1 Smith SE, Rawlins MD. *Variability in human drug response.* London: Butterworths, 1973.
2 Vogel CL, Cobleigh MA, Tripathy D, Debu G, Harris JC, Lyndsay N, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002;20:719-26.
3 Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLS-B region and hypersensitivity reactions to abacavir. *Lancet* 2002;359:1121-2.
4 Urquhart J. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response. *Br J Clin Pharmacol* 2002;54:212-20.
5 Food and Drug Administration. *Innovation or stagnation? Challenge and opportunity on the critical path to new medical products.* Washington: FDA, 2004. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf (accessed 15 Jun 2004).
6 Academy of Medical Sciences. *Strengthening clinical research.* London: Academy of Medical Sciences, 2003. www.acmedsci.ac.uk/p_scr.pdf (accessed 15 Jun 2004).
7 Veenstra DL, Higashi MK, Phillips KA. Assessing the cost-effectiveness of pharmacogenomics. *AAPS PharmSci* 2000;2:E29.
8 Gage BF, Eby C, Milligan PE, Banet GA, Duncan JR, McLeod HL. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. *Thromb Haemost* 2004;91:87-94.
9 Lee SS-J. Race, distributive justice and the promise of pharmacogenomics: ethical considerations. *Am J Pharmacogenomics* 2003;3:385-92.
10 Hapgood R. The potential and limitations of personalised medicine in primary care. *Br J Gen Pract* 2003;53:915-6.

Collecting and sharing information about harms

Appropriate strategies to communicate this information are essential

Prescribing a drug represents a trade-off between its benefits and harms. The harm to benefit ratio varies according to the condition being treated, the drug's pharmacology, and the availability and safety of other therapeutic options. A decision to prescribe a drug therefore has to be made on the basis of all the information available. There is, however, often an imbalance in such information. Although high quality data regarding benefits usually come from randomised controlled trials, systematic reviews, and evidence synopses, information on harms may be limited. This is particularly the case for new drugs, which usually have been given to only a few thousand patients, and often for relatively short periods before licensing.[1] This allows common adverse events to be detected, but not rare events or those that occur only with prolonged exposure. Consequently, established compounds continue to cause much harm[2]—for example, approximately 5% of all admissions to US and European hospitals are due to adverse drug reactions.[w1] A much publicised meta-analysis showed that such reactions caused more than 100 000 deaths in the United States in 1994.[w2]

Monitoring harms after launch of a product is thus crucial, since regulatory action may be necessary to protect public health. Systems to monitor drug safety are well developed in the United States and most EU countries (but hardly at all in developing countries). For example, the probability that a new drug will acquire a "black box warning" or be withdrawn in the United States has been estimated to be 20% over 25 years.[3] In the United Kingdom 4% of all licensed products are withdrawn after marketing because of safety problems.[4] However, a great number of patients have to be treated before an uncommon adverse event is detected and regulatory action taken. For example, 7.5 million patients were exposed to terfenadine before regulatory action was instituted in relation to its QT prolonging effects.[5]

Postmarketing surveillance of drugs uses many methods.[w3] Spontaneous reporting systems—such as the yellow card scheme in the United Kingdom, which is 40 years old—have many strengths, as highlighted by the recently published yellow card review.[6] Spontaneous reporting schemes should be regarded as hypothesis generating tools as any signals need to be confirmed by pharmacoepidemiological studies.[w4] A great limitation of all reporting systems is underreporting: only 10% of serious adverse drug reactions are reported.[1] This has led to a widening of the reporter base—for example, by including pharmacists[7] and nurses.[8] Much inconsistency exists, however, in reporting systems in the European Union and worldwide,[w5] which need to be harmonised. The yellow card review has recommended the introduction of direct reporting by patients in the United Kingdom.[6] Although reporting by patients may be valuable when intensive monitoring is taking place or when reporting is through an intermediate healthcare professional,[w6] it is unclear whether this is also true of direct patient reporting, which needs robust evaluation. The aim of any spontaneous reporting system should be the prompt detection of new drug safety issues. The expansion of the reporter base may contribute, but it is crucial that this does not occur at the expense of an increase in the ratio of signal to noise. Perhaps improved data mining techniques that use statistical techniques such as cluster analysis, link analysis, deviation detection, and disproportionality assessment will be able to cope with "noise" and enable earlier detection of safety signals in databases of information on health care.[9]

There are several reasons to be optimistic that data on harms will improve over the next few years. Firstly, inadequate reporting of adverse event data in randomised controlled trials and the difficulty in identifying information on harms in literature databases are now widely recognised,[w7] and are likely to lead to specific reporting requirements in the CONSORT criteria. Secondly, systematic reviews have had a major influence on the assessment of benefits of medicines, but not of harms, not least because most data on harms are collected from observational studies and case reports, not from randomised controlled trials. The intention of the *BMJ* and the Cochrane Collaboration to improve the reporting of harms in their publications is certainly a step forward.[10] Thirdly, the International Conference on Harmonisation has published guidelines for pharmacovigilance planning (E2E),[w8] which will allow more structured assessment of harms after licensing, and include investigation of drugs in groups that may be at particular risk—for example, elderly

Additional references w1-w11 are on bmj.com

BMJ 2004;329:6–7

people. Fourthly, the EU Clinical Trials Directive specifically addresses pharmacovigilance, and this should contribute to improvements in reporting in European clinical trials.[w9] Fifthly, although research databases have had a major impact on drug safety issues in recent years,[11] they have limitations, including limited power to detect rare events, and they focus on one area of the healthcare system. The announcement of the information technology strategy for the NHS could, if set up to do so, lead to the development of an integrated drug safety database, with enormous potential for earlier detection of adverse drug reactions.

