predictable. Applicants for grants inevitably have an optimistic view of the patient resources available to them. Pharmaceutical companies, with their detailed screening of possible participating centers as the study is planned often with the help of specialist agencies, set an example here even if the population they use is thereby less typical. Controlled trials do not appeal to all patients[4] and it has even been argued that trials are better if patients are not told they will receive placebo[5]. Recruitment criteria sometimes benefit from simplification[6]. Good clinical (research) practice guidelines from the European Commission remain extremely strict in terms of patient information provided, discouraging many ordinary patients from participating. It is also salutary to consider patients' motives for participation. In one study[7] 62% stated their motivation for participation was to help others, 39% to improve their own treatment, and 38% "to comply with the doctor's request." Further factors not imagined a decade ago and perhaps particularly applicable to the UK concern the government's health service reforms. Responsibility and a large share of funding have passed from the providers (hospital trusts) to the purchasers (primary care trusts). Throughput targets have to be met and insidiously, power has passed away from trial investigators to primary care physicians who may be reluctant to fund the large number of extra visits that may be inherent in the conduct of a safe clinical trial.

However, when allowance has been made for all these factors, it remains a very strong impression, based upon analysis of trial registers, that only a small proportion of those patients considered eligible are actually recruited. Moreover, in the last year even more eligible patients are

refusing to give informed consent because of well-publicized anxiety about the pitfalls in the development of new drugs. Patients will not necessarily admit this to attending physicians for fear of compromising their treatment, but this is also the impression among paramedical staff at the front line of recruitment with whom trust is more likely to be shared.

It seems unlikely patient confidence has been lost in clinicians, trials, drugs, and industry as a result of the cautious introduction and evaluation of tumor necrosis factor-α blockers or other biological agents. Although this group of drugs had the potential for serious side effects, perhaps even neoplasia, the cautious and meticulous collection of case control data both by the companies marketing these agents and by independent bodies such as the biologics register of the BSR, has allowed clinicians to prescribe with a confidence that is no doubt intimated to their patients. In contrast, the explosive marketing of highly selective COX-2 inhibitors since September 2004, and the subsequent withdrawal of some, appears to have undermined public confidence. The US Federal Drug Administration (FDA) took the highly unusual step of convening a public meeting of its Arthritis Advisory Committee and its Drug Safety Risk Management Advisory Committee on February 16, 2005, which seemed to cast doubt on the wisdom of a complete withdrawal of some highly selective coxibs, although opinion was evenly divided. This suggested that the overall potential benefits of highly selective COX-2 inhibitors slightly outweighed the risks and created even more public confusion. At the time of writing (and circumstances change almost by the week), rofecoxib and valdecoxib cannot be prescribed, although celecoxib and etoricoxib can be; moreover, in the UK some pharmacists (who often hold the purse strings) and even general practitioners are incorrectly advising patients that all these expensive drugs have been withdrawn. Many patients who responded well to rofecoxib (a sulphone) do not gain such benefit from a comparable dose of celecoxib (a sulphonamide) and wish that they could have had the option of remaining on their former drug once aware of the risk. It is also likely that lumiracoxib (an acidic drug), still to be introduced, will provide a third option.

That the risk of cardiovascular event with some of these drugs has been defined and publicized is undoubted. What has received less attention is the morbidity and mortality that is likely to accrue if patients who took highly selective COX-2 inhibitors because of the serious gastrointestinal side effects experienced with earlier generations of nonsteroidal antiinflammatory drugs (NSAID), have to return to those drugs even with the addition of a gastroprotective agent. There is also a paucity of data on the cardiovascular risk of the first generation of NSAID, which may well be underestimated.

The UK has also suffered a further complication. As ripples from the FDA decision crossed the Atlantic and spread through Europe, the Committee on Safety of Medicines in the UK announced its proposal to withdraw co-proxamol, a compound analgesic available only in the UK that combines a small dose of dextropropoxyphene with paracetamol. The arguments of hepatologists who had to deal with the relatively small number of suicides, which were undoubtedly specifically associated with this drug, overruled the arguments from rheumatologists who noted the large number of patients with arthritis for whom this drug gave specific pain control. Although complete withdrawal will not occur for a further year, new prescribing is formally discouraged such that patients who might have managed their pain after discontinuing rofecoxib with co-proxamol alone, now no longer have this opportunity.

Perhaps the storm will settle. Perhaps some drugs, recently withdrawn, will be reintroduced with appropriate product warnings both to patients and their medical attendants so the choice based upon relative risk is back in the hands of the patients. Perhaps the risk from the alternative therapies to which these patients are meanwhile having to resort, will now be better quantified. Perhaps confidence will be regained and perhaps recruitment to all essential trials on which such decisions need to be made will improve.

However, at present, patient confidence in clinical trials has reached a nadir. It will be ironic if the antics of pharmaceutical companies and regulatory authorities ultimately place patients at even greater risk by making more difficult the trials that are now needed to rectify the situation.

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