12 Adverse Event Detection, Processing, and Reporting

1. Introduction

Registries that collect information on specific drugs and medical devices need to anticipate the need for adverse event (AE) detection, processing, and reporting. This chapter addresses the identification, processing, and reporting of AEs detected in situations in which a registry has contact with individual patients. This document is not a formal regulatory or legal document; therefore, any information or suggestions presented herein do not supersede, replace, or otherwise interpret Federal guidance documents that touch on these subjects. Registry sponsors are encouraged to discuss plans for AE collection and processing with local health authorities when planning a registry.

This chapter primarily focuses on AEs related to pharmaceutical products. Medical devices are significantly different from pharmaceutical products in the manner in which AEs and product problems (complaints) present themselves, in the etiology of their occurrence, and in the regulation governing the defining and reporting of these occurrences, as well as postapproval study requirements. Other sources provide more information about defining and reporting device-related AEs and product problems, and about postmarketing studies (including those involving registries).[1-3]

2. Identifying and Reporting Adverse Drug Events

The U.S. Food and Drug Administration (FDA) defines an adverse drug experience as any AE associated with the use of a drug in humans, whether or not considered drug related,[4] while the International Conference on Harmonisation (ICH) guideline ICH E2A similarly defines an AE as an untoward medical occurrence in a patient administered a pharmaceutical product, whether or not the occurrence is related to or considered to have a causal relationship with the treatment.[5]

For marketed products regulated by FDA, AEs are categorized for reporting purposes according to the seriousness and expectedness of the event (i.e., whether the event was previously observed and included in local product labeling), as it is presumed that all spontaneously reported events are potentially related to the product for the purposes of FDA reporting. Prior to marketing approval, relatedness is an additional determinant for reporting events occurring during clinical trials or preclinical studies associated with investigational new drugs and biologics. For AEs occurring in postapproval studies and reported during planned contacts and active solicitation of information from patients, as when registries collect data regarding one or more FDA-approved products,[6, 7] the requirements for mandatory reporting also include whether there is a reasonable possibility that the drug caused the adverse experience.[4] For registries that do not actively solicit AEs, incidentally reported events (e.g., those reported during clinician or consumer contact for another purpose) should typically be handled and evaluated as spontaneously reported events.

The medical device reporting regulations differ from those for drugs and biologics in that reportable events include both AEs and problems with the device itself.[8] Medical device reporting is required for incidents in which the device may have caused or contributed to a death or serious injury, or may have malfunctioned and would likely cause or contribute to death or serious injury if the malfunction were to recur.[9]

Most registries have the opportunity to identify and capture information on AEs for biopharmaceutical products and/or medical devices. With the passing of the FDA Amendments Act in September 2007 and the increased emphasis on ongoing monitoring of safety profiles, evaluation of risks unknown at the time of product approval, and proactive detection of potential safety issues, registries increasingly continue to be used to fulfill safety-related objectives.[10] Although no

regulations in the United States specifically compel registries to capture and process AE reports (aside from reporting requirements for registries that are sponsored by regulated industries), there is an implicit requirement from the perspective of systematic data collection and promoting public health: any individual who believes a serious risk may be associated with exposure to a medical product should be encouraged to report this AE either to the product sponsor or directly to FDA. The FDA maintains MedWatch*, a Web-based reporting system that allows consumers and health professionals to voluntarily report serious adverse events and other serious problems that they suspect are associated with the use of an FDA-regulated product.[11]

*Note: Adverse events which are potentially vaccine-related should be reported to VAERS.

The minimum dataset required to consider information as a reportable AE is indeed minimal, namely (1) an identifiable patient, (2) an identifiable reporter, (3) product exposure, and (4) an event. However, in addition to direct data collection, AEs can be detected through retrospective analysis of a population database, where direct patient or health care provider contact does not occur. Patient interactions include clinical interactions and data collection by phone, Internet, or other means; perusal of electronic medical records or insurance claims data would not be considered direct patient interaction. Reporting is rarely required for individual AEs observed in aggregate population data, since there is no direct patient interaction where an association might be suggested or inferred. Nevertheless, if aggregate or epidemiologic analyses suggest that an AE is associated with exposure to a drug or medical product, it is desirable that the minimum dataset information be forwarded to the manufacturer of the product, who will determine any need for, and timing of, reporting of study results to the relevant regulatory authorities.