Finally, sharing of data by prescribers, researchers, regulators, and the industry is essential. Legislation to protect personal privacy has been introduced in many countries; although important, it must not deter sharing of information that is needed to protect public health. Inability to share information because of legislation has already had adverse consequences—for example, in the criminal justice system.[12] Information also needs to be available to the general public, the consumers of medicinal products. However, this requires safeguards so that the data are appropriately interpreted, taking into account both harms and benefits of the drug. Without such safeguards, we may face problems similar to the controversy concerning the measles, mumps, and rubella (MMR) vaccine, where an inappropriate focus on potential (and unproved) harms has generated mistrust and led to a decline in public health.[w10] To this end, appropriate strategies to communicate risk to the public are going to be essential.[w11]

Munir Pirmohamed *professor of clinical pharmacology*

Department of Pharmacology, University of Liverpool, Liverpool L69 3GE
(munirp@liv.ac.uk)

Janet Darbyshire *professor of epidemiology*

MRC Clinical Trials Unit, London NW1 2DA
(jhd@ctu.mrc.ac.uk)

Competing interests: Both authors are members of the Committee on Safety of Medicines (CSM), and MP is a member of the CSM subcommittee on pharmacovigilance, but the views expressed here are their own. Both authors are also co-chairing a working group on postmarketing surveillance for the Academy of Medical Sciences Forum. MP has current support from Astra-Zeneca, Pfizer, and Bristol Myers Squibb for research into drug safety issues. The MRC Clinical Trials Unit, of which JHD is director, has received contributions to the costs of trials from Chiron, Wyeth, Novartis, ML Laboratories, Indevus, Aventis, Roche, BMS, Merck, Boehringer Ingelheim, GSK, and Virco.

1 Rawlins MD. Pharmacovigilance: paradise lost, regained or postponed? *J R Coll Phys Lond* 1995;29:41-9.
2 Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients. A systematic review of the prospective and retrospective studies. *Bandolier Extra* 2002:1-16.
3 Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA* 2002;287:2215-20.
4 Jefferys DB, Leakey D, Lewis JA, Payne S, Rawlins MD. New active substances authorized in the United Kingdom between 1972 and 1994. *Br J Clin Pharmacol* 1998;45:151-6.
5 Friedman MA, Woodcock J, Lumpkin MM, Shuren JE, Hass AE, Thompson LJ. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA* 1999;281:1728-34.
6 *Report of an independent review of access to the yellow card scheme.* London: Stationery Office, 2004.
7 Lee A, Bateman DN, Edwards C, Smith JM, Rawlins MD. Reporting of adverse drug reactions by hospital pharmacists: pilot scheme. *BMJ* 1997;315:519.
8 Morrison-Griffiths S, Walley TJ, Park BK, Breckenridge AM, Pirmohamed M. Reporting of adverse drug reactions by nurses. *Lancet* 2003;361:1347-8.
9 Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. *Br J Clin Pharmacol* 2004;57:127-34.
10 Cuervo LG, Clarke M. Balancing benefits and harms in health care. *BMJ* 2003;327:65-6.
11 Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23:686-9.
12 Peto J, Fletcher O, Gilham C. Data protection, informed consent, and research. *BMJ* 2004;328:1029-30.

Assessing the benefit-harm balance at the bedside

We need pragmatic ways of using the best available information

As prescribers, we all aspire towards the goal of providing safe and effective medicines for our patients. At the bedside, we are routinely confronted with the challenge of determining which treatment (if any) offers the most appropriate tradeoff between benefit and harm. In ideal circumstances, we would base this assessment on the findings of a systematic review. But the reality is that systematic reviews and randomised controlled trials tend to focus on efficacy and seldom pay much attention to adverse effects.[1 2] In contrast, product datasheets and drug reference texts (such as the *British National Formulary*) are laden with comprehensive lists of adverse effects. Is there really any need to look beyond these ubiquitous, easily accessible sources of safety data?

However, all is not what it seems. Lists of adverse effects can be extremely lengthy—for example, Bracchi noted 54 adverse effects for fluoxetine—and incorporating them into a useful analysis of the benefit:harm balance seems impossible.[3] More recently, a member of the British public wrote to the national press in bewilderment after discovering that his medication had more than 80 potential adverse effects.[4] The threat of so many adverse effects seemed to swamp the prospect of benefit, and it comes as no surprise that the patient regarded the cure to be worse than the ailment.

A lack of quantitative information on the likelihood of occurrence complicates the problem further. Bracchi attempted to get round this by requesting frequency data from drug manufacturers, but only one of the 120 companies contacted was able to help.[3] In an attempt to improve product datasheets, European regulatory authorities have proposed the use of qualitative terms such as "common" to "very rare." Research has shown, however, that these terms lack precision and are not as well understood as numerical data.[5]

P+ *An additional table showing scenarios for which treatment decisions should be based on a detailed evaluation of the benefit to harm balance is on bmj.com*

BMJ 2004;329:7–8