Effective Health Care Program

Volume 2

Registries for Evaluating Patient Outcomes: A User's Guide

Third Edition

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Third Edition

Volume 2

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Section IV

Technical, Legal, and Analytic Considerations for Combining Registry Data With Other Data Sources

Chapter 15. Interfacing Registries With Electronic Health Records

1. Introduction

With national efforts to invest in electronic health record (EHR) systems and advance the evidence base in areas such as effectiveness, safety, and quality through registries and other studies, interfacing registries with EHRs will become more important over the next few years. While both EHRs and registries use clinical information at the patient level, registries are population focused, purpose driven, and designed to derive information on health outcomes defined before the data are collected and analyzed. On the other hand, EHRs are focused on the collection and use of an individual patient's health-related information. While in practice there may be some overlap in functionality between EHRs and registries, their roles are distinct, and both are very important to the health care system. This chapter explores issues of interoperability and a pragmatic "building-block approach" toward a functional, open-standards–based solution. (In this context, "open standards" means nonproprietary standards developed through a transparent process with participation from many stakeholders. "Open" does not mean "free of charge" in this context—there may be fees associated with the use of certain standards.)

An important value of this approach is that EHR vendors can implement it without major effort or impact on their current systems. While the focus of this guide is on patient registries, the same approach described in this chapter is applicable to clinical research studies, safety reporting, biosurveillance, public health, and quality reporting. This chapter also includes case examples (Case Examples 32, 33, 34, and 35) describing some of the challenges and approaches to interfacing registries with EHRs.

An EHR refers to an individual patient's medical record in digital format. EHRs can be comprehensive systems that manage both clinical and administrative data; for example, an EHR may collect medical histories, laboratory data, and physician notes, and may assist with billing, interpractice referrals, appointment scheduling, and prescription refills. EHRs can also be targeted in their capabilities; many practices choose to implement EHRs that offer a subset of these capabilities, or they may implement multiple systems to fulfill different needs. According to the Institute of Medicine (IOM), an EHR has four core functionalities: health information and data, results management, order entry and support, and decision support.[1]

The current EHR market in the United States is highly fragmented.[2] Until recently, the term "EHR" was broadly applied to systems falling within a range of capabilities. However, since the passage of the American Recovery and Reinvestment Act of 2009 (ARRA), a transformative change has been underway, with a rapid increase in EHR adoption and a strong emphasis on standards and certification. Under ARRA, approximately $27 billion will be spent on incentives and other projects to support the adoption of EHRs over the next several years.[3] These incentives have spurred an increase in EHR implementation from 17 percent of U.S. office-based physicians in 2003 to 72 percent in 2012.[4]

To ensure that the EHRs implemented under the ARRA incentive program contain basic functionalities, new standards and a certification process have been developed. ARRA emphasizes the "meaningful use" of EHRs by office-based physicians and hospitals. Meaningful use refers to the use of certified EHR technology to "improve quality, safety, efficiency, and reduce health disparities; engage patients and families in their health care; improve care coordination; and improve population and public health while maintaining privacy and security."[5] ARRA describes the three main components of meaningful use as (1) the use of a certified EHR in a meaningful manner, such as e-prescribing; (2) the use of certified EHR technology for electronic exchange of health information to improve quality of health care, such as promoting

care coordination; and (3) the use of certified EHR technology to submit clinical quality and other measures.[6]

The Office of the Secretary of Health and Human Services (HHS) has been charged under ARRA with setting standards and certification criteria for EHRs, with interoperability a core goal. Within HHS, the Office of the National Coordinator of Health Information Technology (ONC) is responsible for developing the standards and certification criteria for the meaningful use of EHRs. ONC is using a three-stage approach to developing criteria for meaningful use. Stage 1, released in 2011, sets basic standards for capturing data in an EHR and sharing data between systems. Stage 2, which is under development and scheduled for finalization in 2012, expands the basic standards to include additional functionality and require reporting of more measures (e.g., quality of care measures, base functionality measures). Finally, Stage 3, to be released in 2015, will continue to expand on the standards in Stage 2. ONC is also developing an EHR certification program that will allow EHR vendors to demonstrate that their products contain sufficient functionality to support meaningful use.

Even with increasing standardization of EHRs, there are many issues and obstacles to achieving interoperability (meaningful communication between systems, as described further below) between EHRs and registries or other clinical research activities. Among these obstacles are limitations to the ability to use and exchange information; issues in confidentiality, privacy, security, and data access; and issues in regulatory compliance. For example, in terms of information interoperability and exchange, the Clinical Research Value Case Workgroup has observed that clinical research data standards are developing independently from certain standards being developed for clinical care data; that currently the interface between the EHR and clinical research data is ad hoc and can be prone to errors and redundancy; that there is a wide variety of modes of research and medical specialties involved in clinical studies, thus making standards difficult to identify; and that there are differences among standards developing organizations with respect to health care data standards and how they are designed and implemented (including some proprietary standards for clinical research within certain organizations). With respect to confidentiality, privacy, security, and data access, the Workgroup has pointed out that secondary use of data may violate patient privacy, and that protections need to be put in place before data access can be automated. In the area of regulatory compliance, it notes that for some research purposes there is a need to comply with regulations for electronic systems (e.g., 21 CFR Part 11) and other rules (e.g., the Common Rule for human subjects research).[7]

The new Federal oversight of EHR standards is clearly guided by the need to ensure that the EHRs that benefit from the market-building impact of the provider incentives will serve the broader public purposes for which the ARRA funds are intended.[8] Specifically, the elusive goal that has not been satisfied in the current paradigm is the creation of an interoperable health information technology (HIT) infrastructure. Without interoperability, the HIT investment under ARRA may actually be counterproductive to other ARRA goals, including the generation and dissemination of information on the comparative effectiveness of therapies and the efficient and transparent measurement of quality in the health care system. Ideally, EHR standards will lay the groundwork for what the Institute of Medicine has called the "learning health care system."[9] The goal of a learning health care system is a transformation of the way evidence is generated and used to improve health and health care—a system in which patient registries and similar, real-world study methods are expected to play a very important role. Ultimately, the HIT standards that are adopted, including vocabularies, data elements, data sets, and technical standards, may have a far-reaching impact on how transformative ARRA will be from an HIT perspective.

2. EHRs and Patient Registries

Prior to exploring how EHRs and registries might interface, it is useful to clearly differentiate one from the other. While EHRs may assist in certain functions that a patient registry requires (e.g., data

collection, data cleaning, data storage), and a registry may augment the value of the information collected in an EHR (e.g., population views, quality reporting), an EHR is not a registry and a registry is not an EHR. Simply stated, an EHR is an electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards, and that can be created, managed, and consulted by authorized clinicians and staff across more than one health care organization.[10] As defined in Chapter 1, a registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. Registries are focused on populations and are designed to fulfill specific purposes defined before the data are collected and analyzed. EHRs are focused on individuals and are designed to collect, share, and use that information for the benefit of that individual.

3. EHRs and Evidence Development

The true promise of EHRs in evidence development is in facilitating the achievement of a practical, scalable, and efficient means of collecting, analyzing, and disseminating evidence. Digitizing information can dramatically reduce many of the scalability constraints of patient registries and other clinical research activities. Paper records are inherently limited because of the difficulty of systematically finding or sampling eligible patients for research activities and the effort required to re-enter information into a database. Digitized information has the capacity to improve both of these requirements for registries, enabling larger, more diverse patient populations, and avoiding duplication of effort for participating clinicians and patients. However, duplication of effort can be reduced only to the extent that EHRs capture data elements and outcomes with specific, consistent, and interoperable definitions—or that data can be found and transformed by other processes and technologies (e.g., natural language processing) into standardized formats that match registry specifications. Besides enabling health care information to be more readily available for registries and other evidence development purposes, bidirectionally interoperable EHRs may also serve an efferent role of delivering relevant information from a registry back to a clinician (e.g., information about natural history of disease, safety, effectiveness, and quality).