Figure 12–1 provides a broad overview of the reporting requirements for AEs and shows how the reporting differs according to whether the registry has direct patient interaction, and whether it receives sponsorship and/or financial support from a regulated industry.[12] These industries may include entities with products subject to FDA regulation, including products with FDA approval, an FDA-granted license, and investigational products; and other entities such as manufacturers, user facilities, and distributors.

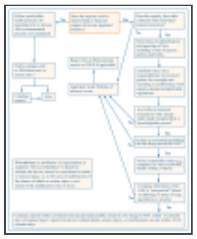

Figure 12–1

Best practices for adverse event reporting to FDA by registries of postmarket products. AE = adverse event; SAE = serious adverse event; FDA = U.S. Food and Drug Administration; PSUR = periodic safety update report.

All AE reporting begins with a suspicion by the physician (or responsible person who obtains or receives information) that a patient exposed to a medicinal product has experienced some AE and that the event has a reasonable possibility of being causally related to the product being used; this is referred to as the "becoming aware" principle. Some registries also collect and record AEs reported directly by the patients or their caregivers. It is important to develop a plan for detecting, processing, and reporting AEs for any registry that has direct patient contact. If the registry receives sponsorship in whole or part from a regulated industry (for drugs or devices), the sponsor has mandated reporting requirements, including stringent timelines. AE reporting requirements for registry sponsors are discussed later in this chapter.

Prior to registry launch, the process for detecting and reporting AEs should be established in collaboration with the sponsor and any oversight committees. (See Chapter 2.) Once the plans have been developed, the registry operator or sponsor should provide training to the physicians or other responsible parties (referred to as "sites" hereafter) on how to identify AEs and to whom they should be reported. AE reporting is based on categorization of the AE according to the seriousness of the event,

its expectedness based on product labeling, and presumed causality or possible association with use of the product, as follows:

- *Seriousness*: Serious AEs (SAEs) include events that result in death, are life threatening (an event in which the patient was at risk of death at the time of the event), require or prolong inpatient hospitalization, result in persistent or significant disability or incapacity, or result in a congenital anomaly. Important medical events may also be considered serious when, based on medical judgment, they may jeopardize the person exposed and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., death or prolonged hospitalization).
- *Expectedness*: All AEs that are previously unobserved or undocumented are referred to as "unexpected," in that their nature and severity are not consistent with information provided in the relevant product information (e.g., approved professional package insert or product label). Determination of expectedness is made by the sponsor on a case-by-case basis. Expected events typically do not require expedited reporting to the regulatory authorities.
- *Relatedness*: Relatedness is a term intended to indicate that a determination has been made that the event had a reasonable possibility of being related to exposure to the product. This assessment of causality may be based on factors such as biological plausibility, prior experience with the product, and temporal relationship between product exposure and onset of the event, as well as dechallenge (discontinuation of the product to determine if the AE resolves) and rechallenge (reintroduction of the product to determine if the AE recurs). Many terms and scales are used to describe the degree of causality, including terms such as certainly, definitely, probably, possibly, or likely related or not related, but there is no standard nomenclature.[13] All spontaneous reports have an implied causal relationship as per regulatory guidance, regardless of the reporter's assessment.

The registry may use forms such as a structured questionnaire or an AE case report form to collect the information from providers or patients. When solicitation of AEs is not prespecified in the registry's operating plans, the registry may permit AE detection by asking general questions to solicit events, such as "Have you had any problems since your last visit or since we last spoke?" and then following up any such reports with probes as to what happened, diagnoses, and other documentation. This practice is not required.

