International Journal for Quality in Health Care 2000; **Volume 12, Number 1**: pp. 69–76

Methodology Matters

Identifying drug safety issues: from research to practice

TEJAL K. GANDHI[1], DIANE L. SEGER[2], DAVID W. BATES[1,3]

[1]Division of General Medicine, Brigham and Women's Hospital and Harvard Medical School, [2]Clinical Systems Research and Development, Partners HealthCare System and [3]Center for Applied Medical Information Systems Research, Partners HealthCare System, Boston, Massachusetts, USA

Abstract

Purpose. Adverse drug events (ADEs), or injuries due to drugs, are common and often preventable. However, identifying ADEs, potential ADEs, and medication errors can be a major challenge. In this review, we describe methodologies that have been used to identify these events and give strategies for identification in non-study settings.

Results. Methods such as voluntary reporting, chart review, and computerized monitoring for events have been most commonly used in studies of ADEs in inpatients. However, voluntary reporting, the method most hospitals currently use, has a very low yield of events. Chart review is much more sensitive but the costs are prohibitive. Computerized monitoring for ADEs (using rules or triggers) is a high yield and relatively inexpensive strategy that should be adopted by organizations. A limitation of this strategy, however, is that it identifies few medication errors and potential ADEs, which are also important. These can be captured through pharmacy logs, chart review, and direct observation. Once events have been identified, they can be classified by type of event, severity, and preventability. In non-study settings, the most practical method for identifying ADEs is computerized monitoring, and for identifying prescribing errors it is pharmacy logs of interventions. Once problems are found, a structure (either individual or committee) must be in place to classify them, identify opportunities for improvement, and carry out the necessary changes.

Conclusions. Health care organizations have the technology to significantly improve their detection of ADEs, medication errors, and potential ADEs. Identification and subsequent classification of events is crucial for quality efforts to improve patient safety.

Key words: Adverse drug events, drug safety, medication errors, methodology

Introduction

Adverse drug events (ADEs) occur commonly in the health care system. According to one estimate, over 100 000 hospitalized patients in 1994 had fatal adverse drug reactions [1]. Numerous groups have evaluated the frequency, preventability, and cost of these events, particularly in the inpatient setting [2,3]. For example, Bates *et al.* found 6.5 ADEs and 5.5 potential ADEs per 100 admissions. Twenty-eight percent of these were judged preventable.

ADEs have important economic and human consequences. Inpatients who suffer an ADE have a mean increase in length of stay of about 2 days and have an increased cost of admission of more than $US2000. In addition, patients suffering from ADEs have nearly three times the mortality rate compared with matched controls [3,4].

Identification of ADEs and medication errors is a crucial first step in improving patient safety, although the approach is likely to be different in research and routine care. One reason it has been difficult to study the issue of ADEs and medication errors is that reliable identification and classification of events is difficult. In many studies, estimates of rates of ADEs have varied substantially, depending on the setting and data sources used. In order to reduce the frequency of ADEs and prevent medication errors, organizations need tools to identify them. Once events are identified, systems must be in place to analyze them and identify opportunities for quality improvement and systems changes.

Address reprint requests to D. W. Bates, Division of General Medicine, Brigham and Women's Hospital, PBB-A3, 75 Francis Street, Boston, MA 02115, USA. E-mail: dbates@partners.org

Table 1 Definitions

Incident	Definition	Example
Adverse drug event (ADE)	Injury due to a drug	Drug rash
Preventable	Due to an error	Coma due to overdose of sedative
Non-preventable (adverse drug reaction)	Injury, but no error involved	Allergic reaction in patient not known to be allergic
Medication error	Any error in any stage of the medication process, including ordering, transcribing, dispensing, administering or monitoring	A dose of non-critical medication is not given
Potential ADE	An incident with potential for injury; all potential ADEs are medication errors	An order was written for an overdose of medication but the mistake was intercepted by the pharmacy

In this review, we will (i) describe the methods used to identify ADEs and medication errors in research, including their strengths and limitations, and will focus especially on those used in the ADE Prevention Study [2,5]; (ii) describe methods to classify events that are found; (iii) discuss what methods can be used in day-to-day practice; and (iv) give suggestions for ways to use these data to improve quality of care.