4. Current Challenges in a Preinteroperable Environment

Data capture for research purposes, in general, can be challenging for clinicians. Many hospitals, health care facilities, and clinicians' offices that participate in studies use more than one data capture system, and change their workflow to accommodate nonharmonized research demands. In other words, hospitals and practices are changing their workflow to accommodate nonharmonized research demands. As a result, data capture can be awkward and time consuming for clinicians and their staff, especially for a registry in which a large number of patients may fit into a broad set of enrollment criteria. While some of this can be overcome without interoperable systems by means of uploads from these systems to registries of certain standard file formats, such as hospital or clinician office billing files, the need to re-enter data from one system to another; train staff on new systems; and juggle multiple user names, passwords, and devices presents a high barrier to participation, especially for clinicians, whose primary interest is patient care and who are often resistant to change. The widespread implementation of EHRs that are not truly interoperable, coupled with the growth in current and future evidence development activities, such as patient registries, may ironically create significant barriers to achieving the vision of a national, learning health care system. In many respects, clinicians may be part of the problem, if they seek EHRs with highly customized interfaces and database schema rather than those that may be more amenable to interoperability.

Most EHRs are not fully interoperable in the core functions that would enable them to participate in

the learning health care system envisioned by the IOM. This deficiency is directly related to a combination of technical and economic barriers to EHRs' adoption and deployment of standards-based interoperability solutions. There are more than 600 EHR vendors,[11] many of which provide heavily customized versions of their systems for each client. For some time there was significant interest in adding clinical research capabilities to already implemented EHR systems,[12] but this so-called "Swiss army knife" approach did not prove to be technically or commercially effective. Issues ranged from standardization of core data sets to achieving compliance with U.S. Food and Drug Administration (FDA) requirements for electronic systems used in clinical research. And because there is no single national EHR, even if this were achievable it would not meet many registry purposes, since registries seek data across large, generalizable populations. In recent years, the industry has primarily turned back to pursuing an open-standards approach to interacting with, rather than becoming, specialized systems.[13] Appendix C describes many of the relevant standards and standards-setting organizations.

Even though many EHR systems are technically uniform, the actual software implementations are different in many ways. As a result, achieving interoperability goals (across the myriad of installed EHRs and current and future registries) through custom interfaces is a mathematical, and therefore economic, impossibility. (See Section 5 below.) An open-standards approach may be the most viable. In addition, as has been tested in many demonstrations and is slowly being incorporated by some vendors into commercial offerings, a user-configurable mechanism to enable the provider to link to any number of registries without requiring customization by the EHR vendor is also an important aspect of a scalable solution.

5. The Vision of EHR-Registry Interoperability

As the EHR becomes the primary desktop interface for physicians and other health care workers, it is clear that registries must work through EHRs in order for interoperability to be feasible. At the same time, there is a rapidly growing need for clinicians to participate in registries to manage safety, evaluate effectiveness, and measure and improve quality of care. As a result, an EHR will need to serve as an interface for more than one registry simultaneously. In considering the need to interface EHRs with patient registries, it is useful to consider the specific purpose for which the patient registry is designed, and how an EHR that is interoperable with one or more registries might lessen the burden, barriers, or costs of managing the registries and other data collection programs. The following potential functions can be thought of with respect to a registry purpose:

- *Natural history of disease*: Identify patients who meet eligibility criteria, alert clinicians, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data to the registry, and receive and present information from the registry (e.g., population views).
- *Effectiveness*: Identify patients who meet eligibility criteria, execute sampling algorithms, alert clinicians, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data or analytics, and receive and present information from the registry (e.g., followup schedules, registrywide results).
- *Safety*: Identify events for reporting through triggers, capture uniform data, review the data prior to transmission, transmit data, receive and present requests for additional information, and receive and present safety information from the registry.
- *Quality*: Identify patients who meet eligibility criteria, present the relevant forms and instructions, capture uniform data, review the data prior to transmission, transmit data to the registry for reporting, and receive and present quality measure information and comparators from the registry.

In a truly interoperable system, registry-specific functionality could be presented in a software-as-a-service or middleware model, interacting with

the EHR as the presentation layer on one end and the registry database on the other. In this model, the EHR is a gateway to multiple registries and clinical research activities through an open architecture that leverages best-in-class functionality and connectivity. Registries interact across multiple EHRs, and EHRs interact with multiple registries.

6. Interoperability Challenges

Interoperability for health information systems requires communication, accurate and consistent data exchange, and use of the information that has been exchanged. The two core constructs, related to communication and content, are *syntactic* and *semantic* interoperability.

6.1 Syntactic Interoperability

Syntactic interoperability is the ability of heterogeneous health information systems to exchange data. There are several layers of syntactic interoperability. First, the physical wiring must be in place, and the TCP/IP (Internet) is the de facto standard. On top of this, an application protocol is needed such as HTTP or SMTP. The third layer is a standard messaging protocol such as SOAP (Simple Object Access Protocol).[14] The message must have a standard sequence, structure, and data items in order to be processed correctly by the receiving system.

When proprietary systems and formats are used, the complexity of the task grows dramatically. For n systems, $n(n\text{-}1)/2$ interfaces are needed for each system to communicate with every other one.[15] For this reason, message standards are preferred. While this seems straightforward, an example portrays how, even for EHR-to-EHR communication, barriers still exist. Currently, the Health Level Seven (HL7) Version 2 message standard (HL7 v2.5) is the most widely implemented standard among EHRs, but this version has no explicit information model; instead, it rather vaguely defines many data fields and has many optional fields. To address this problem, the Reference Information Model (RIM) was developed as part of HL7 v3, but v3 is not fully adopted and there is no well-defined mapping between v2.x and v3 messages.

Syntactic interoperability assures that the message will be delivered. Of the challenges to interoperability, this is the one most frequently solved. However, solving the delivery problem does not guarantee that the content of the message can be processed and interpreted at the receiving end with the meaning for which it was intended.

6.2 Semantic Interoperability

Semantic interoperability implies that the systems understand the data exchanged at the level of defined domain concepts. This "understanding" requires shared data models that, in turn, depend on standard vocabularies and common data elements.[16]

The National Cancer Institute's (NCI) Cancer Bioinformatics Grid (caBIG) breaks down the core components of semantic interoperability into information or data models, which describe the relationships between common data elements in a domain; controlled vocabularies, which are an agreed-upon set of standard terminology; and common data elements, which use shared vocabularies and standard values and formats to define how data are to be collected.

The standardization of what is collected, how it is collected, and what it means is a vast undertaking across health care. Much work has been done and is continuing currently, although efforts are not centralized nor are they equally advanced for different medical conditions. One effort, called the CDASH (Clinical Data Acquisition Standards Harmonization) Initiative, led by the Clinical Data Interchange Standards Consortium (CDISC), aims to describe recommended basic standards for the collection of clinical trial data.[17] It provides guidance for the creation of data collection instruments, including recommended case report form (CRF) data points, classified by domain (e.g., adverse events, inclusion/exclusion criteria, vital signs), and a core designation (highly recommended, recommended/conditional, or optional). Version 1.0 was published in October 2008; v1.1 was published in January 2011 and included implementation guidelines, best practice recommendations, and regulatory references. It remains to be seen how widely this standard will be implemented in the planning and operation of

registries, clinical trials, and postmarketing studies, but it is nonetheless an excellent step in the definition of a common set of data elements to be used in registries and clinical research.