3. Collecting AE Data in a Registry

There are two key considerations regarding AE collection as part of a registry: (1) what data need to be collected to meet the registry's safety-related objectives, and (2) what processes need to be in place to ensure that the registry is in compliance with regulations regarding expedited and periodic AE event reporting, if applicable. The data fields needed for the purpose of analysis by the registry may be minimal (e.g., event and onset date), whereas a complete SAE form for a subset of events reported to the registry may be sought to fulfill the sponsor's reporting requirements. Due to the nature of registries, the goal of collecting enough data to meet the registry's objectives must constantly be balanced with the burden on sites. To this end, the processes for AE reporting should be streamlined as much as possible.

The collection of AE data by a registry is generally either intentionally solicited (meaning that the data are part of the uniform collection of information in the registry) or unsolicited (meaning that the AE information is volunteered or noted in an unsolicited manner and not as a required data element through a case report form). As described further below, it is good practice for a registry to specify when and how AE information (and any other events of special interest) should and should not be solicited from patients by a site and, if that information has been obtained, how and when the site should inform the appropriate persons.

While an AE may be reported to the manufacturer, to FDA (e.g., via MedWatch), or to the registry itself (and then from the registry to the manufacturer), it is strongly encouraged that the protocol describe the procedures that should be followed, and that the sites be trained in these procedures as well as in their general obligations and the relevant public health considerations. A separate safety reporting plan that fully identifies the responsible parties and describes the operational considerations may also be considered to ensure that potentially reportable information is evaluated in an appropriate timeframe, and, for manufacturer-sponsored registries, in accordance with any applicable standard operating procedures. This type of plan also should describe how deviations or systemic failures in detection and reporting processes will be identified, addressed, and considered for corrective action.

Determining whether a registry should use a case report form to collect AEs should be based on the principles described in Chapter 4, which refer to the scientific importance of the information for evaluating the specified outcomes of interest. This may mean that all, some, or no AEs are collected on the case report forms. However, if some AEs are collected in an intentional, solicited manner (e.g., routine collection of a primary or secondary outcome via an AE case report form) and others come to the registry's attention in an unsolicited, "spontaneous" way (e.g., when an AE is reported in the course of a registry contact, such as a call to the sponsor or to registry support staff), then from a practical perspective it is even more important to have a clear process, so that AEs that require reporting are identified. In this scenario, one best practice that is often used in electronic registry studies is to have a notification sent promptly to the sponsor's safety group when a case report form is submitted that contains specific or potential information indicating that a serious AE has occurred. This process allows for rapid followup by the sponsor, as needed.

4. AE Reporting by the Registry

Once suspicion has been aroused that an unexpected serious event has a reasonable possibility of being causally related to a drug, the AE should be reported to FDA through MedWatch, to the company that manufactures the product, or to the registry coordinating center. (See Chapter 11.) A system should be developed such that all appropriate events are captured and duplicate reporting is avoided to the extent possible. Generally, AE reports are submitted directly by the site or by the registry to the manufacturer, since they are often most efficient at evaluating, processing, and reporting for regulatory purposes within the required time periods. Alternatively, sites could be instructed to report AEs directly to FDA according to their normal practices for marketed products; however, this often means that the companies are not notified of the AE and are not able to follow up or evaluate the event in the context of their safety database. In fact, companies are not necessarily notified by FDA if an AE report comes directly to FDA, since only certain reports are shared with industry, and reporters have an option to request that the information not be shared directly with the company.[14] When sites report AEs directly to FDA, this process can also lead to inadvertent duplication of information for events recorded both by the registry and the company.

Systematic collection of all AEs provides a unique resource of consistent and contemporaneously collected comparison information that can be used at a later date to conduct epidemiologic assessments. Ideally, the practice for handling AEs and SAEs should be applied to all treatments (including comparators) recorded in the registry, so that all subjects are treated similarly. In fact, a strong advantage of registries with systematic data collection and internal comparators is that they provide both numerators and denominators for safety events; thus, reporting of comparative known AE rates in the context of a safety evaluation provides valuable information on real-world performance. The contrast with comparators helps promote clarity about whether the observed effects are unique to the product, unique to a class, or common to the condition being treated. Reporting AEs without denominator information is less useful from a surveillance perspective since events rates cannot be calculated without both numerators and denominators. The reliability of the denominator should always be judged, however, by considering the likelihood that all events were reported appropriately.