Methods

Definitions

Definitions are important in the study of ADEs and medication errors, and remain somewhat controversial, though more consensus has been reached in recent years. The following definitions are those from the ADE Prevention Study [2,5]. Adverse drug events are defined as any injury due to a medication [2]; these events can be preventable (e.g. wrong dose) or non-preventable (e.g. rash due to an antibiotic) (Table 1). Non-preventable ADEs are also called adverse drug reactions; the World Health Organization definition of adverse drug reactions excludes reactions associated with error, which are of greatest interest from the prevention perspective [6].

A medication error is defined as any error occurring in the medication process (ordering, transcribing, dispensing, administering, and monitoring) [7]. Medication errors are the broadest category and while most have little potential for harm, some do and are either potential ADEs or preventable ADEs (Figure 1), depending on whether an injury occurred. Potential ADEs are events in which an error occurred but did not cause injury for whatever reason (e.g. error was intercepted before the patient was affected or the patient received a wrong dose but no harm occurred). All potential ADEs are medication errors but not all medication errors are potential ADEs.

The frequency of ADEs, medication errors, and potential ADEs is very different; ADEs are relatively rare compared with medication errors. In one study 1% of medication errors resulted in ADEs, and 7% of medication errors were judged to represent potential ADEs [7]. Systems for identifying and reporting these events need to be clear in what they are capturing. For quality improvement purposes, potential ADEs as well as ADEs are valuable, since they can both lead to patient injury in the future. It is also worthwhile tracking non-preventable ADEs, since they may become preventable in the future [8]. In addition, medication errors are important, because they occur most frequently by far and result in a substantial waste of resources [7].

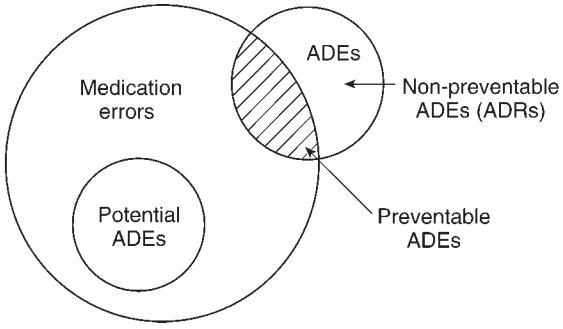

Figure 1 Relationships between medication errors, potential ADEs and ADEs.

Methods of error identification

The major methods of detecting ADEs are voluntary reporting, chart review, computerized monitoring, and searching claims data (Table 2). The main methods of detecting medication errors are direct observation by trained observers, voluntary reporting (especially by pharmacists), and chart review. Research studies of inpatient ADEs have used multiple methods of identification since they are complementary. In

Table 2 Methods of ADE, medication error and potential ADE identification in inpatients

Incident	Method of identification	Yield	Limitations
ADEs	Voluntary reporting	Low	Low yield
	Chart review	Highest	High cost
	Computerized monitoring	High	Finds mostly events associated with numbers
	Searching claims data	Very low	Very low yield
Medication errors	Spontaneous voluntary reporting	Low	Under-reporting, non-representative
	Pharmacy logs	High	Doesn't find administration errors
	Chart review (primarily of orders)	Highest	Low yield for administration errors
	Direct observation	Very high	Finds only administration errors, many with low potential for harm
Potential ADEs	Spontaneous voluntary reporting	Low	Under-reporting, non-representative
	Pharmacy logs	High	Finds very few administration errors
	Chart review (primarily of orders)	Highest	High cost
	Direct observation	Medium	High cost if long periods of observation
	Computerized monitoring	Low	Low yield
	Searching claims data	Very low	Very low yield

particular, a combination of chart review, solicited nurse and pharmacist reporting, and voluntary reporting have been used.

Spontaneous voluntary reporting is one method of identifying ADEs. This has long been the primary mechanism by which institutions identify adverse events [9–14]. However, these reports identify only about 1 in 20 ADEs [15]. Some strategies may increase the yield of spontaneous reporting. For example, one study tried to facilitate spontaneous reporting by prompting physicians daily to report events and by making it easier to report events (through e-mail) [16]. In this study, when prompted, physicians reported events with the same frequency as found by medical record review. Of note, the two methods identified different events and the physician-reporting method was less costly and detected more preventable ADEs. Another study also questioned residents about adverse events as part of physician order entry (for example, at the time discharge orders were entered) to increase reporting [17].