Other examples of information models used for data exchange are the ASTM Continuity of Care Record (CCR) and HL7's Continuity of Care Document (CCD), which have standardized certain commonly reported components of a medical encounter, including diagnoses, allergies, medications, and procedures. The CCD standard is particularly relevant because it is one that has been adopted as part of CCHIT certification. The Biomedical Research Integrated Domain Group (BRIDG) model is an effort to bridge health care and clinical research standards and organizations with stakeholders from CDISC, HL7, NCI, and FDA. Participating organizations are collaborating to produce a shared view of the dynamic and static semantics that collectively define a shared domain of interest, (i.e., the domain of clinical and preclinical protocol-driven research and its associated regulatory artifacts).[18]

Even with some standardization in the structure and content of the message, issues exist in the use of common coding systems. For any EHR and any registry system to be able to semantically interoperate, there needs to be uniformity around which coding systems are to be used. At this time, there are some differences between coding systems adopted by EHR vendors and registry vendors. While it is still possible to translate these coding systems and/or "recode" them, the possibility of achieving full semantic interoperability is limited until uniformity is achieved.

The collection of uniform data, including data elements for risk factors and outcomes, is a core characteristic of patient registries. If a functionally complete standard dictionary existed, it would also greatly improve the value of the information contained within the EHR. But, while tremendous progress has been made in some areas such as cancer[19] and cardiology,[20] the reality is that full semantic interoperability will not be achieved in the near future.

Beyond syntactic and semantic interoperability, other issues require robust, standardized solutions, including how best to authenticate users across multiple applications. Another issue is permission or authorization management. At a high level, how does the system enforce and implement varying levels of authorization? A health care authorization is specific to authorized purposes. A particular patient may have provided different authorizations to disclose information differently to different registries interacting with a single EHR at the same time, and the specificity of that permission needs to be retained and in some way linked with the data as they transit between applications. For privacy purposes, an audit trail also needs to be maintained and viewable across all the paths through which the data move. Security must also be ensured across all of the nodes in the interoperable system.

A third key challenge to interoperability is managing patient identities among different health care applications. See Chapter 17 for further discussion.

7. Partial and Potential Solutions

Achieving true, bidirectional interoperability, so that all of the required functions for EHRs and patient registries function seamlessly with one another, is unlikely to be accomplished for many years. However, as noted above, it is critical that a level of interoperability be achieved to prevent the creation of silos of information within proprietary informatics systems that make it difficult or impossible to conduct large registries or other evidence development research across diverse practices and populations. Given the lack of a holistic and definitive interoperability model, an incremental approach to the successive development, testing, and adoption of open, standard building blocks toward an interoperable solution is the likely path forward. In fact, much has been done in the area of interoperability, and if fully leveraged, these advances can already provide at least a level of *functional interoperability* that could significantly ameliorate this potential problem.

From an EHR/registry perspective, functional interoperability could be described as a standards-based solution that achieves the following set of requirements:

> The ability of any EHR to exchange valid and useful information with any registry, on behalf of any willing provider, at any time, in a manner that improves the efficiency of registry participation for the provider and the patient, and does not require significant customization to the EHR or the registry system.

Useful information exchange constitutes both general activities (e.g., patient identification, accurate/uniform data collection and processing) and specific additional elements, depending on the purpose of the registry (e.g., quality reporting). Such a definition implies an open-standards approach where participation is controlled by the provider/investigator. To be viable, such a model would require that EHRs become certified to meet open standards for basic functional interoperability (the requirements of which would advance over time), but also allow EHRs the opportunity to further differentiate their services by how much they can improve the efficiency of participation.

While the goal of functional interoperability likely requires the creation and adoption of effective open standards, there have been several approaches to partially addressing these same issues in the absence of a unified approach. HIT systems, including some EHRs, have been used to populate registry databases for some time. The Society of Thoracic Surgeons, the American College of Cardiology, and others use models that are based on a central data repository that receives data from multiple conforming systems, on a periodic basis, through batch transfers. Syntactic interoperability is achieved through a clear specification that is custom-programmed by the HIT systems vendor. Semantic interoperability is achieved by the publication of specifications for the data collection elements and definitions on a regular cycle, and incorporation of these by the systems vendors. Each systems vendor pays a fee for the specifications and for testing their implementation following custom programming. In some cases, an additional fee is levied for the ongoing use of the interface by the systems vendor. Periodically, as data elements are modified, new specifications are published and the cycle of custom programming and testing is repeated. While there is incremental benefit to the provider organizations in that they do not have to use multiple systems to participate in these registries, the initial and periodic custom programming efforts and the need to support custom interface requirements make this approach unscalable. Furthermore, participation in one registry actually makes participation in other, similar registries more difficult, since the data elements are customized and not usable in the next program.

The American Heart Association's Get With The Guidelines® program uses a Web services model for a similar purpose. The advantage of the Web services model is that the data are transferred to the patient registry database on a transactional basis (immediately), but the other drawbacks in custom programming and change management still apply. This program also offers an open standards approach through IHE RFD[21] or Healthcare Information Technology Standards Panel (HITSP) TP50, both described below. These examples describe two models for using EHRs to populate registry databases; other models exist.

8. Momentum Toward a Functional Interoperability Solution

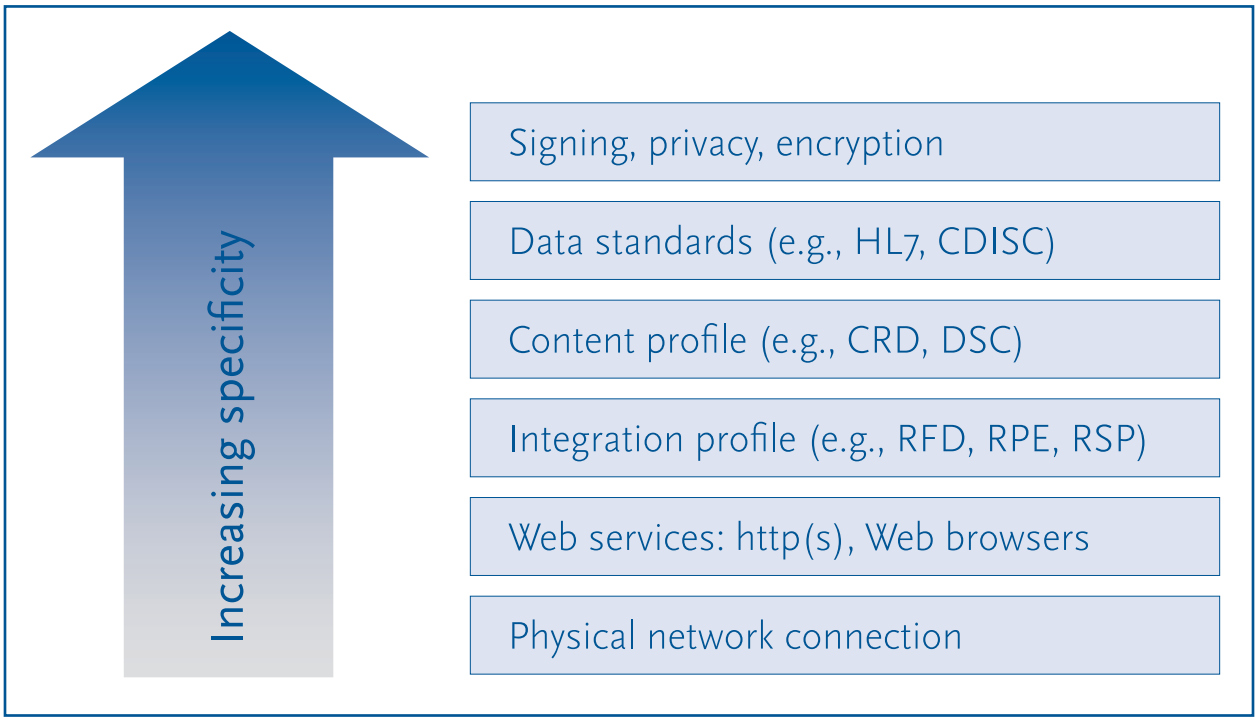
Significant momentum is already building toward adopting open-standard building blocks that will lead incrementally to functional interoperability solutions. For example, the EHR Clinical Research Value Case Workgroup has focused its use cases on two activities: achieving the ability (1) to communicate study parameters (e.g., eligibility information, CRFs) and (2) to exchange a core data set from the EHR.[22] Others in the standards development community have taken a stepwise approach to creating the components for a first-generation, functional interoperability solution. As described below, this solution has already overcome several of the key barriers to creating an open, scalable model that can work simultaneously between multiple EHR systems and registries. Some issues addressed through these efforts