For postapproval registries not financially supported by pharmaceutical companies, health care providers at registry sites should be instructed that if they suspect or otherwise become aware of a serious AE that has a reasonable possibility of being causally related to a drug or product, they should report the event directly to the product manufacturer (who must then report to FDA under regulation) or to FDA's MedWatch program (or local health authority if the study is conducted outside of the United States). Reporting can be facilitated by providing the MedWatch Form 3500,[15] information regarding the process for submission, and MedWatch contact information.

For registries that are sponsored or financially supported in full or in part by a regulated industry and that study a single product, the most efficient monitoring system to avoid duplicate reporting is one in which all physicians participating in the registry report all AEs (or SAEs only) directly to the sponsor or centralized designated responsible personnel, who then reports to the regulatory authorities. However, when products other than those exclusively manufactured by the sponsor are involved, including other treatments, sponsors will need to determine how to process AE reports received for these other products. Since sponsors are not obligated to report AEs for their competitors, it is good practice from a public health perspective to specify how the site should address those AEs (e.g., whether to report directly to the other product's manufacturer or to FDA). Options for the sponsor include (1) recommending that sites report the AEs of comparators directly to the manufacturer or to FDA; (2) collecting all AEs and forwarding the AE report directly to the comparator's manufacturer (who would then, in turn, report to FDA); and (3) actually reporting the AE for the comparator product directly to FDA. As standard practice in pharmacovigilance, many sponsors report events potentially associated with another manufacturer's drug to that manufacturer's safety department as a courtesy, rather than report events directly to FDA, and choose to continue that practice when conducting a registry or other observational study.

Some disease registries are not focused on a specific product, but rather on conducting natural history studies or evaluating treatment patterns and outcomes in a particular patient population prior to marketing approval of the sponsor's product. In these situations, it is recommended that sites follow their own standard practices for spontaneous AE reporting, including reporting any events associated with a product known to be manufactured by the sponsor.

In most circumstances in which a serious drug-associated AE is suspected, sites are encouraged to submit supportive data to sponsors, such as laboratory values, vital signs, and examination results, along with the SAE report form. If the event is determined to be an AE, the sponsor will include it in the safety database, evaluate it internally, and transfer the AE report to the regulatory authorities if required. It should be noted that the regulations represent minimum requirements for compliance; special circumstances for a particular product may result in additional events being reportable (e.g., expected events of particular interest to regulators). It should not be expected that registry participants be aware of all the reporting nuances associated with a particular product. To the extent possible, guidance on reporting events of special interest should be provided in the protocol and in any safety training.

If an external party manages a registry, SAEs should be submitted to the sponsors as quickly as possible after the registry becomes aware of the event. In this situation, the registry is an agent of the sponsor, and FDA's 15-calendar-day reporting requirement starts as soon as the event has come to the attention of the registry. (See Section 7 below.) This submission can be accomplished by phone or fax, or by means of automated rules built into the vehicle used for data collection (such as automatic triggers that can be designed into electronic data capture programs). For direct regulatory submissions, the MedWatch Form 3500A[16] should be used for postapproval reporting for drugs and therapeutic biologics unless other means of submission are agreed upon. For vaccines, the Vaccine Adverse Event Reporting System should be consulted.[17] Foreign events may be submitted on a CIOMS form (the World Health Organization's Council for International Organizations of Medical Sciences),[8, 18, 19] or a letter can be generated that includes the relevant information in narrative format.

