Use of Registries in Product Safety Assessment
Draft White Paper for AHRQ Patient Registries Handbook II

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EXECUTIVE SUMMARY

Purpose
The purpose of this paper is to evaluate the utility of registries and other prospective observational studies in identifying potential safety signals through adverse event collection and evaluation. Whether as part of a post-marketing requirement or as a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being used to address unresolved safety issues and/or provide proactive risk assessment in the post-approval setting.

Use of Registries for Product Safety Assessment
Registries commonly enroll patients who are not just different from those people who are generally included in clinical trials, but in particular are more complicated in terms of the complexity of their underlying disease, their co-morbidities, and their concomitant medications. Product registries, by definition, focus on patients treated with a particular medicinal product or device and if the representativeness and relevant characteristics of the exposed population are carefully considered, they can be important resources for safety information, especially in the immediate post-approval setting. Disease registries also can make a meaningful contribution to understanding adverse event rates in that they can provide, large, systematic data collection for target populations of interest. Their generally broad enrollment criteria allow systematic capture on a diverse group of patients and, provided that they collect information about the potential events of interest, the registry can be used to provide a background rate of the occurrence of these events in the affected population in the absence of a particular treatment, or in association with relevant treatment modalities for comparison. Registries, including those used to follow former clinical trial participants, are well suited to identify effects that can only be observed in a large and diverse population over an extended period of time.

In addition to product and disease registries, using registries not specifically designed for safety to detect adverse events is less common, though not infrequent. These registries may be designed to fulfil any number of other purposes, including examining comparative effectiveness, studying the natural history of a disease, providing evidence in support of national coverage decisions or documenting quality improvement efforts. One way to capitalize on this type of data collected for another purpose, which is insufficient for meaningful stand-alone analysis and interpretation, is to pool with other data. As with any pooling of disparate data, the creation of a core dataset for analysis is critical and is highly dependent on the consistency in event coding and case identification.

The technical challenges involved in using various types of registries for product safety assessment, such as defining exposure and risk windows, capturing off-label use, understanding the representativeness of the registry population and other recognized aspects of product use in the real world, namely switching therapies during follow-up, use of multiple products in combination or in sequence, dose effects, delayed effects and patient compliance, are discussed. Specific circumstances where registries have been used for this specific purpose (pregnancy registries, orphan diseases, controlled access systems) are also briefly reviewed.

Registries not designed to evaluate safety, particularly those that are not sponsored by a regulated manufacturer raise additional questions regarding what their appropriate role should be in both detection and reporting on potential safety concerns.

Conclusion

The ongoing challenge in the use of both existing data and prospective data collection efforts such as registries remains casting a wide enough net to capture not only rare events, but also increases in more common events and events that are not anticipated, i.e., not part of a pre-approval or post-approval potential risk assessments. Large registries, linkage and distributed network schemes and sentinel surveillance are all tools being actively developed to create an integrated approach to medicinal product safety and specifically signal detection and verification. Thoughtfully designed registries can play an important role in these newly emerging strategies that seek to utilize multiple available data sources to generate and strengthen hypotheses in product safety. In contributing to the evidence hierarchy around the generation of signals for detection and confirmation of potential adverse events, registries are likely to make their strongest contributions in four areas: (1) through detection of novel adverse events, as reported by treating physicians, that constitute a signal necessitating further study; (2) through the establishment of registries of pregnant women and other hard to study subpopulations of product users; (3) through the linkage of registries with additional data sources such as the Medicare-SEER data linkage thereby broadening the range of questions that can be addressed beyond the constraints of data collected for a registry; and (4) through the use of registries to confirm or validate signals generated in other data, such as from automated signal generation in large claims databases.

Ideally, a clear and prospective understanding among stakeholders is needed regarding if and under what circumstances signal monitoring within registries is appropriate, the timing or periodicity of any such analyses, what should be done with the information once it is identified and what, if any, are the ethical obligations for collecting, analyzing, and reporting safety information if not a planned objective

of the registry and the registry sponsor is not directly required to conduct such reporting by regulation. For research registries, the reviewing IRB may assist in delineating such ethical obligations.

KEY POINTS

- When designing a registry for the purposes of safety assessment, the size of the registry, the enrolled population and duration of follow-up are all critical to ensure validity of the inferences made based on the data collected.
- Consideration in the design phase must also be given to other recognized aspects of product use in the real world (e.g., switching therapies during follow-up, use of multiple products in combination or in sequence, dose effects, delayed effects, and patient compliance).
- Registries designed for safety assessment purposes should formulate a plan that ensures appropriate information will reach the right stakeholders (either through reporting to product manufacturer(s) or directly to regulatory authorities) in a timely manner.
- Registries not designed specifically for safety assessment purposes should, at a minimum, ensure that standard reporting mechanisms for potential adverse events information are described in the registry's standard operating procedures and made clear to participating healthcare providers.

PREFACE

The purpose of this paper is to evaluate the utility of registries and other prospective observational studies in identifying potential safety signals through adverse event collection. Signal detection through existing datasets (e.g., administrative claims data), and the specific technical and statistical methodologies considerations involved, are addressed in detail elsewhere and are beyond the scope of this paper (for example, in the DEcIDE Network Effective Health Care Research Report "Improving Patient Safety and Pharmacovigilance: Methods Using Observational Data and Cohort Studies" by Sauer et al, August 2008).[1]

INTRODUCTION

Once a drug or device is approved for use by a regulatory authority, it is generally used by larger and more diverse populations than are typically studied in the clinical trials leading up to approval. As a result, the period after approval is an important phase for identifying and understanding product safety concerns associated with both acute and chronic use. The need for post-marketing (also called post-approval) safety assessment as it exists today was, for the most part, born out of well-publicized product safety issues which were initially detected by clinicians recognizing a pattern of rare serious events, such as phocomelia caused by prenatal exposure to thalidomide[2] and rare vaginal cancers that occurred in young women who had *in utero* exposure to diethylstilbestrol.[3] The detection of serious adverse drug reactions post-authorisation has led to much debate about the adequacy of both industry and regulatory approaches to pre-authorization assessment and testing and post-marketing product safety and safety signal detection.