include: the need for flexibility in presenting a uniform data collection set that can be modified from time to time without custom programming by the EHR vendor; the need to leverage existing, standardized EHR data to populate portions of the data collection set; and the need to be able to submit the data on a transactional basis to a registry, clinical trial, or other data recipient in a standard format.

A building-block approach to the technical side of this issue is an effective and pragmatic way to build in increments and allow all players in the industry to focus on specific components of interoperability; early successes can then be recognized and used as the basis for the next step in the solution. This is a change from the earlier approaches to this issue, where the problem (and the solution) was defined so broadly that complete semantic interoperability seemed to be the only way to solve the problem; this proved overwhelming and unsupportable. Instead, a working set of industry-accepted standards and specifications that already exist can focus tightly on one aspect of interfacing multiple data capture systems, rather than considering the entire spread of issues that confound the seamless interchange between health care and research systems.

There are many different standards focused on different levels of this interface, and several different key stakeholders that create, work with, and depend on these standards (see Appendix C). A useful way to visualize these technical standards is to consider a stack in which each building block is designed to facilitate one aspect of the technical interface between an EHR and a data collection system (Figure 15–1). The building blocks are modest but incremental changes that move two specific systems toward interoperability and are scalable to different platforms.

Figure 15–1. A building-block approach to interoperability

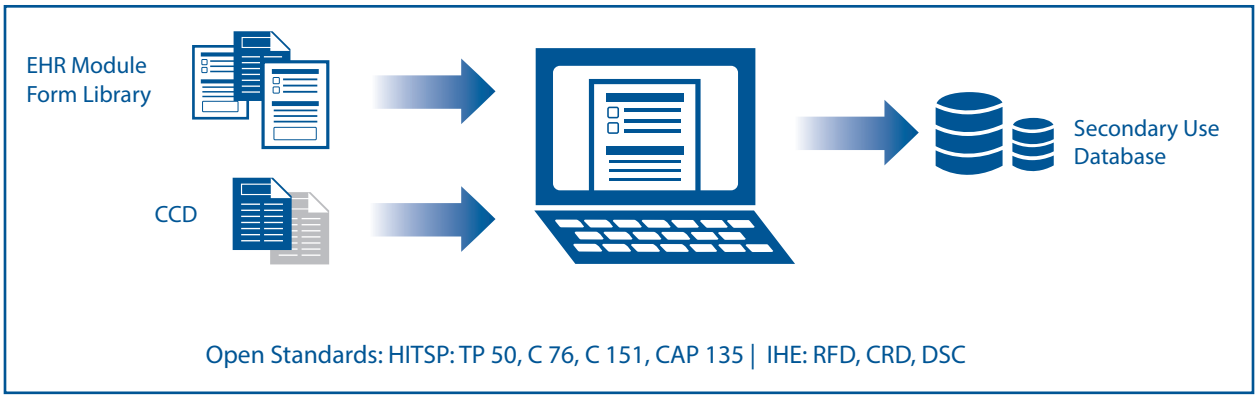


HL7 = Health Level Seven; CDISC = Clinical Data Interchange Standards Consortium; CRD = Clinical Research Data Capture; DSC = Drug Safety Content; RFD = Retrieve Form for Data Capture; RPE = Retrieve Protocol for Execution; RSP = Redaction Services Profile.

This theoretical stack starts with the most basic technical components as the ground layers. Physical network connections, followed by Web services, secure hypertext transfer protocol (http), secure socket layer (SSL) communications protocol, and Web browsers create the foundation of the interoperability structure. These standard technologies are compatible across most systems already.

A standard integration profile, Retrieve Form for Data Capture (RFD), is the base of specific interoperability for health care data transfer, and it takes advantage of the Web standards as a way to integrate EHRs and registry systems. RFD is a generic way for systems to interact. In a sense, RFD opens a circuit or provides a "dial tone" to allow an EHR to exchange information with a registry or other clinical research system. RFD was created and is maintained by Integrating the Healthcare Enterprise (IHE). It is also accepted under HITSP as TP50. Specifically, RFD provides a method for gathering data within a user's current application to meet the requirements of an external system (e.g., a registry). In RFD, as Figure 15–2 shows, this is accomplished by retrieving a registry or other data collection form from a source; displaying it within the EHR system to allow completion of the form, with data validation checks, either through direct user entry or automated population from the EHR database; and then returning an instance of the data back to the registry system. Importantly, the EHR initiates the transaction.

Figure 15–2. Retrieve form for data capture diagram



CAP = Capability; CCD = Continuity of Care Document; CRD = Clinical Research Data Capture; DSC = Drug Safety Content; EHR = Electronic Health Record; HITSP = Healthcare Information Technology Standards Panel; IHE = Integrating the Healthcare Enterprise; RFD = Retrieve Form for Data Capture; TP = Transaction Package.

Once an EHR is RFD-enabled, it can be used for multiple use-cases. RFD opens a circuit and allows for information exchanges of different purposes, including registries and clinical trials, quality initiatives, safety, and public health reporting.[23]

Content profiles such as Clinical Research Data Capture (CRD) build the next level, allowing standard content defined within an EHR to be mapped into the data collection elements for the registry, eliminating duplicate entry for these defined elements. CRD and the Drug Safety Content (DSC) profiles, managed by IHE, build upon the IHE RFD integration profile. Correspondingly, HITSP C76, or Case Report Pre-Populate Component (for Drug Safety), leverages the HITSP TP50 retrieve form for data capture (RFD) transaction package.

CRD allows the functional interoperability solution to leverage standardized content as it becomes defined and available within EHRs. In other words, it is an incremental approach to leveraging whatever content has been rigorously

defined and resident within the EHR and is also usable and acceptable to the registry (i.e., content that matches some portion of the registry's defined data elements and definitions). To the extent that these data reside in a common format, they can be used for autopopulation of the registry forms without custom programming. CRD leverages the Continuity of Care Document (CCD), an HL7 standard. In this scenario, the EHR generates the CCD to populate a case report form. The registry uses only the relevant data from the CCD, as determined by the registry system presenting the form. Alternatively, CRD specifies that CDASH, a CDISC standard for data collection elements, may be used as the content message to prepopulate the case report form.

