During recent years, a sizeable number of drugs have been withdrawn from the market because of their harmful side effects.¹⁻⁷ Reasons most frequently cited were adverse events of the hepatic, hematologic, and cardiovascular systems. In three high profile withdrawals in 2000, cisapride (Propulsid), a chronic heartburn drug approved in 1993; troglitazone (Rezulin), a diabetes drug approved in 1997; and Lotronex, a treatment for irritable bowel syndrome, were pulled from the market because of serious side effects. In each case, new knowledge about its side effects altered the risk/benefit ratio, rendering making further prescription unacceptable. Not only have some drugs been withdrawn, but others have been required to add special warnings to their labels because of new information about side effects not identified during preapproval clinical trials.⁸⁻⁹ Table 1 lists drugs withdrawn in the United States during the 1990s.

To understand one possible reason that a recently approved drug may emerge as unsafe, one must understand the way drug safety profiles are developed. Animal studies begin the process. Next, during human clinical studies (Phase 1 through Phase 3), researchers collect data on adverse events experienced by subjects enrolled in the studies at investigational sites—academic medical centers, hospitals, research centers, private practice clinics. Clinical data for the research subjects is recorded in medical records, then transferred from those source documents to case report forms (CRFs). Adverse events are included in that data. Adverse events from all the clinical sites involved in a study are entered into a database and then summarized into frequency distributions by body system and study drug (active drug versus comparative drug). Those frequency distributions become drug safety profiles of known side effects. Of particular interest are serious adverse events (SAEs), that is, events that result in death, hospitalization, or prolonged hospitalization; are life threatening; or cause permanent disability. Special care, as discussed later, must be exercised in recording and reporting SAEs. Particularly close attention is paid to analyzing SAEs.

Problems in the construction of drug safety profiles occur when adverse event data are incompletely or inaccurately captured during premarketing clinical studies. Risk/benefit ratios developed from clinical studies may be inaccurate because the adverse event data are faulty and regulatory reviewers are presented with risk/benefit ratios that later, during postmarketing, dramatically change. The objectives of this article are to • describe the kinds of inaccuracies that occur in collecting adverse event data • discuss the regulatory and legal implications of these inaccurate data • identify ways in which drug safety data collection can be improved at clinical sites.

We begin with a brief overview of adverse event data and their collection during clinical studies. Next, we identify the good clinical practice (GCP) standards and guidelines that apply to the collection and documentation of the data—focusing on the “best practices” that
should occur at clinical sites. Then we identify the kinds of errors and omissions we have observed in adverse event identification and documentation. This discussion, which includes examples, is followed by a review of the regulatory and legal problems that result from these errors and omissions in drug safety data. We conclude with a discussion about improving investigational site performance.

Clinical trials and adverse events
During a clinical trial, some subjects experience at least one adverse event while on study. The events may occur at home or at a health care facility; they may be identified while the subjects are inpatients or reported during an outpatient visit. An event may be readily noticed by care providers, subjects themselves, or relatives; sometimes only a laboratory or diagnostic test uncovers the event. An event may last for less than a minute, could be permanently disabling, or may result in death. Events that occur before a subject has completed the informed consent process or after a subject is off study are not usually considered recordable adverse events.

The process for documenting an AE at a clinical site is shown in Figure 1. The event is almost always first captured in the medical record. If it is a serious one, it is reported to the sponsor and the institutional review board (IRB) immediately after it becomes known. Most events are of short duration and are not serious. Serious events must be followed up even after a subject is off study, until the event stops or is determined to be a permanent condition.

Adverse events may, or may not, be related to or caused by the drug under study. Many other possible causes of an event include other drugs, progression or relapse of the underlying disease being tested, an intercurrent disease, care provider error, noncompliance with treatment regimens, and laboratory and equipment malfunctions that create false-positive test results. If a subject is hit by a bus while on study and is injured, it’s an adverse event. If a subject with multiple sclerosis becomes depressed while on study, the depression is an adverse event.

Adverse events can occur as singular events or in clusters or series of related events, sometimes described as a syndrome such as flu-like symptoms. “Splitters” are those clinicians who prefer to record each event separately, while “lumpers” are those clinicians who prefer to record one syndrome to cover the cluster of events.