Trials conducted as part of clinical development are by necessity of limited duration, size and population representativeness. Clinical trial populations tend to be restricted to those who have limited concurrent disease and who are on few concomitant medications and typically trial protocols include lengthy lists of inclusion and exclusion criteria which further restrict the trial population. Unless intended for a very narrow indication or a very rare disease, requiring clinical trials to be inclusive of all patients likely to ever be exposed to the product is not feasible. Even in the case of a narrow indication, the potential long term and delayed effects of a product are unlikely to be established during clinical trials.

To address the acknowledged limitations of what is known about the safety profile of a product at the time of authorization, post-marketing pharmaco- and medical device vigilance is traditionally, and by regulation, performed through spontaneous adverse event reporting. The exact requirements for spontaneous reporting to the regulatory authorities are inconsistent internationally, and dependent upon the country/region, approval type and product type. It is widely acknowledged, however, that spontaneous reporting captures an extremely small percentage of the actual events occurring and while useful for identifying rare and potentially significant events; it has limited use in the detection of other equally important types of events, including increases in events with a high background rate. This form of post-marketing surveillance is reactive in that one waits for adverse events/reactions to be spontaneously reported, assesses them for causality, and estimates the importance of the information.

As well as collecting only an indeterminate fraction of adverse reactions, this method of surveillance depends upon someone reporting. There is some evidence that physicians who report adverse events are not typical of physicians in general, and other reporters such as patients, lawyers, and consumer groups may have unclear motivations for reporting, which introduces further bias into the equation. The current methods available for adverse event reporting are seen by many as burdensome and not amenable to incorporation into a physician's normal workflow. Waiting for reports to arrive and accumulate may also delay the detection of adverse reactions. On the other hand, a massive uptake of a new drug or device, such as seen with Viagra® (sildenafil citrate) – or coronary artery stents– may lead to a sudden flood of reports of non-serious as well as serious adverse events that could potentially overwhelm established systems.

In order to address problems with traditional pharmaco- or medical device vigilance when there are particular known limitations of knowledge of the safety profile of a product and/or further address unresolved safety concerns, some products are approved subject to post-marketing commitments, which may be requested for safety purposes as well as to address other outstanding questions.

In Europe, in response to concerns over pharmacovigilance, marketing authorization applicants are required to submit an European Union-risk management plan (EU-RMP) when seeking a marketing authorisation for the majority of new chemical entities and biologics. This EU-RMP states what is known and not known about the safety profile of a medicinal product, how its safety profile will be monitored, investigated and characterised and what risk minimisation activities will be undertaken. While many products will require only routine pharmacovigilance, for others more pro-active methods of pharmacovigilance will be necessary to supplement the use of spontaneous adverse reaction reporting and periodic safety update reports. Although occasionally additional clinical trials may be mandated, it is more common for observational pharmacoepidemiologic studies to be conducted to ascertain the safety profile of a product under real world use.

Other observational methods of tracking and evaluating safety data have historically included active surveillance systems, such as prescription event monitoring (PEM) systems used in the United Kingdom (Drug Safety Research Unit)[4], New Zealand (NZ Intensive Monitoring Programme), Japan (J-PEM) and elsewhere targeting new products, and the retrospective use of administrative claims data. In the UK, the requirement that access to most secondary care is through a general practitioner has led to the use of their electronic health care systems for pharmacovigilance purposes; however, this type of integrated approach is not yet widely accessible elsewhere. In May 2008, the FDA launched the Sentinel Initiative, an effort to create an integrated, electronic system in the U.S. for adverse event monitoring incorporating multiple existing data sources including claims data and electronic medical record systems.[5]

Medical devices in the U.S. have different surveillance programs than drugs. The Safe Medical Devices Act of 1990 requires that high-risk medical devices be tracked after marketing and that product corrections and removals must be reported to the FDA if the action was taken to reduce health risks. Most medical device safety tracking is accomplished through reports submitted to the FDA from medical facilities when devices are implanted or explanted. In addition, hospitals, nursing homes, ambulatory

surgery centers and outpatient treatment facilities are required to report to the FDA whenever they believe that a device caused or contributed to the death of a patient.[6]

Whether as part of a post-marketing requirement or as a desire to supplement spontaneous reporting, prospective product and disease registries are also increasingly being considered as a resource for examining unresolved safety issues and/or as a tool for proactive risk assessment in the post-approval setting. The advantage of registries is that their observational and inclusive design may allow for surveillance of a diverse patient population that can include sensitive subgroups and other groups not typically included in initial clinical trials such as pregnant women, minorities, older patients, children, or patients with multiple co-morbidities and those taking concomitant medications. In contrast to clinical trials in which the inclusion criteria are generally tightly focused and restrictive by design, registry populations are generally more representative of the population actually using the product or undergoing a procedure, since the inclusion criteria are usually broad and potentially may include all patients exposed regardless of age, co-morbidities, and concurrent treatments. Data collection may lead to insights in provider prescribing practices or off-label use and lead to information regarding the potential for studying new indications within the expanded patient population. Follow-up duration can be long to encompass delayed risks, consequences of long-term use and/or effects of various combinations and sequencing of treatments. Such information can be used as a source of publications and assist the medical community with developing recommendations for monitoring patient safety and product usage as well as contribute to the understanding of the natural history of the disease.