9. The Next Increment

As the basic components of functional interoperability are being tested and implemented, more attention is being focused on the next increments of the building-block approach. The important challenges to be addressed include: patient identification/privacy protection; the potential and appropriate use of digital signatures; other related and emerging profiles, such as querying the EHR for existing data through the Query for Existing Data (QED) profile; and transferring process-related study information as captured in the study protocol (Retrieve Protocol for Execution [RPE]). More extensive work in data mapping and the development of use cases around content are also needed.

9.1 Patient Identification/Privacy Protection

Patients within the context of clinical care are identified by a patient identifier, usually referred to as a medical record number. When these patients participate in a registry, they will also have a patient identifier within the context of the registry's programs. In some cases, where explicit authorization has been obtained, the medical record number may be shared across programs and can be used as a common identifier that links the patient across systems. In other cases, there is a need to anonymize the patient identifier. In the latter situation, infrastructure can be deployed to create unique, anonymized patient identifiers that serve to protect the patients' identity and facilitate secure patient identity management (e.g., Patient Identifier Cross-Referencing [PIX]).[21]

Beyond anonymizing, it also may be desirable to maintain a cross-referencing of patient identifiers or aliases across multiple systems so that the medical record number within the EHR can be linked back to the identifier within the registry or clinical trial without revealing the patient identity. Pseudonymization is a procedure by which all person-related data are replaced with one artificial identifier that maps one-to-one to the person.[22] Pseudonymization allows for additional use cases where it is necessary to link a patient seen in different settings (such as linking back to source records for additional information or monitoring).[23] See Chapter 17 for a more detailed discussion of this topic.

9.2 Digital Signatures

Certain registry purposes (such as regulatory reporting) require electronic signatures—for example, when the clinician or investigator attests to the completeness and accuracy of information being submitted for a research purpose. The current paradigm is the investigator's physical or electronic signature on a paper or electronic case report form. The potential and appropriate use of digital signatures may further broaden the set of use cases by which EHRs may be used for secondary purposes. Other approaches to facilitating identity management, signing, and verification, such as Private Key Infrastructure (PKI), provide advantages in terms of nonrepudiation and detection of tampering. In the next wave of the interoperability effort, it will be important to define those scenarios that will require the strength of an enhanced digital signature.

9.3 Other Related and Emerging Efforts

As the building blocks of interoperability develop, additional flexibility will be gained as the registry and EHR can more fully communicate in a common language, both to request more clinical data and to provide the EHR with more

information on the workflow requirements of the registry or other study protocol. These requirements point to other work being done to address these issues. Below are three examples from IHE profiles, some of which are under development by the Quality, Research, and Public Health (QRPH) Domain:

- *Retrieve Protocol for Execution (RPE)*: This integration profile allows an EHR to retrieve a protocol or a complex set of clinical research instructions necessary to fulfill the specified requirements of a protocol. The availability of these definitions and a set of transactions defined by RPE can provide an EHR with content that may be used to identify patients for a research program based on defined inclusion/exclusion criteria; manage the patient visit schedule and appropriate case report forms or assessments that need to be completed in the appropriate sequence; and/or assist with other clinical activities such as ordering protocol-specified tests or laboratory reports.[24] RPE eliminates the need to manually enter data in two places (an EHR and an electronic data capture system collecting data for clinical research), resulting in a lower user burden on sites participating in research, as they are able to contribute EHR data to research protocols without leaving their EHR session.
- *Redaction Services Profile (RSP)*: This integration profile addresses the privacy concerns around the exchange of electronic health data. It provides a way to redact certain data (e.g., personal identifiers) before transmitting that data from one system to another (e.g., from an EHR to a QRPH system), and acts as a "safety net" by ensuring that only the necessary and specified data is transmitted. In addition to this function, it also records and maintains an audit trail of the transmissions it facilitates, to support data quality processes.[25]
- *Drug Safety Content (DSC)*: This content profile from the QRPH Domain details which data (and in what format) should be used in the RFD prepopulation transaction between the Form Manager and Form Filler. It is specifically used for reporting adverse events and other data related to drug safety.[26]

9.4 Data Mapping and Constraints

While the efforts described above continue to expand the use of electronic medical record data for a variety of secondary purposes, it is clear that clinical and research teams, standards, and terminologies need to be further harmonized to maximize the benefits of information sharing across the variety of clinical and research systems. Effective and efficient management requires that harmonization efforts are furthered among vendors and standards organizations. It also requires that use cases continue to be honed and explicitly defined so that new clinical document constraints can be applied as necessary for each specified use case. Use cases will range across study types and across purposes, including drug safety, biosurveillance, and public health. Each clinical document constraint should strive to capture and deliver the information necessary to fully support the level of information sharing required by the scenario that maximizes both the efficiency of the clinical care/research workflow and the value of previously collected relevant data.

10. What Has Been Done

A number of efforts have demonstrated success in implementing several of the aforementioned building-block standards to achieve functional interoperability for registry purposes, including safety, effectiveness, and quality measurement. In one case, a registry that focused on effectiveness in pain management was made interoperable with a commercial EHR using RFD communication.[27] In a second case, the Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) project,[28] interoperability was achieved for the purpose of reporting adverse event information to FDA. (See Case Example 35.) In a third case, a commercial EHR was made interoperable with a quality reporting initiative for the American College of Rheumatology (ACR),[29] and to a Physician Quality Reporting Initiative (PQRI) Registry for reporting data to the Centers for Medicare & Medicaid Services (CMS).[30] In each case, both the registry and the EHRs were able to exchange useful information and decrease the effort required by the participating physicians.

11. Distributed Networks

It should be noted that the models of interoperability discussed above presume that data are shared between a distributed EHR and a patient registry (or another recipient such as a regulatory authority or a study sponsor). Alternative models may leave all data within the EHR but execute analyses in a distributed fashion and aggregate only results. To effectively accomplish distributed analyses requires either semantic interoperability or the ability to map to a conforming database structure and content, as well as the sophistication of a large number of EHR systems to run these types of queries in a manner that does not require providers to customize or program their systems. Several groups are advancing these concepts, and they may eventually prove to be very suitable for particular registry purposes (e.g., safety or public health surveillance).

PopMedNet™ is one example of a distributed network model.[31-33] It is a software application that enables the creation of a distributed health data networks and supports the operation and governance of these networks.[34] Through the application, researchers can create and distribute queries to network data partners, who can then execute the queries and return the aggregate results to the researchers. Data partners retain control of their data and can review queries before responding. The PopMedNet application is designed to support a variety of data networks; therefore, the application does not use a specific data model or governance structure, but instead allows each data network to customize its implementation.

Currently, the PopMedNet application is being used for several research projects, including FDA's Mini-Sentinel project; the Agency for Healthcare Research and Quality's (AHRQ) Scalable PArtnering Network for CER: Across Lifespan, Conditions, and Settings (SPAN); and the Population-based Effectiveness in Asthma and Lung Diseases (PEAL) project. The Mini-Sentinel project is designed to facilitate the development of an active surveillance system for monitoring the safety of medical products. SPAN uses the application to conduct comparative effectiveness research in obesity and attention deficit hyperactivity disorder. The PEAL project aims to understand factors that affect prescribing and adherence to asthma medications.[35] The software application was initially developed by the HMO Research Network Center for Education and Research on Therapeutics and the University of Pennsylvania under contract to AHRQ as part of the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) program. Additional development was supported by AHRQ under the SPAN project and by FDA under the Mini-Sentinel project.[36]

12. Summary

Achieving EHR-registry interoperability will be increasingly important as adoption of EHRs and the use of patient registries for many purposes both grow significantly. The linkage of registries with health information exchanges (HIEs) is also important, as HIEs may serve as data collection assistants with which registries may need to interact.[37] Achieving interoperability between these data sources is critical to ensuring that the massive HIT investment under ARRA does not create silos of information that cannot be joined for the public good.[38] Such interoperability should be based on open standards that enable any willing provider to interface with any applicable registry without requiring customization or permission of the EHR vendor. Interoperability for health information systems requires accurate and consistent data exchange, along with use of the information that has been exchanged. In addition, care must be taken to ensure that integration efforts comply with legal and regulatory requirements for the protection of patient privacy.