5. Coding

Coding AEs into a standard nomenclature should be done by trained experts to ensure accuracy and consistency. Reporters, patients, health care providers, and registry personnel should do their best to capture the primary data clearly, completely, and in as "natural" clinical language as possible. Since reporters may use different verbatim terms to describe the same event, it is recommended that sponsors apply coding conventions to code the verbatim terms. The Medical Dictionary for Regulatory Activities (MedDRA®) is customarily used throughout the product development cycle and as part of pharmacovigilance; however, other coding systems are also used. For example, SNOMED-CT (Systematized Nomenclature of Medicine-Clinical Terms) is used instead of MedDRA in some electronic health records. Coding the different verbatim language to preferred terms allows similar events to be appropriately grouped, creates consistency among the terms for evaluation, and maximizes the likelihood that safety signals will be detected.

Sponsors or their designees should review the accuracy of the coding of verbatim AEs into appropriate terms. If coding is performed by someone other than the sponsor, any applicable coding conventions associated with the underlying condition or product should be shared. Review of the coding process should focus on terms that do not accurately communicate the severity or magnitude of the AE or possibly mischaracterize the AE. Review of the coded terms compared with reported verbatim terms should be performed in order to ensure consistency and accuracy of the AE reporting and to minimize variability of coding of similar AE terms. Attention to consistency is especially important, as many different individuals may code AEs over time, and this situation contributes to variability in the coding process. In addition to monitoring AEs individually for complete clinical evaluation of the safety data, sponsors should consider grouping and analyzing clinically relevant coded terms that could represent similar toxicities or syndromes. Combining terms may provide a method of detecting less common and serious events that would otherwise be obscured. However, sponsors should be careful when combining related terms to avoid amplifying a weak signal or obscuring important overall findings when grouping is overly broad. In addition to monitoring individual AEs, sites and registry personnel should be attentive to toxicities that may cluster into syndromes.

6. Adverse Event Management

In some cases, such as when a safety registry is created as a condition of regulatory approval, a data safety monitoring board (DSMB), data monitoring committee (DMC), or adjudication committee may be established with the primary role of periodically reviewing the data as they are generated by the registry. Such activities are generally discussed directly with the regulatory authorities, such as FDA. These authorities are typically involved in the design and critique of protocols for postapproval studies. Ultimately, registry planning and the registry protocol should anticipate and clearly delineate the roles, responsibilities, processes, forms, and lines of communication for AE reporting for sites, registry personnel, the DSMB, DMC, or adjudication committee if one exists, and the sponsoring organization. Documentation should be provided for definitions and approaches to determining what is considered unexpected and possibly related to drug or device exposure. The management of AE reporting should be clearly specified in the registry protocol, including explanations of the roles, responsibilities, processes, and methods for handling AE reports by the various parties conducting the registry, and for performing followup activities with the site to ensure that complete information is obtained. Sponsors who are stakeholders in a registry should have a representative of their internal drug safety or pharmacovigilance group participate in the design and review of the registry protocol and have a role in the data collection and reporting process (discussed in Chapter 2) to facilitate appropriate and timely reporting and communication.

For postapproval studies financially sponsored by manufacturers, the overall company AE monitoring systems are usually operated by personnel experienced in drug safety (also referred to as pharmacovigilance, regulatory safety, product safety, and safety and risk management). If sites need to report or discuss an AE, they can call the contact number provided for the registry, and are then prompted to press a number if reporting an AE. This number then transfers them to drug safety surveillance so that they can interact directly with personnel in this division and bypass the registry coordinating group. These calls may or may not be tracked by the registry. Alternatively, the registry system can provide instructions to the site on how to report AEs directly to the sponsor's drug safety surveillance division. By this method, the sponsor provides a separate contact number for AE reporting (independent of the registry support staff) that places the site in direct contact with drug safety personnel. This process minimizes the possibility of duplicate AE reports and the potentially complicated reconciliation of two different systems collecting AE information. Use of this process is critical when dealing with products that are available via a registry system as well as outside of a registry system, and it allows sites to have one designated drug safety representative for interaction.

Sponsors of registries designed specifically for surveillance of product safety are strongly encouraged to hold discussions with the regulatory authorities when considering the design of the AE monitoring system. These discussions should be focused on the purpose of the registry, the “best fit” model for AE monitoring, and the timing of routine registry updates. With respect to internal operations chosen by the sponsor to support the requirements of an AE monitoring system, anecdotal feedback suggests that health authorities expect compliance with the agreed-upon requirements. Details regarding implementation are the responsibility of the sponsor.