Stimulated voluntary reporting is another strategy that has been used to detect ADEs. In this technique, one approach is to interview nurses and pharmacists to solicit information [2]. In another study, housestaff were paid a small amount to inquire on work rounds about events that had occurred in confidential peer interviews [18]. This real-time verbal inquiry eliminated the need to remember to report and made reporting quick and easy. In this study, over 100 events were reported verbally whereas only one report was filed on the hospital incident reporting system.

Another method commonly used for ADE identification is retrospective chart review, looking for events documented in the chart. This method requires training of chart reviewers as to definitions of ADEs and what triggers to look for (Table 3). Chart review can also be used to identify medication errors and potential ADEs. Screening for medication errors also requires substantial training of reviewers in terms of criteria to pursue (Table 4). The major limitations of chart review are that it is costly, time-consuming, and requires that medical personnel document events that occur. In the outpatient setting in particular, only a very small percentage of events actually make it to the medical chart [19]. In addition, chart review is highly dependent upon the reviewers and their ability to conduct adequate chart reviews. Despite training, there can be significant variation in the ability of reviewers to abstract ADE data [20,21].

Computerized monitoring to screen for ADEs is a promising technique [6,22,23]. These computer programs can screen administrative and clinical databases based on certain rules and identify events (Table 5). When the monitor reveals an event, a pharmacist then performs a targeted chart review to verify it, which is much less labor-intensive than routine chart review. For example, Classen *et al.* used a computer-based monitor to detect ADEs and identified 731 in an 18-month period [22]. This monitor resulted in an eightfold increase in ADE identification compared with spontaneous reporting alone. Using a similar computer-based strategy, Jha *et al.* compared events found to those identified using chart review and stimulated voluntary report by nurses and pharmacists [6]. Of 617 ADEs detected by at least one method, 76 were identified by monitor and chart review. The computer monitor identified 45% of total events, chart review 65%, and voluntary report 4%. In this study, the computer strategy

Table 3 Chart review triggers that may signal ADEs or medication errors

1. Change in mental status
2. Abnormal laboratory values (i.e. elevated BUN/Cr, elevated drug level, dropping hematocrit, heme positive stool, positive *Clostridium difficile* culture)
3. A sudden change in patient condition (e.g. new confusion)
4. A new rash or diarrhea
5. A changed MD order or clarified MD order
6. Orders for antidotes (i.e. narcan, benadryl, reversed, mucomyst)
7. An abnormal happenstance
8. A critical incident noted in notes or on flow sheets (i.e. a drop in blood pressure possibly due to furosemide, oxygenation desaturation due to an unordered IV fluid bolus)
9. Time changes on the medication administration record
10. Narcotic orders that are outdated when the problem is caused by a narcotic
11. Late doses
    Regular doses: dose delayed $\geq$6 hours from order to administration
    Stat. Doses: dose delayed >1 hour from order to administration
    (As times are not always recorded, these limits are based on the reviewers' best estimate.)

Table 4 Screening criteria for medication errors in the inpatients and outpatient settings

- Legibility – is the medication order or prescription clear and easy to read?
- Medication name – is it spelled correctly and is this the correct medication based on indication as there are many sound-alike medications available (e.g. Celexa versus Celecoxib, Xanax versus Zanac)
- Medication dose form – is this the appropriate form based on the medication strength, route and frequency (e.g. Procardia versus Procardia XL 30 mg p.o. t.i.d.)
- Route - is this appropriate for the medication form (e.g. SR medication forms should not be crushed)
- Dose – is this an underdose, overdose, omitted dose or not commercially available (e.g. 0.5 mg versus 5 mg)
- Dose unit – is this correct or can it lead to an overdose or an underdose (e.g. mcg versus mg)
- Frequency – is this appropriate based on indication
- Duration of therapy – is this appropriate based on indication
- Number to be dispensed and refill number on outpatient prescriptions – do these coincide with the directions for use and duration of therapy
- Directions/warnings for use – are there any to decrease the likelihood of side-effects (e.g. take erythromycin with food)

required 11 person-hours per week, chart review 55 person-hours/week, and voluntary report 5 person hours/week.