While full semantic interoperability remains distant, a great deal of useful work has been and is being done. For example, the adoption of open standards such as HITSP TP50, C76 and IHE RFD, CRD, and DSC greatly enhance the ability of EHRs and registries to function together and reduce duplication of effort. *Functional interoperability* is a goal that can be achieved in the near term with significant gains in improving workflow and reducing duplication of effort for providers and patients participating in registries.

The successive development, testing, and adoption of open-standard building blocks, which improve functional interoperability and move us incrementally toward a fully interoperable solution, is a bridging strategy that provides benefits to providers, patients, EHR vendors, and registry developers today.

Case Examples for Chapter 15

Case Example 32. Using system integration software to capture registry data from electronic health records

Description	The PINNACLE Registry is an office-based, ambulatory cardiology quality improvement registry. The registry collects data to facilitate performance metric evaluation in coronary artery disease, atrial fibrillation, hypertension, and heart failure.
Sponsor	American College of Cardiology Foundation (ACCF)
Year Started	2007
Year Ended	Ongoing
No. of Sites	Over 500
No. of Patients	Over 2,000,000 patient records

Challenge

Collection of registry data in an outpatient setting can be challenging. Sites wishing to participate in the PINNACLE Registry can choose to collect and submit their data on paper or electronically. Paper data collection (i.e., having a dedicated clinical abstractor abstract data manually from an existing medical record into a data collection form) can be disruptive to practice workflow. This method also requires such a significant investment in human resources (from both the site and the registry) that the PINNACLE Registry is no longer accepting new sites that submit data on paper.

Electronic data submission involves directly abstracting relevant registry information from electronic health records (EHRs). The registry certified two EHR vendors as fully compatible and able to submit data automatically to the registry, which minimizes the data entry burden on sites. However, many potential sites use other EHRs, and the lack of standardized terminology and data collection formats among the many EHR options available to practices makes it challenging to provide an integration solution that serves the largest possible number of sites.

Proposed Solution

Recognizing these challenges, the American College of Cardiology Foundation (ACCF) partnered with a technology partner to develop the PINNACLE Registry System Integration Solution (SI). The SI is comprised of (1) a Microsoft SQL–based database, which stores registry measures and the data mapping specifications for the relevant EHR, (2) a .NET 4.0-based Windows Service, which interfaces with the EHR and extracts the relevant registry data, and (3) a .NET 4.0-based Windows Client, which configures the data extractions and adjusts mappings to suit the practice's specific use of the EHR. The SI is compatible with any EHR system, including those that have been highly customized at the practice level.

The registry team works with potential sites to complete a technical questionnaire, providing details about the practice's technical environment and EHR system. The SI software is then installed on the practice's server, is programmed to collect registry data elements that are already captured in the existing EHR system, and exports the data directly to the registry database. The primary human resource requirement is from the practice's information technology team who work with the technology partner to install the solution on the practice's server.

Results

Currently, 80 percent of sites participating in the PINNACLE Registry use the SI to submit their data. The SI software has been successfully

Case Example 32. Using system integration software to capture registry data from electronic health records (continued)

Results (continued)

installed and implemented at 396 sites, which combined use 19 different EHR products. Installation and data mapping is underway at sites using 14 other EHR products.

The PINNACLE Registry System Integration Solution allows for the collection of registry data with minimal disruption of practice workflow. By eliminating the need for manual chart abstraction and data entry, some barriers to practice participation are removed. However, this means that if data are missing in the EHR, the same data will be missing in the registry record. Because of the lack of standardization in EHR systems, the SI solution does require time and resources during the startup phase to implement in a particular practice. Until such standards exist, the SI solution is a viable solution for capturing registry data with minimum workflow disruption and minimum human capital commitment.

Key Point

Extracting registry data directly from ambulatory EHRs can reduce the data entry burden on participating sites. A software solution that executes this extraction automatically may take time to set up initially, but minimizes workflow disruption during continued registry participation. An integrated solution that is flexible enough to accommodate many different EHR vendors and levels of customization can reduce barriers to registry participation for many sites.

For More Information

https://pinnacleregistry.org/Pinnacle/PINNACLERegistry/DataCollection.aspx

Case Example 33. Creating a registry interface to incorporate data from multiple electronic health records

Description	The MaineHealth Clinical Improvement Registry (CIR) is a secure Web-based database system that provides a tool for primary care physicians in the outpatient setting to consolidate and track key clinical information for preventive health measures and patients with common chronic illnesses.
Sponsor	The project is the result of a collaboration between Maine Medical Center (MMC) Physician-Hospital Organization, MaineHealth, and MMC Information Services.
Year Started	2003
Year Ended	Ongoing
No. of Sites	106 primary care practices (450 providers)
No. of Patients	More than 200,000

Challenge

A physician-hospital organization (PHO) developed a Web-based patient registry to improve quality of care and track patient outcomes across a large network of physicians. Many practices in the network used EHRs and did not have sufficient staff to enter patient data a second time into a registry. In addition, the practices used a wide range of electronic health records (EHRs), and each had unique technical specifications. The registry needed a technical integration solution to reduce the data entry burden on practices that used EHRs, but, due to resource limitations, it could not develop customized interfaces for each of the many different EHRs in use.

Proposed Solution

The registry elected to allow practices to submit data from their EHRs to the registry in a one-way data transfer. An interface was written against an XML specification. Practices wishing to participate in the registry without doing direct data entry must be able to export their data in a file that conforms to this specification (although HL7 files are accepted when necessary). Data

Case Example 33. Creating a registry interface to incorporate data from multiple electronic health records (continued)

Proposed Solution (continued)

transfers occur on a schedule determined by each site—some send their data in real time while others send on a monthly basis.

Once the registry receives data files, registry staff members review each portion of the data (demographics, vaccinations, office visits, etc.) before signing off on the file and incorporating the data into the registry. Extensive error checking and validation are completed during the initial specification phase to minimize the amount of manual data checking needed during each transfer. The validation phase involves both technical staff and quality improvement staff at the practices to ensure that the data are transferred and mapped correctly into the registry database.

Results

Of the 106 primary care practices participating in the registry, about 60 percent enter data directly into the registry, and about 40 percent contribute data via XML transfer. The organization and management of this initiative have required strong internal support from the registry and from participating practices. Management teams and technical resources were needed during the startup phase and continue to be essential as more practices contribute data via XML transfer.

Key Point

Technical interface solutions between registries and EHRs can be successful, but require a robust organizational commitment from the registry sponsor and participating sites to provide the necessary resources during the setup and launch phases.