GCP standards and guidelines
Good clinical practice (GCP) is the global term used throughout the drug development industry to denote appropriate processes and procedures to be followed when conducting clinical studies involving humans. The following general GCP principles regarding AEs apply:

- Before being enrolled as a subject, the patient should be given information about known risks and side effects of the study drug and study procedures.
- If new information about these risks becomes available during the study, subjects on study should be notified of this information.
- All AEs should be recorded on medical records and on case report forms; all signs, symptoms, and pertinent clinical information should be captured.
- AEs must be rigorously followed up to determine their outcome.
- Principal investigators (PIs), although usually blinded as to treatment arm, must make a clinical determination as to whether or not the test article was causally related to the adverse event; this determination must be the PI’s independent opinion and cannot be altered without the PI’s concurrence.
- The PI has a duty to warn the study’s medical monitor about medically unusual adverse events.
- SAE reports must be timely, factually accurate, and consistent with medical

| TABLE 1  Products withdrawn from U.S. market, 1990–1999a |
|-------------------|-----------------|-------|-------------|
| Generic name      | Class or use    | Year  | Reason      |
| astemizole        | antihistamine   | 1999  | drug interaction |
| bromfenac         | NSAID           | 1998  | hepatic failure; off-label abuse |
| chlorzemanone     | muscle relaxant-central acting | 1996 | hepatotoxicity, Steven-Johnson syndrome, toxic epidermal necrolysis |
| encaidine         | anti-arrhythmic | 1991  | cardiototoxicity and excess mortality |
| fenfluramine      | anorexiant-sympathomimetic | 1997 | cardiac valvular disease |
| flosequinar       | vasodilator     | 1993  | increased mortality |
| grepafloxacin     | quinolone anti-infective | 1999 | cardiovascular reaction |
| mibefradil        | calcium channel blocker | 1998 | drug interactions |
| temafloxacin      | quinolone anti-infective | 1992 | hypoglycemia, hemolytic anemia, renal failure |
| terfenadine       | antihistamine   | 1997  | drug interactions and cardiovascular toxicity |
| tetravalent rhesus-human reassortant rotavirus vaccine | rotavirus vaccine | 1998 | intussusception |

Documentation of an adverse event at a clinical site.

Frequently observed problems in the field—“the devil is in the details”

Clinical auditors discover a myriad of problems with the recording and reporting of AEs and SAEs—from the absence of any documentation that an event even occurred to inaccurate, inadequate, and missing records, among an assortment of other problems.

PIs often delegate to other physicians and to investigational site study coordinators—who could be nurses, medical technicians, or lesser clinically trained staff—the responsibility of identifying AEs from their review of subjects’ source documents. These include medical records, study diaries, and other notes designed to capture firsthand observations of a subject’s clinical course while on study. AEs identified in this review are then supposed to be recorded on the subjects’ case report forms (CRFs). Unless a thorough review of all available source documentation is performed, AEs will be missed. Site staff may spend insufficient time conducting the review or may be ill equipped to perform the review satisfactorily because of lack of experience and/or training. At times, site staff members may consider an AE too inconsequential to be recorded on the CRF.

AEs that are recorded may not be accurately or adequately documented, and the events may not be followed up. Subjects in a clinical study have the responsibility to notify the study coordinator and/or the PI when they experience an AE. This becomes more important, of course, when the study is conducted on an outpatient basis and the site is relying, in part, on telephone contact reports and diaries that subjects maintain about their compliance with the treatment regimen and AEs. Subjects, however, are not always forthcoming in reporting AEs for a variety of reasons, including underestimation of the significance of the event, forgetfulness, or the belief that they might be dismissed from the study.

Problems with SAEs, on the other hand, pose a more serious risk to the soundness of the study and, more importantly, to the safety of the subject and ultimately the general public.

Sites must immediately report all SAEs to their IRBs and to the study sponsor. This does not always happen. As with AEs, sometimes SAEs are not even identified for the same reasons described previously. When they are, the reports are sometimes incomplete and/or inaccurate.

Two types of SAE reports should be completed, an initial report and a follow-up report. These reports should fully document what is known at the time of reporting about the event, the subject’s clinical course preceding the event, and the subject’s clinical status. SAEs can be underreported. That is, the less serious components or sequelae of a subject’s clinical condition may be described instead of the more serious. For example, a subject may have had pulmonary edema, yet the report notes only “shortness of breath.”