There are also many challenges to the utility of using registry data for providing more clarity about safety concerns and for prospective risk surveillance. These challenges relate largely to how products are used and the legal, regulatory and ethical responsibilities of registry sponsors. Most registries that follow specic products do so through cooperation from physicians who prescribe those medical products. This approach is very useful for studying products that are used according to their labeled indications, but even allows for effective surveillance of products that are used off-label but still by the same practitioners who would use it for the labeled indication. For example, a product might be approved for moderate-to-severe asthmatics, and be used in patients with mild asthma, yet the same medical providers would already be included in the registry and could easily provide information about all their product use. Off-label use is much more difficult to study when medical product is used by a wide variety of medical care providers, such as drugs that promote wakefulness or are thought to increase a patient's ability to concentrate, or immunomodulators. The legal, regulatory and ethical aspects of registry sponsors also affect whether they are required to report any adverse events that may be observed, since only those legal entities that market a medical product are required to report adverse events. For all other parties, such reporting is ethical and desirable, but not enforceable or required.

The purpose of this paper is to examine the role of registries as one of the available tools for enhanced understanding of product safety through adverse event detection and evaluation. Both the role of registries created specifically for the purposes of safety assessment and those in which the collection of safety data is ancillary to the registry's primary objectives will be examined. The legal obligations of

regulated industries are discussed in other references, and only mentioned briefly here. The potential ethical obligations, technical limitations and resource constraints that face registries with multiple different purposes in considering their role in adverse event detection and reporting is also discussed.

REGISTRIES SPECIFICALLY DESIGNED FOR SAFETY ASSESSMENT

Disease and product registries that systematically collect data on all eligible patients are a tremendous resource for capturing important information on safety. Registries commonly enroll patients that are not just different from, but in particular are more complicated than those included in clinical trials, in terms of the complexity of their underlying disease, their co-morbidities, and their concomitant medications.

Design considerations: Disease registry versus product registry

Product registries, by definition, focus on patients treated with a particular medicinal product or device. Disease registries include information not only on products or procedures of interest, but also include information on similar patients who receive other treatments, other procedures, or no treatment for the same clinical indications. Disease registries also can make a meaningful contribution to understanding adverse event rates in that they can provide large, systematic data collection for target populations of interest. Their generally broad enrollment criteria allow systematic capture on a diverse group of patients and provided that they collect information about the potential events of interest, the registry can be used to provide a background rate of the occurrence of these events in the affected population in the absence of a particular treatment, or in association with relevant treatment modalities for comparison. This information is important both for designing registries (for study size calculations) and for interpreting registries, since they can provide useful benchmarks against which to assess the importance of any signals that may have been detected elsewhere. Some would argue that disease registries, rather than product registries, and especially those managed by healthcare professionals, are more likely to be successful in collecting unbiased, interpretable long-term safety data as they may allow objective comparisons across generations of drugs, devices or other interventions.[7]

Consideration should be given during registry design to inclusion/exclusion criteria, appropriate comparator groups, and analysis planning. Registries involving products new to the market must be cognizant of possible bias whereby patients prescribed the new product are not comparable to the general disease population. For example, new oncology products are frequently initially only second or third line therapy for patients for whom other treatments have failed. In some settings, cost considerations mean that new therapies are restricted to narrower populations than indicated by the approved indication.

In some settings, registries are used to collect specific adverse events or events of interest. Once the types of adverse events and/or other special events of interests have been identified, in order to be successful the registry must be designed to efficiently collect the data. Without adequate training of clinical site staff to recognize and report events of interest, the registry will be reduced to haphazard and inconsistent reporting of adverse events. Upon registry inception, clinicians or other healthcare professionals who may encounter patients participating in the registry should be educated about what

adverse events or other special events of interest should be noted, and how and within what parameters (e.g., time) they should report untoward events that may occur while they are participating in the registry, or they may prefer to simply accept passive reporting. For example, if a physician asked a patient how he was feeling and the patient replied that he just returned from the hospital, it would be incumbent on the physician to obtain additional information to determine whether this might be a reportable event, regardless of whether the patient may have recognized it as such. This is particularly important in registries designed to capture all suspected adverse reactions as opposed to specific adverse events. Such an active role by participants as well as their treating clinicians can contribute to a very robust safety database. In addition to identifying events known to be of interest, the systematic collection of follow-up data may capture information regarding risks not previously identified, risks associated with particular subgroups (e.g., pediatric or geriatric patients, patients with liver impairment, fast or slow metabolizers) or differences in event severity or frequency not appreciated during clinical development. Consideration should also be given to implementation of routine follow-up of all registry patients for key adverse events as well as vital status and patient contact and enrollment information at pre-specified visits or intervals, to ensure that analyses of the occurrence of adverse events among the registry population are not hampered by a great deal of missing data. Otherwise, the possibility that patients "lost to follow-up" may differ from those with repeat visits with regard to risk of AEs cannot be excluded.

Healthcare provider and patient reported outcomes

Registries and other prospective data collection approaches have the advantage of incorporating both healthcare provider and patient reported data. Although patients and their advocates may spontaneously report post-marketing adverse events to manufacturers and directly to regulatory bodies, this is likely to be uncommon. Furthermore, spontaneous reports from patients directly that lack healthcare provider confirmation may fall outside of standard aggregating processes by regulatory bodies. As a result, significant events that are not clinically recognized may be substantially under-reported.

In addition, registries may collect provider level data, such as training level, number of patients seen annually and practice type and locations that may contribute to understanding differences in event rates and reporting. This, along with the patient data (such as concomitant environmental exposures and adherence) differentiates registries from other electronic data sources and in many cases allows for improved assessment of confounding and ability to assess the "realness" of a signal internally prior to further signal evaluation or action.