For More Information

http://www.mmcpho.org/technology/mainehealth_clinical_improvement_registry_cir/

Case Example 34. Technical and security issues in creating a health information exchange

Description	The Oakland Southfield Physicians Quality Registry is a practice-based registry designed to promote health outcomes and office efficiencies, and to identify early interventions and best practices in primary care practices. The registry integrates and exchanges health information from many sources through the Oakland Southfield Physicians Health Information Exchange (OSPHIE).
Sponsor	Oakland Southfield Physicians
Year Started	2006
Year Ended	Ongoing
No. of Sites	150
No. of Patients	Network covers more than 250,000 patients

Challenge

In 2006, the practice association launched a registry to improve the quality of care in its primary care practices. However, the association quickly realized that it needed to integrate and exchange health information from multiple sources, such as payer claims, pharmacy claims, practice management systems, laboratory databases, and other registry systems, on behalf of more than 150 primary care practices.

Proposed Solution

To support this requirement, the practice association constructed an HIE. The HIE is a data warehouse made up of multiple data sources that facilitates the collaborative exchange of health information with a network of trading partners and then integrates the patient disease registry data with a wide range of supplemental clinical information. The HIE allows the registry to securely exchange data with trading partners (third-party payers, laboratories, hospitals, registry systems, etc.) via a variety of methods and in a variety of structures. By pushing

Case Example 34. Technical and security issues in creating a health information exchange (continued)

Proposed Solution (continued)

information both to the registry system and to other systems, the HIE eliminates duplicate data entry. Data transfers occur at established intervals, based on record updates or availability of information.

A key aspect of the system is the master patient and physician index, which allows data from various sources to be linked to the proper patient. Prior to import, data received in the registry are validated against a master patient and physician index for accuracy.

Results

Through data sharing with the Oakland Southfield Physicians registry, the practice association has been able to facilitate the alignment of multiple data sources, with evidence-based care guidelines available at point of care—a value partnership striving to improve health outcomes as well as the efficient access to key health care data points. This solution relies on building trust between trading partners in support of both the secure transfer of information and recommended use.

The HIE has successfully incorporated data from practice management systems, laboratory providers, an e-prescribing system, a registry system, and third-party payers (medical and pharmacy claims detail). Relevant data are currently transmitted on behalf of the participating physicians in a real-time capacity from the HIE to both the registry system and the e-prescribing system. The data warehouse also generates monthly "gaps-in-care reports" for physician clinical quality review and patient outreach.

Key Point

An HIE may be a useful tool for integrating and exchanging data between registries and other systems. When integrating data from many sources, a master patient and physician index can be a critically important tool for ensuring that the incoming data are linked to the appropriate patient.

For More Information

http://www.ospdocs.com/OSP+Advantage/Clinical+Quality+Registry-21.html

Case Example 35. Developing a new model for gathering and reporting adverse drug events

Description	The Adverse Drug Event Spontaneous Triggered Event Reporting (ASTER) study uses a new approach to the gathering and reporting of spontaneous adverse drug events (ADEs). The study was developed as a proof of concept for the model of using data from electronic health records to generate automated safety reports, replacing the current system of manual ADE reporting. The goals are to reduce the burden sof reporting and provide timely reporting of ADEs to regulators.
Sponsor	Brigham and Women's Hospital, Partners Healthcare, CDISC, CRIX International, Claricode, and Pfizer Inc.
Year Started	Pilot launched in 2008
Year Ended	Pilot ended in 2009
No. of Sites	N/A
No. of Patients	N/A

Challenge

Health care data are rapidly being translated into electronic formats; however, to date, safety reporting has not taken full advantage of these electronic data sources. The spontaneous adverse event reporting system, which relies on reports submitted manually by health care professionals, is still the primary source of data on potential ADEs. However, the availability of large amounts of data in electronic formats presents the opportunity to rethink the spontaneous adverse event reporting system. A new model could take advantage of the increasing availability of electronic data and improving technology to automate the process of gathering and reporting ADEs. The goals of automated ADE reporting are to reduce the burden of reporting on physicians, improve the frequency with which ADEs are reported, and increase the timeliness and quality of ADE reports.

An automated model, however, must overcome many challenges. The system must be scalable, must incorporate data from many sources, and must be flexible enough to adapt to the needs of many diverse groups. The model must address point-of-care issues (such as burden of reporting), data exchange standards (so that the data are interpretable and valid), and processes for reviewing the ADE reports.

Proposed Solution

The ASTER study attempted to address these challenges and demonstrate the potential viability of an automated model for facilitating the gathering and reporting of ADEs. ASTER allowed data to be transferred from an electronic health record (EHR) to an adverse event (AE) case report form and submitted directly to the U.S. Food and Drug Administration (FDA) in the format of an individual case safety report. The process of gathering and reporting ADEs through ASTER involves four steps based on the open-standard "Retrieve Form for Data Capture (RFD)":

1. A physician indicates in the EHR that a drug was discontinued due to an ADE.
2. The system immediately generates an ADE report form that is prepopulated with demographic, medication, vital signs, and laboratory data. The physician sees the form in the EHR.
3. The physician enters a small amount of additional data, such as outcomes of the adverse event, to complete the ADE report form.
4. The form is then processed by a third-party forms manager, who sends it to FDA as a reported spontaneous AE from the physician, in a standard format.

Results

The pilot phase of ASTER began in 2008. The goal of this phase was to demonstrate proof of concept for the new model. Specifically, it was

Case Example 35. Developing a new model for gathering and reporting adverse drug events (continued)

Results (continued)

hypothesized that (1) if an EHR could help a clinician identify potential AEs, and (2) if the burden of completing an AE form was significantly reduced, then the rate of reporting of spontaneous AEs to FDA could be significantly increased. ASTER recruited 26 physicians, 91 percent of whom had not reported an AE to FDA in the prior year. Following implementation, more than 200 events were reported over a period of 3 months.

Many questions need to be answered before the ASTER model can become more widely used in the United States. For example, initial findings from ASTER suggest that an increased number of events are being reported using this model; this creates a need for the receiver of the reports (i.e., FDA) to have sufficient capacity to respond to the reports. Also, the fields captured in the ASTER model are based on the paper form fields. Moving to a truly digital system may require a change in the data collected to better align with the way data are collected in electronic formats. In 2012, FDA published the results of a quality assessment of the data they received during the ASTER pilot. While the assessment noted the potential value of such an automated reporting system, it also provided suggestions for improving the quality and utility of the data. In the pilot, users selected an ADE description from a predefined list of relatively broad terms; the authors of the FDA report suggested that either this list be amended to include standardized terms for these clinical events, or users enter free text to describe the ADE, which could later be coded. Other suggestions included the implementation of real-time edit checks to catch illogical data such as an ADE date that precedes the initiation date of the suspected drug.

This ADE reporting model is now being expanded to include AEs related to medical devices. The "ASTER-D" project, focused on device safety reporting, builds upon the ASTER concepts. A pilot study is currently underway, sponsored by FDA's Center for Devices and Radiological Health (CDRH).

Key Point

New models for gathering and reporting ADEs may be able to leverage electronic health data and emerging technologies to both improve the timeliness of reporting and reduce the burden of reporting on health care professionals.

For More Information

http://www.asterstudy.com/

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Chapter 16. Linking Registry Data With Other Data Sources To Support New Studies

1. Introduction

The purpose of this chapter is to identify important technical and legal considerations for researchers and research sponsors interested in linking data in a patient registry with additional data, such as data from claims or other administrative files or from another registry. Its goal is to help these researchers find an appropriate way to address their critical research questions, remain faithful to the conditions under which the data were originally collected, and protect individual patients by safeguarding their privacy and maintaining the confidentiality of the data under applicable law.