Searching claims or administrative databases for ADEs is much less sensitive than chart review or computerized monitoring, but is also less costly to perform. However events still need to be confirmed, as events found by screening claims data have a positive predictive value of about 50% [23]. In the outpatient setting, one study evaluated the sensitivity of screening with ICD-9 codes for detecting ADEs and found it least sensitive, when compared with using more detailed search rules (looking for allergies, laboratory data, and certain medical terminology) in an electronic medical record [23].

Pharmacy logs of interventions performed represent a valuable source of medication errors and potential ADEs [24,25]. These logs are maintained by pharmacists and track suggestions made to physicians such as dosing adjustments. The success of this process depends on pharmacists' review of orders and their subsequent documentation of errors found and changed, but it represents a very practical, inexpensive method for identifying problems.

Direct observation has also been used to identify medication errors. The disguised-observation technique was developed by Barker and McConnell for the detection of medication errors [26]. An observer accompanies the person giving medications, witnesses the administration of each dose, and compares it with the original physician orders to determine whether there was compliance with the order. This technique requires substantial training of observers and usually can only be done over short periods of time, not on a routine basis. Its major advantage is that it is the most sensitive technique for identifying dosing and administration errors, and many errors can be identified in a short time.

Data suggest that ADEs in the outpatient setting are an important problem as well [1,27–29]. However, in the outpatient setting, far fewer studies of ADEs have been done, due to obvious challenges. In contrast with inpatients,

Table 5 Examples of rules for computerized monitoring

1. Medication triggers
Receiving flumazenil
Receiving charcoal
Receiving naloxone
2. Laboratory triggers (including drug levels)
Serum potassium >6.5 mmol/l
Serum digoxin >1.7 ng/ml
Serum vancomycin >50mg/l
Serum theophylline >20 mcg/ml
3. Medication combination triggers
Receiving benzodiazepine and receiving anti-epileptic
Receiving prednisone and diphenhydramine
4. Medication and laboratory triggers
Receiving nephrotoxin and blood creatinine has risen >0.5 mg/dl in last 24 hours
Receiving ranitidine and platelet count has fallen to less than 50% of the previous value

outpatients are responsible for both obtaining and administering their medications. In addition, the process is much less controlled in terms of dosing, timing, and compliance. Also, physicians have less regular contact with outpatients and are less likely to hear about their problems. Chart review has limitations related to high costs and inadequate documentation. Therefore, most previous studies of outpatients have relied heavily on patient report [27–29], which also has inherent limitations. Dependence on patients' recall during interviews or on responses to questionnaires substantially limits certainty that symptoms are related to a medication [30]. As a result, the standard definition of an ADE that was used in inpatient studies is problematic in the setting of patient-reported side-effects; we have labeled such patient-reported events as drug complications, rather than ADEs [19]. In one study of ADEs in the outpatient setting that compared retrospective chart review to patient survey, 18% of patients reported a problem with a medication on survey. However, on chart review of those same patients, only 3% had documented ADEs [19]. Thus, in this study there was little overlap between patient reported events and events on chart review. Further work needs to be done to determine the best way to identify ADEs and errors that occur in the ambulatory setting, but as in the inpatient setting, multiple techniques will probably be necessary.

Methods of error classification

Once identified, incidents can be classified as medication errors, potential ADEs, ADEs, or none of the above. Our general approach has been to have two physicians independently review the events [2,7]. Kappa statistics have been used to determine the agreement between physician reviewers about the presence of an ADE or potential ADE and these have ranged from 0.81 to 0.98. Second, preventability is assessed on a 4-point scale (definitely preventable, probably preventable, probably not preventable, and definitely not preventable) [31]. Results are then collapsed into preventable and not preventable [2]. Kappa statistics for this assessment have generally been 0.9. The third major classification is for severity of the event. The severity scale we have used is: fatal, life threatening (e.g. hemorrhagic stroke from excess heparin), serious (e.g. gastrointestinal bleed from non-steroidal anti-inflammatory drugs requiring blood transfusion), and significant (e.g. drug rash) [24,25]. Reliability has been lower for this assessment, probably because of the larger number of categories, with kappa values in the range 0.32–0.37 [2]. After classifying events according to event type, preventability, and severity, the reviewers meet and reach a consensus. If no consensus can be reached (very unusual), a third reviewer evaluates the incident.