Data on SAE reports sometimes do not match those on the CRF and/or the medical record. For example, start and stop dates may be inconsistent and concomitant therapies may be missing or don’t match.

At times a subject may experience an SAE within an SAE, and the second SAE is frequently overlooked and not reported. In one case, a subject was hospitalized for an emergency laparotomy for an obstructed bowel; he then had a heart attack post-op. Therefore, the subject experienced a second SAE (unreported heart attack) while being treated for the first SAE (obstructed bowel).

Figure 2 displays examples of several problems associated with SAE reporting (they are highlighted in bold in the bottom half of the form). Subject #0333 was in a study for treatment of peripheral vascular disease (PVD). After the first treatment, the subject was found to have an absent right popliteal pulse (8 September 1999). This event was not reported as an SAE on the SAE report or on the CRF.

On 4 October 1999 the subject was hospitalized for an aortogram to evaluate the popliteal pulse problem, but the procedure was postponed because of the subject’s abnormal lab values. No notation of this was made on the SAE report. These abnormal values should have been reported as another SAE because this event extended the subject’s hospital stay. On 20 October 1999 the subject’s sister called the site to say that the subject had moved to another city, was hospitalized there, sent to a nursing home, and later placed in hospice care.

On 25 November 1999 the subject’s sister called again to say that the subject died of renal failure. The site did not report this SAE.

Other general problems with SAE
Peripheral vascular disease (PVD) pharmaceuticals site audit timeline (all identifiers have been changed for this illustrative example).

**Figure 2.** Peripheral vascular disease (PVD) pharmaceuticals site audit timeline (all identifiers have been changed for this illustrative example).

Reporting include cases where the follow-up SAE report does not provide evidence that the subject was sufficiently followed through termination of the event or for a sufficient period of time if the event was ongoing. These reports, too, have problems with inconsistencies within the report and/or with the initial report, the CRF, and the medical records.

No one, including those who frequently review study records at clinical sites, can determine the overall frequency or severity of these problems. In audits of over 200 clinical sites in the United States, Europe, United Kingdom, Australia, and South Africa, however, we observed a sufficient number of identification and documentation issues with adverse events to suggest that some drug safety profiles may have been compromised.

**Regulatory and legal implications**

Increasingly, alleged failures to conduct clinical trial according to GCP are the subject of both FDA regulatory actions and private lawsuits. This reflects greater attention to drug safety issues in the wake of the numerous postapproval drug withdrawals previously mentioned. It also reflects other recent events and reports that have spotlighted clinical trial conduct, including investigator conflicts of interest, questionable subject recruitment practices, informed consent abuses, IRB shortcomings, increasing regulatory emphasis on AE reporting, and high-profile research problems such as occurred recently in the gene therapy area. The following examples demonstrate the trend toward GCP failures precipitating private lawsuits as well as regulatory actions.

**FIAU trials.** The 1993 deaths of five people in Eli Lilly and Company’s clinical trials of fialuridine (FIAU) for hepatitis B sparked several unprecedented lawsuits that began to erode the longstanding practical immunity from such suits by medical researchers. This marked the beginning of the application of product liability and medical malpractice principles to the clinical trial arena. Key in the case was whether researchers missed early signals of toxicity, including several deaths, especially since some of the subjects who died had begun the trial in good health and were asymptomatic. The adequacy of the underlying animal trials was also challenged. In this case, the researchers were ultimately exonerated by a special NIH committee, based in large part upon their having had complete records and proper clinical monitoring.

**“Fen-Phen” litigation.** Private plaintiffs, FDA, and the FBI were separately involved in probes of American Home Products Corporation (AHP) and whether it properly handled SAE-related study information for Redux (dextfenfluramine, an improved version of Pondimin, which was part of the fen-phen diet drug cocktail). AHP ultimately agreed to pay $3.75 billion to settle the majority of the fen-phen lawsuits, which
had precipitated a serious decline in the value of the company.13

University of Pennsylvania Gene Therapy Program litigation. The recent and highly publicized problems at the University of Pennsylvania's Institute for Human Gene Therapy included the death of a reasonably healthy 18-year-old volunteer. His death was attributed to the study treatment. Concerns were magnified by revelations of the sponsor's failure to inform FDA of fatal reactions in prior animal studies, and violations of inclusion criteria and other requirements. These included failure to observe the study's pre-agreed toxicity-based "stopping rule." The violations generated a 15-page FDA warning letter to the institution, halted its gene therapy program, and derailed the career of a prominent scientist because of FDA's effort to disqualify him as a clinical investigator. It also resulted in a lawsuit against the University of Pennsylvania, the researcher, the ethics consultant, and others and caused NIH and FDA to reevaluate clinical research oversight from the ground up.14,15