Effects observed in larger population over time

Registries, including those used to follow former clinical trial participants, are well suited to identify effects that can only be observed in a large and diverse population over an extended period of time. The ability to follow patients longitudinally may identify drug-drug interactions (including with new drugs as they come to market and are utilized) and genetic and other patient characteristic-related differences in drug metabolism. One of the most consistent risk factors for adverse events is the total number of medications taken by a patient.[8] Polypharmacy is commonplace, especially in the elderly, and healthcare providers are often unaware of over-the-counter, herbal and other complementary

medications taken by the patient. Registries that collect data from patients can collect this data directly or if the registry is used solely by healthcare practitioners, data collection forms can be designed specifically to request that patients are asked about such use. When designing a registry for the purposes of safety, the size of the registry, the enrolled population and duration of follow-up are all critical to ensure validity of the inferences made based on the data collected. If the background rate of the adverse event in the population of interest is not established and the time period for induction is not well understood, it is extremely difficult to determine an exact meaningful target size or observation period for the registry, and the registry may be too small and have too brief an observation period to detect any, or enough events of interest to provide a meaningful estimate of the true adverse event rate. In addition, the broad inclusion criteria typical of registries make it likely that sub-groups of exposed patients may be identified and analyzed separately. Such stratified analyses may require a larger sample size to achieve rate estimations with confidence intervals narrow enough to allow meaningful interpretation within strata.

As is also true for clinical trials, which are often not powered for safety but rather for efficacy endpoints, describing safety outcomes from observational studies in statistical terms is not always straightforward. Post-marketing data may or may not confirm event rate estimates seen in clinical trials and may also identify events not previously observed. During clinical development, risk of events not yet seen but possibly associated with a product class or the product's mechanism of action are often identified as part of ongoing risk assessment and these events usually continue to be events of interest post-approval. A particular inferential challenge arises when such an event is never observed. The "rule of three" is often cited as a means of interpreting the significance of a specific event *not* being observed (therefore a numerator of zero) in a finite population. Using asymptotic risk estimation, the rule posits that in a large enough study (i.e., > 30 patients) if no event occurs there can be 95% confidence that the event (or events) do not actually occur more often than one in n/3 people, where n is the number of people studied.[9] The rule, originally described by Hanley and Lippman-Hand in 1983, is probably summarized best as a means for "estimating the worse case that is compatible with the observed data".[10] For the purposes of registries, this rule must be carefully applied since complete catchment of events is not assured; however, it provides some guidance regarding registry size and interpretation of results.

Challenges

In planning a registry for safety, it is essential to consider how patients will be identified and recruited from the perspective of understanding which types of patients are included, and equally if not more important, what types of patients are likely *not* to be included in the registry. For example, safety registries often seek information about all treated patients, regardless of whether the product is prescribed for an approved indication. While it is conceptually straightforward to design a registry that would include information on all product users, the practical difficulties include raising awareness about the existence of the registry, the desirability and importance of collecting information on all treated patients, and the challenge of specifying the adverse events and other events of interest without causing undue concern about product safety. Drawing attention to the registry among healthcare providers who use the treatments off-label is especially challenging, due to competing concerns of being inclusive

enough to capture all use – on-label or not – and, if the sponsor of the registry is also a manufacturer, avoiding the appearance of promoting off-label use when contacting physician specialties who are known to use the product off-label. In addition, diseases targeted for off-label use may be markedly different from indicated uses and pose different safety issues. In Europe when there is limited knowledge about the safety of the product pre-authorization and a registry is part of a risk management plan, manufacturers may be required to notify, prior to launch of the product, all physicians who may possibly prescribe the product about the existence of a registry (sometimes also called in this context a post-authorization safety study or PASS) including details of how to register patients.

It is more challenging to be able to evaluate the utility of a registry when the entire population-at-risk has not been included; however, this situation is far more common than registries capturing every single treated patient, and therefore merits careful consideration. Registries organized for research purposes are typically voluntary by design, thereby undermining most efforts for inclusiveness. Two key questions concern the target population, in terms of representativeness and the potential to generalize the results, and the size of the registry. When considering the target population, it is important to assess whether the patients in the registry are representative of typical patients and what types of patients may be systematically excluded or not enrolled in the registry. For example, do patients come from a diverse array of health care settings or are they only recruited from tertiary referral hospitals, in which case the patients can be expected to be more complicated or have more advanced disease than other patients with a similar diagnosis? The ability to use registries for quantification of risk is highly dependent on understanding the relationship between the enrolled population and the target population. While it is intellectually appealing to dismiss the value of any registry that does not have complete enrollment of all treated patients or a documented approach to sampling the entire population, registries that systematically enroll typical patients can be tremendously informative and may be the only way that data can be collected because of legal constraints on the use of registries.

Consider, for example, the National Registry for Myocardial Infarction (NRMI), one of the first cardiac care registries. NRMI was originally intended to obtain information about time to treatment for patients presenting with myocardial infarction to acute care hospitals. The program ultimately resulted in 70 publications (out of more than 500) that provided detailed information on both specific adverse events for specific products and comparative information on safety events. Although it was quite large in terms of hospitals and patients, it included neither all MI patients nor all patients on the product for which it described safety information, but was considered to be representative of the target population.

Defining exposure and risk windows

Many patients will enter a registry at various stages in their disease course or medical management of their disease. Therefore, it is essential to collect information on the timing of events in relation to the initial diagnosis and in relation to the timing of treatments. It is simplest to collect pre-specified clinical data recorded on standardized forms at scheduled assessments, which leads to uniformity within the analysis. However, many registry patients present themselves for data collection on a more naturalistic schedule, i.e., data are collected whenever the patient return for follow-up care, whether or not the visit corresponds to a pre-specified data collection schedule. The more haphazard schedule is more reflective of 'real-world' settings, yet results in non-uniform data collection for all subjects. Rather than

discard this non-uniform data, it can be analyzed both by categorizing patient visits in terms of time windows of treatment duration, e.g., consider data from all visits occurring within thirty days of first treatment, then within 90 days, 180 days, etc and also by using time in terms of patient days/years of treatment. This type of analysis facilitates characterization of the type and rate of occurrence for various adverse events in terms of their induction period. When the collection of adverse event data is completed through an ongoing active process and is expected to be long term, periodic analysis and reporting should be structured around specified time points, e.g., annually, semi-annually or quarterly and may align with the periodic safety update reports. The rigor of pre-specified reporting schedules requires periodic assessment of safety and can support systematic identification of delayed effects.