In routine quality improvement, formal classification of events with two physician reviewers is not necessary. The most practical approach may be classification of type, severity, predictability, and preventability by one person followed by evaluation by a multi-disciplinary drug safety committee. These classifications are especially helpful in prioritizing which events should be focused on and in what priority.

Another classification tool is the Naranjo algorithm, which is a reliable, valid tool for assessing the likelihood that a specific reaction is due to a given drug [32]. This algorithm is a 10-question validated instrument used to determine the likelihood that an event is an adverse drug event. Sample questions include 'Are there previous conclusive reports on this reaction?' and 'Did the adverse reaction reappear when the drug was re-administered?' Points are assigned to each response and the results summed. One to four points is considered a possible ADE, 5–8 probable, and 9 or more definite. The main limitations of the Naranjo algorithm are that it is focused on the likelihood that a drug caused the patient's symptoms, and not whether the patient is actually experiencing an effect related to some medication. In addition, some questions are essentially non-contributory outside of the randomized trial setting (e.g. whether the patient had the effect with a placebo).

Discussion

Translating research into practice

Following better epidemiological data about the magnitude of the problem and a series of highly publicized medication errors with serious patient consequences, hospitals, federal, and state organizations have intensified efforts to prevent patient injuries, particularly those due to medication errors [33]. However, strategies used in research to study ADEs may not be translatable into routine practice because these studies have used many more resources than are routinely available. How can hospitals and practices effectively monitor for these events under normal conditions? Usual approaches include voluntary reporting, stimulated voluntary reporting, computerized screening for ADEs, screening of claims data, direct observation, and convening of focus groups (Table 6).

Changing the culture to promote spontaneous voluntary

Table 6 Recommendations for ADE identification in practice

Approach	Advantages	Disadvantages
Stimulated reporting (particularly by pharmacists)	• Can find potential ADEs as well as ADEs • Inexpensive	• Under-reporting
Computerized monitoring	• More sensitive • Can be done automatically based on rules • Inexpensive	• Requires information system (or electronic medical record) and programming • Number of events that can be found depends on information system links
Claims data screening	• Inexpensive • Doesn't require advanced information systems	• Not as sensitive • Fewer rules can be applied
Direct observation	• Best for finding administrative errors • High yield in short time	• Requires observers • Few ordering errors found • Expensive
Focus group	• Targets major issues • Inexpensive	• Can't be done on a routine basis • Will find major issues but not daily events or trends

reporting is an important first step [34]. Creating a culture of safety is critical to encourage adequate reporting of errors and subsequent systems changes. In addition, the current system of blaming individuals for errors must be changed. Spontaneous voluntary reporting does not occur if health care personnel are concerned about personal consequences. Leape has advocated creating a new culture in health care that moves beyond blaming and punishing individuals when they make mistakes and follows industries like aviation and nuclear power [34]. In these industries, injury prevention is recognized as everyone's responsibility with the joint goal of recognizing errors, addressing systems problems, and preventing future events in a culture of safety.

Facilitating error detection so that it can be done easily and quickly is essential. Stimulated reporting, particularly by pharmacists who enter events into pharmacy logs, can be very useful and cost-effective. Monthly reviews of these logs to look for trends and possible interventions can then be done. Screening for adverse events using computerized monitoring is a relatively low cost method for event identification. This approach can be effective even in hospitals with a limited amount of computerized data, for example computerized pharmacy and laboratory data. If the laboratory and pharmacy data can be linked, the amount of useful screens increases substantially, and computerized monitoring is far better than simply screening claims data. Hospitals could begin, for example, by screening all markedly elevated drug levels on a routine basis. One community teaching hospital was able to develop, implement, and evaluate a computer alert system to detect ADEs and detected opportunities to reduce ADE-related injury at a rate of 64/1000 admissions and estimated that the cost of evaluating the events was the equivalent of one-fourth of a full-time equivalent at their institution [35]. At an academic hospital, comprehensive monitoring would take one full-time equivalent [6]. The Health Care Financing Administration recently proposed a requirement for such monitoring in a set of draft regulations [36]. Also, focus groups and forums for oral communication of events can be useful methods to identify events. These groups should be multi-disciplinary (including physicians, nurses, and pharmacists) and can allow for rapid and easy identification of major issues and themes that need addressing.