It should also be noted that FDA's Proposed Rule for Safety Reporting Requirements for Human Drug and Biologics Products (68 FR 12406, March 14, 2003) suggests that the responsible point of contact for FDA should be provided for all expedited and periodic AE reports, and preferably, this individual should be a licensed physician. Although this proposed rule has never been finalized, the principle is similar to the Qualified Person for Pharmacovigilance (QPPV) in Europe, whereby a specific, qualified individual is identified to provide responses to health authorities, upon request, including those regarding AEs reported via the registry system. Updated pharmacovigilance regulations issued by the European Medicines Agency are expected to be implemented in July 2012.[20, 21]

7. Adverse Event Required Reporting for Registry Sponsors

The reporting requirements of the sponsor directly affect how registries should collect and report AEs. Sponsors that are regulated industries are subject to the requirements shown in Table 12–1. ICH guidelines describe standards for expedited reporting[5, 22] and provide recommendations for periodic safety update reports[23] that are generally accepted globally.

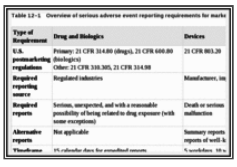

Table 12–1

Overview of serious adverse event reporting requirements for marketed products.

Requirements for regulated industries that sponsor or financially support a registry include expedited reporting of serious and unexpected AEs made known to them via spontaneous reports. For registries, the 15-calendar-day notification applies if the regulated industry believes there is a reasonable possibility that the unexpected SAE was causally related to product exposure. Best practices for international reporting are that all “affiliates” of a sponsor report serious, unexpected, and

possibly related events to the sponsor in a timely fashion, ideally within 2 calendar days; this allows the sponsor, in turn, to complete notification to the responsible regulatory authority within a total of 15 calendar days. Events that do not meet the requirements of expedited reporting (such as nonserious events or serious events considered expected or not related) may require submission through inclusion in an appropriate safety update, such as the New Drug Application or Biologic Licensing Application Annual Report, Periodic Report, or Periodic Safety Update Report, as applicable.[4] In many cases, sponsors are also required to provide registry safety updates to the health authority. Thus, sponsors may coordinate registry safety updates (i.e., determining the date for creating the dataset—the data cutoff date) with the timing of the New Drug Application Annual Report, Periodic Report, Periodic Safety Update Report, or other agreed-upon periodic reporting format. Devices, however, have different reporting requirements (see http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm). In any event, sponsors should discuss safety reporting requirements for their specific registries with the applicable health authorities (such as FDA and European Medicines Agency) before finalizing their registry protocol.

In some cases, a registry sponsor may encourage sites to systematically report all potential SAEs to the sponsor. Given the potential for various assessments by different sites of the seriousness and relatedness of a particular AE—and therefore, inconsistency across sites in the evaluation of a particular AE—this method has certain advantages. In addition, expectedness is not always a straightforward assessment, and the expectedness of events can have significant variability depending on the local approved product labeling. For this reason, it is important that this determination be made by the sponsor and not the reporter of the event. Although this approach may result in substantially greater demands on the sponsor to evaluate all reports, it helps ensure compliance and avoid underreporting. Furthermore, sponsors must make their own assessments regarding the causality of individual solicited events. This requirement typically does not affect the need for reporting, but allows the sponsor to provide its own evaluation in the full context of the safety database. For these reasons, planning for high-quality and consistent training in AE reporting requirements across sites is the preferred approach for a patient registry.

Regardless of who assesses presumed relatedness, sponsors should be prepared to manage the increased volume of AE reports, and sponsors' registry staff should be trained to understand company policy and regulations on AE reporting in order to ensure compliance with local regulations. This training includes the ability to identify and evaluate the attributes of each AE and determine whether the AE should be reported to the health authority in keeping with local regulation. Sponsors are encouraged to appoint a health care practitioner to this role in order to ensure appropriate assessment of the characteristics of an AE.