University of Oklahoma litigation. Another recent example of civil lawsuits related to GCP issues is an action filed by former study subjects (and the estates of several now-deceased former study subjects) against the University of Oklahoma Health Sciences Center. The lawsuit alleges that the animal studies serving as a basis for the human trial were inadequate, that this was hidden from regulators and study subjects, that the study drug was improperly manufactured and controlled, that informed consent procedures were improper, that documentation lacked rigor, that unauthorized study protocol changes were made, and that relevant information was not reported to the IRB and FDA.

As an example of the breadth such lawsuits now encompass, in this case the plaintiffs charge practically every person and entity with any connection to the study—the principal investigator, IRB members, high-level university officials, the Medical Center itself, several other cancer centers cosponsoring the study, and the drug sponsor. The array of charges is also exhaustive. These include breach of the right to be treated with dignity, violation of FDA and DHHS regulations, civil rights violations, fraud on the FDA, intentional and negligent infliction of emotional distress, negligence, common law fraud/intentional misrepresentation, assault and battery, lack of informed consent, strict products liability, and punitive damages.16

Fred Hutchinson Cancer Center litigation. Even the prestigious Fred Hutchinson Cancer Research Center has recently become the subject of a class action lawsuit amid allegations of having failed to properly warn subjects of research risks and potential financial conflicts of interest related to the study drugs. The increase in research risks allegedly should have become apparent to those conducting and monitoring the trial during its course, in part due to the AEs that occurred.17 This research center is the world's leading bone marrow transplant center, a leading stem-cell transplant center, and the nation's leading grant recipient of National Cancer Institute funds.

These examples are by no means exhaustive. Today, no research institution or clinical trial is immune from potentially intense scrutiny of its GCP compliance. Even when a study seemingly goes well, later problems with the drug can easily trigger a full retrospective GCP review. FDA, especially in the wake of the gene therapy problems, has increased its emphasis on AE reporting and the coordination of such reports with NIH.18

For all clinical studies, FDA conducts on-site inspections and data audits to ensure proper study conduct and reporting through the agency's Bioresearch Monitoring Inspections (BIMO) Program.19 FDA has noted that protocol violations, inadequate record keeping, and AE investigation and reporting are among its top concerns with clinical investigators. Serious or repeated infractions can result in clinical trial participation restrictions or disqualification, consent decrees, and prosecutions. IRBs and research sites also undergo inspection and potential FDA sanctions. Serious GCP problems can also jeopardize funding from NIH and other sources.

As the cited examples demonstrate, GCP problems identified by government regulators often become public. Such problems can also foster private lawsuits. This is due to the substantial overlap of common standards—whether the study was conducted with diligence and was protective of subject rights and safety. Proper identification, follow-up, and reporting of AEs to sponsors and IRBs are essential in such an analysis. Rigorous oversight monitoring helps to ensure that these principles are observed. Failure to take and document these steps risks lawsuits from study subjects and whistleblowers, regulatory problems (including product approval and enforcement actions), and significant damage to a company's reputation and financial capitalization.

Improving the quality of clinical trials
Three major players in the clinical trials arena can improve the quality of drug safety data at clinical sites—principal investigators, monitors, and sponsors' clinical management.

The "captain of the ship"—principal investigators. All data errors and omissions are the PI's responsibility. Although the PI may delegate study tasks and a subinvestigator or study coordinator may be the root cause of unreported AEs, the PI is responsible, and should periodically check this work to ensure that problems identified above do not occur or do not continue. Should the FDA inspect a site and find problems with AE collection and description, the PI is the person who receives the Form 483 citation and possibly a warning letter. PIs must also make sure that AEs are followed up, that appropriate care is rendered, and that study drug and even subject study participation be stopped in order to prevent further harm or jeopardy to the subject. Frequently, PIs—incorrectly—tell us that the only AEs they believe should be recorded on CRFs are those attributable to the study drug. Failure to exercise timely and appropriate clinical judgment about adverse events or...
to report them in a timely manner jeopardizes the subject’s health, the quality of the drug’s safety profile, and the health of future patients once the drug is approved.