In addition to variability in the timing of follow-up, consideration must be given to other recognized aspects of product use in the real world, namely switching therapies during follow-up, use of multiple products in combination or in sequence, dose effects, delayed effects, and patient compliance. The current real world practices for the treatment of many conditions, such as chronic pain and many autoimmune diseases include either agent rotation schemes or frequent switching until a balance between effectiveness and tolerability is reached, which creates significant difficulties in determining exposure-outcome relationships. Switching between biologicals may lead to problems with immunogenicity because even products that are clinically the same, e.g. erythropoietins, will have different immunogenic potential due to differences in manufacturing processes and starting cell lines. In addition, as with many clinical studies, patient adherence during registry follow-up is an important confounder to consider. Over time, patients may take drug holidays and self-adjust dosages, and these actions should be, but are not always, captured via the data collected in the registry, especially if the interval between follow-up time points is long or the action is not known by the treating physician. Assessing the temporality of unanticipated events may then be hampered by the inability to fully characterize exposure.

Delayed effects may include late onset immunogenicity, the development of subclinical effects associated with chronic use that are not appreciated until years later, and effects that develop after stopping treatment as a result of products with a long half-life or extended retention in the body. An example of this can be seen in the case of bisphosphonates used for bone resorption inhibition in the treatment of osteoporosis where the product is retained in the bone for at least 10 years after stopping therapy, and there is some evidence that long-term bone turnover suppression puts patients at increased risk of osteonecrosis and nonspinal fractures.[11] In addition, many biologics aimed at immunomodulation carry an increased risk of future malignancy that is not fully appreciated, as do novel therapies directed at angiogenesis. Although registries are well suited to long term follow-up, consideration must be made for how long is long enough to appreciate these effects.

Non-compliance can have a substantial effect on the ability to assess adverse events, in particular if dose or cumulative dose effects are suspected. Patient compliance may be affected by expense, complexity of dosing schedule, convenience/mode of administration and misunderstanding of appropriate administration, and is not fully ascertained by data sources that capture prescriptions rather than actual product use. It is possible with products used to treat chronic diseases to estimate compliance in

electronic health records by estimating when repeat prescriptions should be issued and measuring the observed versus expected frequency. Although registries may be designed directly to track compliance through patient diaries and other methods of direct reporting, challenges remain in accurately capturing compliance and minimizing recall bias.

Special Conditions: Pregnancy Registries

The use of specially-designed registries for specific safety monitoring has a long tradition. For example, pregnancy registries are commonly used to monitor the outcomes of pregnancies during which the mother or father was exposed to certain medical products. The Antiretroviral Pregnancy Registry is an example of a registry that collected information on a broad class of products to determine the risk of teratogenesis.[12] Pregnancy registries provide in-depth information about the safety of one or more products and are particularly useful since, unless the product is used for life-threatening diseases or to treat a pregnancy related illness, for obvious ethical reasons pregnant women are generally excluded from clinical investigations used for product approval. In addition, using computerized claims or billing data for pregnancy safety monitoring is hampered by patients often not presenting early in pregnancy, lack of relevant data on other exposures (since these are often unrelated to reimbursement) and difficulty linking maternal and infant records; therefore, prospective data collection currently remains the best source of meaningful safety data related to pregnancy.

Special Conditions: Orphan Drugs

A product may be designated an orphan drug (or biologic, or medicine in the EU) if it fulfils certain conditions which include being used for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting a small number of patients. Often these diseases are extremely rare and dossiers submitted for authorization purposes may have only tens of patients included in clinical trials. Obviously, the safety profile of such products is extremely limited and follow up of patients treated with the product post-authorization is likely to be a requirement.

With some orphan drugs, the disease may have been usually fatal before therapy was available. These products pose special problems in trying to determine the safety profile of the product in that the natural history of the disease when treated is not known and trying to disentangle the effects of the product from those of the ongoing disease may be particularly problematic. In many of these diseases, the problem may be due to faulty enzymes in metabolic pathways leading to accumulation of toxic substrates that cause the known manifestations of the disease. Treatment may involve blocking another enzyme or pathway leading to the accumulation of different substances for which the effects may also not be known but are less immediately toxic. Registries in these situations may be particularly important in trying to unravel the different parts of the puzzle.

Special Conditions: Controlled distribution/PLAS

Registries may also be part of risk evaluation and mitigation strategies (REMS) in the U.S., such as restricted distribution systems referred to as performance-linked access systems (PLAS), which may be used to monitor the safety of marketed products. One of the earliest PLAS was a blood monitoring program for clozapine ("no blood, no drug") implemented in 1990 to prevent agranulocytosis. Other examples include the STEPS program for thalidomide (System for Thalidomide Education and Prescribing Safety), implemented in 1998 to prevent fetal exposure, the TOUCH controlled distribution for nataluzimab (Tysabri) for patients with multiple sclerosis to detect the occurrence of progressive multifocal leukoencephalopathy (PML), and the iPLEDGE system implemented for isotretinoin in 2006, which tightly links the dispensing of isotretinoin for female patients of child bearing potential to documentation of a negative pregnancy test, prescriber confirmation that contraceptive counselling has occurred, and prescriber and patient identification of contraceptive methods chosen. In many of these programs, access to the product is linked directly to participation in a registry. Therefore, all patients treated with this product should be in the registry because they cannot otherwise obtain access to this treatment. The registry is looking for a known adverse event (such as PML) and collects data specifically related to that adverse event. The registry also collects information on other factors that may raise a patient's individual risk for developing this adverse event, which helps provide important clinical context that would not otherwise be available in a systematic fashion on a large population of treated patients.[13] While PLAS registries are driven by safety concerns, they are primarily focused on prescribing or dispensing controls rather than signal detection. As a result, they utilize very limited data collection forms to minimize burden and this can limit their utility for certain types of analyses.