When biopharmaceutical or device companies are not sponsoring, financially supporting, or participating in a registry in any way, AE reporting is dependent upon the “become aware” principle. If any agent or employee of the company receives information regarding an AE report, the agent or employee must document receipt and comply with internal company policy and regulatory requirements regarding AE reporting, to ensure compliance with applicable drug and device regulations.

8. Special Case: Risk Evaluation and Mitigation Strategies (REMS)

Under the FDA Amendments Act (2007), FDA established a legally enforceable new framework for risk management of products with known safety concerns, called Risk Evaluation and Mitigation Strategies (REMS).[6, 10, 24] The purpose of REMS is to ensure that the benefits of a particular drug outweigh the risks. New REMS programs can be imposed by FDA during clinical development, as part of the approval process, or at any time postapproval, should a new safety signal be identified. Although each REMS is customized depending on the product and associated safety issues, potential components include some combination of—

- A medication guide and/or patient package insert. Medication guides are informational packets distributed with some prescription drugs, which provide important information to patients about possible side effects and drug-drug interactions. The FDA has indicated the situations in which a medication guide is required to be available and distributed to patients.[25] A medication guide alone can and frequently does constitute a REMS.
- A communication plan that specifies targeted education and outreach for physicians, pharmacists, and patients.
- Elements to assure safe use (ETASU), in some cases. ETASU may include restriction of prescribing to health care providers with particular training, experience, and certification; dispensing of the drug in restricted settings; documentation of safe use conditions (such as laboratory results or specific patient monitoring); and registries.[24]

Unlike the less structured disease or exposure registries discussed above, a restricted-access system associated with an ETASU is designed for approved products that have particular risk-benefit profiles that require more careful controls. The purpose of ETASU is to mitigate a certain known drug-associated risk by ensuring that product access is tightly linked to some preventive and/or monitoring measure. Examples include systems that monitor laboratory values, such as white blood cell counts during clozapine administration to prevent severe leucopenia, or routine pregnancy testing during thalidomide administration to prevent in utero exposure of this known teratogenic compound. When these programs include registries, the registries often prospectively collect a battery of information using standardized instruments.

Data collection under ETASU may carry special AE reporting requirements, and as a result of the extensive contact with a variety of potential sources of safety information (e.g., pharmacists and patients), care should be taken to identify all possible routes of reporting. If special requirements exist, they should be made explicit in the registry protocol, with clear definitions of roles, responsibilities, and processes. Training of involved health care providers, such as physicians, nurses, and pharmacists, can be undertaken with written instructions, via telephone or with face-to-face counseling. Training of these health care providers should also extend beyond AE reporting to the specific requirements of the program in question. Such training may include the intended use and associated risk of the product, appropriate patient enrollment, and specific patient monitoring requirements, including guidelines for product discontinuation and management of AEs, as well as topics to cover during comprehensive counseling of patients. The objectives of the ETASU system and overall REMS should be clearly stated (e.g., prevention of in utero exposure during therapy via routine pregnancy testing), and registration forms that document the physician's and pharmacist's attestation of their commitment to requirements of the patient registry system should be completed prior to prescribing or dispensing the product.

9. Reporting Breaches of Confidentiality or Other Risks

In addition to addressing regulatory responsibilities for reporting adverse events, registries must also understand regulatory and ethical requirements and expectations regarding breaches of confidentiality or the reporting of other risks to patients that may arise during the course of a registry. The Health Information Technology for Economic and Clinical Health Act (HITECH Act) requires HIPAA-covered entities (entities covered by the Health Insurance Portability and Accountability Act of 1996) and their business associates to provide notification following a breach of unsecured protected health information.[26] See Chapter 7 for a detailed discussion of the HITECH Act. State breach notification laws may also apply to registry data.

Beyond these legal requirements, registries should establish clear notification procedures for breaches of confidentiality or other risks that become known during the course of the registry, whether or not they are governed by HIPAA or subject to State laws.

References for Chapter 12

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