Monitors. Site monitoring of a clinical study is an FDA requirement. This is one way that the study sponsor demonstrates that the study is well controlled. Monitoring is typically performed by clinical research associates (CRAs) on behalf of the sponsor company. It is one of several first-line prevention mechanisms for detecting data discrepancies and for identifying regulatory problems in a clinical trial. 20

When data discrepancies are later identified after a study is completed, it is often the CRA who takes most of the blame. Monitoring is a difficult job, requiring patience, close attention to detail, and perseverance in following up on unresolved issues. In almost all cases, monitors are required to perform 100% source data verification of CRF data. Such verification is labor intensive, and data discrepancies, including AEs and their sequelae, can easily be missed in light of the usual “pressure-cooker” atmosphere in which monitors routinely perform their work.

Notwithstanding these constraints, monitors—by virtue of accepting their professional role—must be vigilant in their work processes to ensure as much error-free data collection as possible. They need to take great care in performing source data verification to eliminate collection of discrepant data.

During their site visits, monitors must request and review all available source documentation, including all volumes of hospital records, in order to conduct thorough source data verification. Study coordinators often tell auditors that site monitors do not routinely review medical records, relying only on study notes compiled by site staff. AEs and SAEs are frequently “buried” in the medical records and therefore, unless records are thoroughly reviewed, the AEs are not recorded. Monitors must be assertive in discussing safety issues and problems with the PIs, study coordinators, and the sponsor’s medical monitor. When site staff members write narrative descriptions of SAEs, the monitor needs to be involved in reviewing the information for clarity and accuracy.

Finally, monitors should take full advantage of all training opportunities provided. They must be thoroughly familiar with the protocol requirements and should have an understanding of the disease or clinical condition being studied. They should attend in-service training and outside professional conferences as frequently as possible.

Sponsors. Drug manufacturers, as the sponsors of clinical trials, have a responsibility for improving the quality of monitoring. First, they should encourage more qualified individuals to become CRAs. In recent years there has been a huge increase in demand for clinical monitors; job attrition rates have increased as well. This has led to hiring recent college graduates with marginal clinical or research skills.

Clinical management must provide monitors, especially inexperienced ones, with the training and skills necessary to perform competently, preferably with a mentoring or co-monitoring system for a sufficient period of time. In-service training, and outside training through conferences and workshops, should be provided systematically in areas such as negotiation skills and competency-based training. Management should attempt to mitigate the pressure-cooker atmosphere wherever possible. There needs to be a balance between speed of enrollment, GCP compliance, and a work environment for monitors that encourages excellence. More competitive salaries and benefits could also help sponsors attract and retain qualified staff.

The quality of study data could also be improved by conducting GCP audits. Monitors perform a quality control function for a study, and auditors perform quality assurance. The auditor takes a perspective different from that of a monitor in reviewing and evaluating study data, thus providing a second look with “different eyes.”

PIs often tell auditors that the only “training” they received about a study was at the general investigator’s meeting provided by the sponsor prior to initiation of the study. Usually this is insufficient. Staff need to be fully conversant with the sponsor’s expectations regarding capturing and recording of AEs. Almost always, questions and issues arise as soon as a study is initiated.

An investigative site staff’s competence to conduct a study satisfactorily involves a dynamic process. Mistakes and misunderstandings need to be identified and corrected early and throughout the study to ensure timely enrollment of evaluable subjects and quality data. It would be helpful if site staff were trained on how to complete an SAE report by providing them with illustrative examples. Sponsors must consistently reinforce the crucial requirement that the quality of safety data is just as important as the quality of efficacy data. Investigators take on this public health responsibility when they agree to conduct an investigational drug, device, or diagnostic study.

Improved recording and reporting of adverse events will lead to improved drug safety profiles and fewer approvals of unsafe drugs. Other drug safety improvements include longer on-study time periods for subjects, more rigorous analysis of AEs for subtle trends and hidden signals, a better understanding of the sample sizes needed to detect the precursors of side effects that occur only rarely, and more research about the effects of differing populations and compliance between pre- and postmarketing consumers.

Three major players in the clinical trials arena are capable of improving the quality of drug safety data at clinical sites—principal investigators, monitors, and sponsors’ clinical management.

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