All of these identification methods require resources as someone has to review the events found and subsequently decide about system changes. A hospital's portfolio should generally include several of these approaches. For example, one approach would be to use spontaneous reporting by pharmacists, computerized monitoring on an ongoing basis, and periodic focus groups. Most hospitals should have at least one full-time equivalent devoted to this issue (generally a pharmacist).

As errors accumulate that either have potential to cause an injury or have done so, actions must occur to address the problem. A critical issue is having the administrative and management support to provide resources to be able to make the changes necessary. A multi-disciplinary group (often the medication safety subcommittee of the Pharmacy and Therapeutics committee) including physicians, nurses, and pharmacists can evaluate data on medication errors and ADEs and best decide what can be done to solve the problems [5]. This group needs the power and resources to create change. In hospitals that have been most successful in improving their systems, a key leader has been charged with the issue, usually the pharmacy director. It is not practical to react to

each error, but if patterns are identified, the systems involved can be changed.

Implementation of advanced systems to prevent errors, such as physician order entry or bar coding of medications, is another method by which hospital systems can address and prevent ADEs. While such systems require initial investment, they can result in quantum improvements in reducing medication errors, ultimately saving money. One study demonstrated that physician order entry decreased the rate of serious medication errors by 55% [21], and another showed that the rate of all medication errors fell 81% with such a system [37]. Other systems such as implementation of bar coding also have great potential [38].

Thus, the research methods of identifying and classifying medication errors, potential ADEs, and ADEs have to be adapted for use in routine practice. However, such adaptation is feasible. Currently most hospitals and virtually all outpatient systems have inadequate approaches for measuring, on a routine basis, the quality of their medication use process. The result has been a 'hidden epidemic' of error in the medication process. However, the tools are now available to allow organizations to monitor and improve their systems in an ongoing way, which has the potential to result in substantial improvements in drug safety.