In Europe, use of registries for risk minimization activities can be more problematic due to differences in national legislation and enactment of the data protection directive. In some countries, it is possible to mandate registration of patients in relation to particular products (e.g., clozapine in the UK and Ireland), but, in others, other methods must be found. For these reasons, registries are more frequently used on a voluntary basis to monitor safety and capture adverse reactions while controlled distribution with compulsory distribution of educational material, prescribing algorithms, treatment initiation forms, etc., to anyone likely to prescribe the product forms the risk minimization part. Despite the fact that patient registration is voluntary, high enrollment rates can be achieved particularly when physicians recognize that information on the safety profile of the product is limited. Obviously if a product has a high potential for off-label use, patients enrolled in a registry may not be generalizable to all those treated with the product, but this can be factored into data analysis and interpretation. A voluntary registry coupled with controlled distribution may in fact be fairly representative since off-label use may be severely limited by difficulties in obtaining the product.

Special Conditions: Medical Devices

Medical devices pose different analytic and data challenges from drugs. On the one hand, it is much more straightforward to identify when a device is implanted and explanted if those records can be obtained; however, since not all medical devices are covered by medical insurance, it can be more difficult to identify all the appropriate practitioners and to locate all the records. Medical devices that can be attached and detached by the consumer, such as hearing aids, are very difficult to study in that,

much like products used on an as-needed basis, special procedures are required to document their use; these procedures are costly and intrusive, and are rarely used.

Nonetheless, despite the challenges, the safety of medical devices is very important due to their widespread use, in particular long-term in-dwelling devices for which recall in the event of a malfunctioning product is inherently complicated. For example, in the late-1970s/early-1980s when a particular type of Bjork-Shiley prosthetic heart valve was found to be defective and prone to fracture leading to sudden cardiac death in the majority of cases, detailed studies of explanted devices, patient factors and manufacturing procedures led to important information that was used to guide decision-making about which devices should be explanted.[14,15] Identification of the characteristics of valves at high risk of failure was very important due to the peri-operative mortality risk from explanting a heart valve, regardless of its potential to fail. This same logic applies to many other medical devices that are implanted and intended for long-term use.

REGISTRIES DESIGNED FOR PURPOSES OTHER THAN SAFETY

The role of registries not specifically designed for safety to detect adverse events is not clearly defined. These registries may be designed to fulfil any number of other purposes, including examining comparative effectiveness, studying the natural history of a disease, providing evidence in support of national coverage decisions or documenting quality improvement efforts. These registries may gather data on adverse events and report those data (to regulatory authorities, manufacturers or others), but the registry may not be able to reliably detect all events, which would result in an underestimation of the true risk in the exposed population(s). A strength of comparative effectiveness registries, however, lies in the systematic collection of data for both the product of interest and concomitant, internal controls.

As an example of the limitations of assessing safety events in registries not designed for safety, a registry may be sponsored by a payer to collect data on every person receiving a certain medication. The purpose of the registry may be to assess prescribing practices and determine which patients are most likely to receive this product. The registry may also contain useful data on events experienced by patients exposed to the product, but not be considered a comprehensive collection of safety data or may provide information regarding a known risk or outcome rather than generating data that could identify a previously unappreciated event. Alternatively, a registry may be designed to study the effectiveness of a new product among a population subset, such as the elderly. The registry may be powered to analyze certain outcomes, such as re-hospitalizations for a condition or quality of life, but may not be specifically powered to assess overall safety in this population.

It is more challenging to accurately and precisely detect adverse events of interest when a registry has not been designed for a specific safety purpose. In this situation, the registry must collect a wide range of data from patients to try to catch any possible events, or be adapted later should safety become a primary objective. Some events may be missed because the registry did not anticipate them and did not solicit data to identify those events. Also, much the same as for registries designed specifically to detect adverse events, some events may be so rare that they do not occur in the population enrolled in the

registry or do not occur during the registry follow-up period. In these circumstances, registries can be designed to provide useful data on some of the events that may occur in the exposed population. Such data should not be considered complete or reliable for determining event rates however, but when combined with other sources of safety data, trends or signals may become more apparent within the dataset.

Ad Hoc Data Pooling

One way to capitalize on data collected for another purpose, which is insufficient for meaningful stand-alone analysis and interpretation, is to pool with other data. As with any pooling of disparate data, the creation of a core dataset for analysis is critical and is highly dependent on the consistency in event coding and case identification. Adverse event data coded using the same coding dictionary (i.e., MedDRA) may still be plagued by an inconsistency in the application of coding guidelines and standards. Re-coding of verbatim event reports may be required, if feasible, prior to analysis. Another consideration is the duration and vigor of follow-up in the registries to be pooled. Differences in the duration of follow-up and the methodology utilized must be assessed when combining data for analysis. Particular care is needed when combining datasets from different European countries since differences in medical practice and reimbursement may mean that superficially similar data may actually represent different subgroups of an overall disease.

While the types of registries described above may not be individually powered to detect safety issues, combining data from registries for other purposes could significantly enhance the ability to identify and analyze safety signals across broader populations. Core datasets for adverse events have been suggested for electronic health records systems and as part of national surveillance mechanisms (e.g., through distributed research networks). In such a network, each participating registry or data source collects a standardized core data set from which results can be aggregated to address specific surveillance questions. For example, there is significant national interest in understanding the long-term outcomes of orthopaedic joint implants. Currently, there are several prominent registries in the U.S. with varying numbers and types of patients and types of implants. Many of these registries collect data for quality improvement purposes, but have sufficient data elements to potentially report on adverse events. However, only by aggregating common datasets across many of these registries can a representative population be evaluated and enough data accrued to understand the safety profile of specific types of devices in particular populations.[1]

As described above, while not every registry is designed to evaluate safety, even registries designed for other purposes might contribute to aggregate information about potential harm from healthcare products or services. Yet, many registries, especially disease registries, are conducted by non-regulated