References

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *J Am Med Assoc* 1998; **279:** 1200–1205.
2. Bates DW, Cullen D, Laird N *et al.* Incidence of adverse drug events and potential adverse drug events: implications for prevention. *J Am Med Assoc* 1995; **274:** 29–34.
3. Classen DC, Pestotnik SL, Evans RS *et al.* Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. *J Am Med Assoc* 1997; **277:** 301–306.
4. Bates DW, Spell N, Cullen DJ *et al.* The costs of adverse drug events in hospitalized patients. *J Am Med Assoc* 1997; **227:** 307–311.
5. Leape LL, Bates DW, Cullen DJ *et al.* Systems analysis of adverse drug events. *J Am Med Assoc* 1995; **274:** 35–43.
6. Jha AK, Kuperman GJ, Teich JM *et al.* Identifying adverse drug events: development of a computer-based monitor and comparison to chart review and stimulated voluntary report. *J Am Med Inform Assoc* 1998; **5**(3)**:** 305–314.
7. Bates DW, Boyle DL, Vander Vliet MB *et al.* Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995; **10:** 199–205.
8. Bates DW. How worried should we be? *J Am Med Assoc* 1998; **279:** 1216–1217.
9. Faich GA. National adverse drug reaction reporting 1984–1989. *Arch Intern Med* 1991; **151:** 1645–1647.
10. Berry LL, Segal R, Sherrin TP, Fudge KA. Sensitivity and specificity of three methods of detecting adverse drug reactions. *Am J Hosp Pharm* 1988; **45:** 1534–1539.
11. Rogers AS, Israel E, Smith CR *et al.* Physician knowledge, attitudes, and behavior related to reporting adverse drug events. *Arch Intern Med* 1988; **148:** 1596–1600.
12. Keith MR, Bellanger-McCleery RA, Fuchs JE, Jr. Multidisciplinary program for detecting and evaluating adverse drug reactions. *Am J Hosp Pharm* 1989; **46:** 1809–1812.
13. Schiff GD. Using a computerized discharge summary data base check for adverse drug reaction monitoring. *Qual Rev Bull* 1990; **15**(4)**:** 149–155.
14. Kessler DA. Introducing MEDWatch. A new approach to reporting medication and device adverse effects and product problems. *J Am Med Assoc* 1993; **269:** 2765–2768.
15. Cullen DJ, Bates DW, Small SD *et al.* The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Joint Comm J Qual Improv* 1995; **21:** 541–548.
16. O'Neil AC, Petersen LA, Cook EF *et al.* Physician reporting compared with medical-record review to identify adverse medical events. *Ann Intern Med* 1993; **119:** 370–376.
17. Bates DW, Makary MA, Teich JM *et al.* Asking residents about adverse events in a computer dialogue: How accurate are they? *Joint Comm J Qual Improv* 1998; **24:** 197–202.
18. Weingart SN. *Identifying 'barriers to care': confidential clinician-reported surveillance of adverse events among medical and surgical inpatients.* National Patient Safety Foundation, 1999: pp. 292–296.
19. Gandhi TK, Bates DW, Burstin HR *et al.* Drug complications in outpatients. *J Gen Intern Med* 2000; in press.
20. Sanazaro PJ, Mills DH. A critique of the use of generic screening in quality assessment. *J Am Med Assoc* 1991; **265:** 1977–1981.
21. Bates DW, Leape LL, Cullen DJ *et al.* Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *J Am Med Assoc* 1998; **280:** 1311–1316.
22. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. *J Am Med Assoc* 1991; **266:** 2847–2851.
23. Honigman B, Bates DW, Light P. Computerized data mining for adverse drug events in an outpatient setting. *Proc AMIA Annu Fall Symp* 1998; 1018 (abstract).
24. Lesar TS, Briceland LL, Delcoure K *et al.* Medication prescribing errors in a teaching hospital. *J Am Med Assoc* 1990; **263:** 2329–2334.
25. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics* 1987; **79:** 718–722.
26. Allan EL, Barker KN. Fundamentals of medication error research. *Am J Hosp Pharm* 1990; **47:** 555–571.
27. Chrischilles EA, Segar ET, Wallace RB. Self-reported adverse drug reactions and related resource use. A study of community-dwelling persons 65 years of age and older. *Ann Intern Med* 1992; **117:** 634–640.
28. Hanlon JT, Schmader KE, Koronkowski MJ, *et al.* Adverse drug events in high risk older outpatients. *JAGS* 1997; **45:** 945–948.
29. Hutchinson TA, Flegel KM, Kramer MS *et al.* Frequency, severity

and risk factors for adverse drug reactions in adult outpatients: a prospective study. *J Clin Epidemiol* 1986; **39:** 533–542.

30. Jones JK. Assessing potential risk of drugs: the elusive target. *Ann Intern Med* 1992; **117:** 691–692.

31. Dubois RW, Brook RH. Preventable deaths: Who, how often, and why. *Ann Intern Med* 1988; **190:** 582–589.

32. Naranjo CA, Busto U, Sellers EM *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; **30:** 239–245.

33. Leape LL. Promoting patient safety by preventing medical error. *J Am Med Assoc* 1998; **280:** 1444–1447.

34. Leape LL. Error in medicine. *J Am Med Assoc* 1994; **272:** 1851–1857.

35. Raschke RA, Golihare B, Wunderlich TA *et al.* A computer alert system to prevent injury from adverse drug events. Development and evaluation in a community hospital. *J Am Med Assoc* 1998; **280:** 1317–1320.

36. Health Care Financing Administration. Medicare and Medicaid Programs; hospital conditions of participation; provider agreements and supplier approval. *Federal Register* 1997; **62:** 66726–66757.

37. Bates DW, Teich J, Lee J *et al.* The impact of computerized physician order entry on medication error prevention. *J Am Med Info Assoc* 1999; (in press).

38. Bates DW. Medication errors. How common are they and what can be done to prevent them? *Drug Safety* 1996; **5:** 303–310.

Accepted for publication 16 November 1999