[1] It is essential to have an understanding of how every data set that will be used was created. For example, what is recorded in administrative health insurance claims depends largely on what benefits were covered and how medications are dispensed. Non-covered items generally are not recorded. For example, mental health services are often contracted for under separate coverage (so-called 'carve-outs'), and not covered under tradition health insurance coverage; thus the mental health consultations are not likely to be included in administrative databases derived from billing claims data. Also, some injectable medications, e.g., certain antibiotics, may be administered in the physician's office and thus would not be recorded through commonly used pharmacy reporting systems that are based on filling and refilling prescriptions. The absence of information may lead to false conclusions about safety issues.

entities such as provider associations, academic institutions and non-profit research groups whose role in adverse events reporting is unclear. Furthermore, sample sizes needed to understand safety signals are generally much larger than those needed to achieve useful information on quality of care or the natural history of certain diseases and the analyses can require a high degree of statistical sophistication. Enrolling additional patients or committing additional resources for specialized analyses to achieve a general societal benefit through safety reporting is not feasible for most registries whose primary purpose is not safety. However, encouraging registries to participate in aggregation of data when such participation is at minimal cost and enhances the common good may be both reasonable and appropriate. Many efforts are underway to improve the feasibility of broader safety reporting from both registries and electronic health records that serve other purposes. These efforts include recommending standardized core data sets for safety to enhance the aggregation of information in distributed networks and making registries interoperable with facilitated safety reporting mechanisms or other registries designed for safety.[16] As such, facilitated reporting methodologies become more common and easy for registries to implement; there will be fewer reasons for non-participation. In addition, linkage of population-based registries, such as the Surveillance, Epidemiology and End Results (SEER) cancer registry program, with other data sources, such as Medicare, have proven invaluable for evaluating safety and other outcomes.

SIGNAL DETECTION IN REGISTRIES AND OBSERVATIONAL STUDIES

Although subject to debate, according to the World Health Organisation (WHO) definition, a safety signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously." Hauben and Aronson (2009) define a signal as: "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, which would command regulatory, societal or clinical attention, and is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions."[17] The authors further posit that signals, following assessment, could subsequently be categorized as indeterminate, verified, and refuted.

Additional attempts at defining or describing a safety signal for purposes of guiding product sponsors, regulators and other researchers have come from various sources, including CIOMS, the FDA and the MHRA. Nelson and colleagues recently provided the FDA with a comprehensive evaluation of signal detection methods for use in post-market surveillance, and include a discussion of "conventional Phase IV observational safety studies," which would encompass registries, as part of a multi-pronged approach to surveillance.[18] They note that despite a focus on automated health care data sources such as large health care claims databases for primary surveillance and as the basis for the Sentinel Network, the need for more detailed data around exposure and outcome measurement, as well as collection of relevant confounder data will require that prospective observation studies be conducted to address pre-specified safety-related hypotheses.

Establishing a threshold of effect size and robustness of data that would justify action, such as initiation of additional studies, FDA action or changes in payor coverage, remains an important question and unlikely to be uniformly applicable to all products and situations. A draft guidance report is expected from the CIOMS Working Group VIII, whose main goal is to harmonize the development, application, and interpretation of signal detection methods for use with drugs, vaccines, and biologics.

Once a signal that warrants further evaluation is identified, it is typically assessed based on the strength of the association between exposure and the event, biological plausibility, any evidence provided by dechallenge and rechallenge, the existence of experimental or animal models and the nature, consistency and quality of the data source.[19] Signals may present themselves as idiosyncratic events affecting a subset of the exposed population who are somehow susceptible, events related to the pharmacological action of the drug, or increased frequency of events normally occurring in the population (such as in the example of cardiovascular events and rofecoxib). Signals may involve the identification of novel risks, or new (or more refined) information regarding previously identified risks. If an event does appear to be product-related, further inquiry is required to examine whether the occurrence appears to be related to a specific treatment, a combination or sequence of treatments, or a particular dosage and/or duration of use. Events with long induction periods are particularly challenging for ascribing a causal relationship, since there are likely to be many intervening factors, or confounders, that could account for the apparent signal.

The constant challenge is to separate a potential safety signal from the "noise," i.e., to detect meaningful trends and to have a basis for evaluating whether the signal is something common to people who have the underlying condition for which treatment is being administered, or whether it appears to be causally related to use of a particular product. All currently used methods for signal detection have their limitations. Attempts to use quantitative and in some cases automated signal detection methods as part of pharmacovigilance, including data mining using Bayesian algorithms or other disproportionality analyses, are hampered by confounders and other biases inherent to spontaneously reported data.[20,21] Other methodologies also attempt to identify trends over time and include potential patterns associated with other patient characteristics such as concomitant drug exposures.

These methods of automated signal detection lack clinical context and only draw attention to deviations from independence between product exposure and events. No conclusions regarding causality can be drawn without a further qualitative assessment of extrinsic factors (e.g., an artificial spike in reporting due to media attention) and potential confounders. Depending on the original data source, the ability to address these issues within the database itself may be impossible and either abstracted medical record data or prospective data collection is required to gather reliable data. The long-term follow-up and longitudinal data generated by many registries merits particular methodological considerations, including how often to perform testing, what threshold is meaningful for a given event, and does that threshold change over time.

While some registries can serve as a source of initial safety signalling or hypothesis generation, they also may be utilized for further investigation of a signal generated from surveillance and quantitative analysis. As an example, existing data from the Swedish Coronary Angiography and Angioplasty Registry

(SCAAR) sponsored by the Swedish Health Authorities was used to look at long term outcomes related to bare-metal and drug-eluting stents once it became clear through FDA-designed and other registries in the post-market setting that off-label use was very common and the risk of restenosis and other long-term outcomes in the real world patient population were not fully understood. Due to the existence of comprehensive national population registries in Sweden, researchers were able to reliably combine SCAAR data, which captured unselected consecutive angiography and percutaneous coronary intervention procedure data, with vital status and hospitalization data to examine fatality rates and cardiac events on a population level.[22] This use of procedure and national registries provides as an example of a registry including a well-defined population allowing for safety assessments coincident with comparative effectiveness.

POTENTIAL OBLIGATIONS FOR REGISTRY DEVELOPERS IN REPORTING SAFETY ISSUES

In considering what actual and potential obligations there are or may be for registries in product safety assessment, it is useful to separate the issues into several parts. First, there are two key questions that can be asked for each registry. What is the role of registries not designed for safety purposes to look for adverse events and what are the obligations, especially for those registries not sponsored by regulated manufacturers, to further investigate and report these findings. As discussed above, registries can be classified by whether or not they were designed for a safety purpose and also by whether or not they have specified regulatory obligations for reporting. Beyond those distinctions, there are several factors that need to be considered, including the ethical obligations of the registry developer, the technical limitations of the signal detection, and resource constraints.

Registries designed for safety assessment purposes should have a clear and deliberate plan in place for not only detecting the signal of interest, but for how they intend to handle unanticipated events and what and how any such events will be reported to appropriate authorities. Only in the case of registries supported by the regulated industries are rules for reporting drug or device adverse events explicit. Therefore, other registries should still formulate a plan that ensures appropriate information will reach the right stakeholders (either through reporting to the manufacturer or directly to the regulator) in a timely manner similar to those required by the regulated industries, as there should not be two different standards for reporting information intended to safeguard the health and well-being of all.

Registries that are not designed specifically for safety assessment purposes, particularly those that are not sponsored by a manufacturer, raise more complex issues. While researchers have an obligation to the patients enrolled in any research activity to alert them should information regarding potential safety issues become known, it is less clear how far this obligation extends. Duing its review of research registries, an IRB or IEC may specify the creation of an explicit incidental findings plan prior to approval. Such a plan is often a part of studies producing or compiling non-clinical imaging and genetic data. In addition, some investigators will have a obligation to report to an IRB any unanticipated problems involving risks to subjects or others under the federal regulations on human research protections. In turn, IRBs have an obligation to report such incidents to relevant federal authorities.

At a minimum, all registries should ensure that standard reporting mechanisms for adverse event information are described in the registry's standard operating procedures. These mechanisms should also be made clear to investigators and, where feasible, those efforts can be facilitated. For example, all registries in the U.S. can make available to registry participants access to the MedWatch forms [23] and train those investigators on appropriate use of those forms for reporting spontaneous events. As described earlier, in the near future it should be possible for registries that collect data electronically to actually facilitate the reporting of adverse events using open standards. This is attractive because it both reduces the work of the investigator in generating the report and ensures that it will go to a surveillance program that is prepared to investigate and manage both events and potential safety signals.

Obligations beyond facilitation are less clear. Furthermore, there are both technical and resource obstacles to thoroughly investigating potential signals and risks of generating inaccurate and potentially injurious information (e.g., each product safety issue that becomes public invariably results in discontinuation of use of potentially life-saving products by some patients). As described earlier, registries designed for safety assessment ideally should have both adequate sample size and signal evaluation expertise to assess safety issues. Registries not designed for safety purposes may not have enough patients or statistical signal detection expertise to investigate potential signals, or the economic resources to devote to unplanned analyses and investigations. It would seem that, as a minimum, registries not designed for safety purposes should use facilitated (via training, providing forms, etc.) reporting of individual events through standard channels to meet their ethical obligations, and that they should check with any institutions with which they are affiliated to determine whether they are subject to additional reporting requirements. However, should a registry identify potential signals through its own analyses, there are obligations that arise. While registries that are approved under institutional review boards (IRBs) report safety issues to those IRBs, what may need more definition is how incidental analytic findings, which may represent true or false signals, should best be further investigated and reported for the public good. One approach would be to report summary information to the relevant regulatory authority for further evaluation. For avoidance of doubt, registry developers should consider these issues carefully during the planning phase of a registry and explicitly define the practices and procedures for adverse event detection and reporting, the planned analyses of adverse events and how incidental analytic findings will be managed. Such a plan should lay out to what extent registry owners will analyze their data for adverse events, the timing of such analyses, what types of unanticipated issues will be investigated internally, what thresholds would merit action and when information will be provided to regulators or other defined government entities depending on the nature of the safety issue.

CONCLUSION

The ongoing challenge in the use of both existing data and prospective data collection efforts such as registries remains casting a wide enough net to capture not only rare events, but also increases in more common events and events that are not anticipated, i.e., not part of a pre-approval or post-approval potential risk assessments. In some cases, existing registries may add additional data collection to

address questions regarding possible adverse events that arise after registry initiation. In addition, it must be considered that all observational data sources are only as strong as their ability to measure and control for potential biases, including confounding and misclassification. Large registries, linkage and distributed network schemes and sentinel surveillance are all tools being actively developed to create an integrated approach to medicinal product safety and specifically signal detection and verification. Thoughtfully designed registries can play an important role in these newly emerging strategies that seek to utilize multiple available data sources to generate and strengthen hypotheses in product safety. In contributing to the evidence hierarchy around the generation of signals for detection and confirmation of potential adverse events, registries are likely to make their strongest contributions through detection of novel adverse events associated with product use as reported by treating physicians that constitute a signal necessitating further study, through the establishment of registries of pregnant women and other hard to study subpopulations of product users, through the linkage of registries with additional data sources such as the Medicare-SEER data linkage thereby broadening the range of questions that can be addressed beyond the constraints of data collected for a registry, and through the use of registries to confirm or validate signals generated in other data, such as from automated signal generation in large claims databases. Ideally, a clear and prospective understanding among stakeholders is needed regarding if and under what circumstances signal monitoring within registries is appropriate, the timing or periodicity of any such analyses, what should be done with the information once it is identified and what, if any, are the ethical obligations for collecting, analyzing, and reporting safety information if not a planned objective of the registry and the registry sponsor is not directly required to conduct such reporting by regulation. For research registries, the reviewing IRB may assist in delineating such ethical obligations.

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