There are two equally important questions to address in the planning process: (1) What is a feasible technical approach to linking the data, and (2) is the linkage legally feasible under the permissions, terms, and conditions that applied to the original compilations of each data set? Legal feasibility depends on the applicability to the specific purpose of the data linkage of Federal and State legal protections for the confidentiality of health information and participation in human research, and also on any specific permissions obtained from individual patients for the use of their health information. Indeed, these projects require a great deal of analysis and planning, as the technical approach chosen may be influenced by permitted uses of the data under applicable regulations, while the legal assessment may change depending on how the linkage needs to be performed and the nature and purpose of the resulting linked data set. Tables 16-1 and 16-2, respectively, list regulatory and technical questions for the consideration of data linkage project leaders during the planning of a project. The questions are intended to assist in organizing the resources needed to implement the project, including the statistical, regulatory, and collegial advice that might prove helpful in navigating the complexities of data linkage projects. This chapter presumes that investigators have identified an explicit purpose for the data linkage in the form of a scientific question they are trying to answer. The nature of this objective is critical to an assessment of the applicable regulatory requirements for uses of the data. For example, to the extent the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule applies, the use or disclosure of protected health information (PHI) for the registry purpose will need to fall into one of the specific regulatory permissions and comply with the relevant requirements for the permission (e.g., health care quality–related activities, public health practice, research, or some combination of these purposes), or individual authorization must be obtained. If research is one purpose of the project, then the Common Rule (Federal human subjects protection regulations) is also likely to apply to the project. More information on HIPAA and the Common Rule is provided in Chapter 7.

The application of the HIPAA Privacy and Security Rules depends on the origins of the data sets being linked, and such origins may also influence the feasibility of making the data linkage. Investigators should know the source of the original data, the conditions under which they were compiled, and what kinds of permissions, from both individual patients and the custodial institutions, apply to the data. Health information is most often data with two sources, individual and institutional; these sources may have legal rights and continuing interests in the use of the data.

It is important to be aware that the legal requirements may change, and that, in fact, the protections limiting the research use of health information are likely to change in response to continued development of electronic health information technologies.

This chapter has six sections focusing on core issues in three major parts: Technical Aspects of Data Linkage Projects, Legal Aspects of Data Linkage Projects, and Risk Mitigation for Data Linkage Projects. The Technical Aspects section discusses the reasons for and technical methods of linking data sets containing health information, including data held in registries. It should be noted that this list of techniques is not intended to be

comprehensive, and these techniques have limitations for certain types of studies. The Legal Aspects section defines important concepts, including the different definitions of "disclosure" as used by statisticians and in the HIPAA Privacy Rule. This section also discusses the risks of identification of individuals inherent in data linkage projects and describes the legal standards of the HIPAA Privacy Rule that pertain to these risks. Finally, the Risk Mitigation section summarizes both recognized and developing technical methods for mitigating the risks of identification. Appendix D consists of a hypothetical data linkage project intended to provide context for the technical and legal information presented below. Case Examples 36, 37, 38, and 39 describe registry-related data linkage activities. Chapter 18 provides information on analyzing linked data sets. While some of the concepts presented are applicable to other important nonpatient identities that might be at risk in data linkage, such as provider identities, those issues are beyond the scope of the discussion below.

2. Technical Aspects of Data Linkage Projects

2.1 Linking Records for Research and Improving Public Health

Data in registries regarding the health of individuals come in many forms. Most of these data were originally gathered for the delivery of clinical services or payment for those services, and under promises or legal guarantees of confidentiality, privacy, and security. The sources of data may include individual doctors' records, billing information, vital statistics on births and deaths, health surveys, and data associated with biospecimens, among other sources.

The broad goal of registries is to amass data from potentially diverse sources to allow researchers to explore and evaluate alternative health outcomes in a systematic fashion. This goal is usually accomplished by gathering data from multiple sources and linking the data across sources, either with explicit identifiers designed for linking, or in a probabilistic fashion via the characteristics of the individuals to whom the data correspond. From the research perspective, the more data included the better, both in terms of the number of cases and the details and the extent of the health information. The richer the database, the more likely it is that data analysts will be able to discover relationships that might affect or improve health care. On the other hand, many discussions about privacy protection focus on limiting the level of detail available in data to which others have access.

There is an ethical obligation to protect patient interests when collecting, sharing, and studying person-specific biomedical information.[1] Many people fear that information derived from their medical or biological records will be used against them in employment decisions, result in limitations to their access to health or life insurance, or cause social stigma.[2, 3] These fears are not unfounded, and there have been various cases in which it was found that an individual's genetic characteristics or clinical manifestations were used in a manner inconsistent with an individual's expectations of privacy and fair use.[4] If individuals are afraid that their health-related information may be associated with them or used against them, they may be less likely to seek treatment in a clinical context or participate in research studies.[5]

A tension exists between the broad goals of registries and regulations protecting individually identifiable information. Approaches and formal methodologies that help mediate this tension are the principal technical focus of this chapter. To understand the extent to which these tools can assist data linkages involving registry data, one needs to understand the risks of identification in different types of data.

There is a large body of Federal law relating to privacy. A recent comprehensive review of privacy law and its effects on biomedical research identified no fewer than 15 separate Federal laws pertaining to health information privacy.[6] There are also special Federal laws governing health information related to substance abuse.[7] A full review of all laws related to privacy, confidentiality, and security of health information would also consider separate State privacy protections as well as State laws pertaining to the

confidentiality of data. Nevertheless, the legal aspects of this chapter focus only on the Federal regulations commonly referred to as the HIPAA Privacy Rule.

2.2 What Do Privacy, Confidentiality, and Disclosure Mean?

Privacy is a term whose definition varies with context.[8] In the HIPAA Privacy Rule, the term refers to *protected health information* (PHI)—individually identifiable health information transmitted or maintained by a covered entity or business associate—that is to be used or disclosed only as expressly permitted or required by the Rule, and that is safeguarded against inappropriate uses and disclosures. The Privacy Rule addresses to whom the custodian of PHI, a *covered entity* or its business associate, may transmit the information and under what conditions. The Rule also establishes three levels of identifiability of health information: (1) fully identifiable data; (2) data that lack certain direct identifiers, otherwise known as a *limited data set*; and (3) de-identified data. Registries commonly acquire identifiable data and may create the last two categories of data in accordance with the Privacy Rule. Along this spectrum of data identifiability, the HIPAA Privacy Rule applies different legal standards and protections,[5] extending the most stringent protections to data containing direct identifiers and none for de-identified information, which is not considered PHI. Not all registries contain PHI; Chapter 7 provides more information on how PHI is defined under HIPAA.

Confidentiality broadly refers to a quality or condition of protection accorded to statistical information as an obligation not to permit the transfer of that information to an unauthorized party.5 Confidentiality can be afforded to both individuals and health care organizations. A different notion of confidentiality, arising from the special relationship between a clinician and patient, refers to the ethical, legal, and professional obligation of those who receive information in the context of a clinical relationship to respect the privacy interests of their patients. Most often the term is used in the former sense and not in the latter, but these two meanings inevitably overlap in a discussion of health information as data. The methods for disclosure limitation described here have been developed largely in the context of confidentiality protection, as defined by laws, regulations, and especially by the practices of statistical agencies.

Disclosure for purposes of this discussion has two different meanings: one is technical and the other is regulatory and contained in the HIPAA Privacy Rule.

In the field of statistics, disclosure relates to the attribution of information to the source of the data, regardless of whether the data source is an individual or an organization. Three types of disclosure of data possess the capacity to make the identity of particular individuals known: *identity disclosure, attribute disclosure, and inferential disclosure*.

Identity disclosure occurs when the data source becomes known from the data release itself.[9, 10]

Attribute disclosure occurs when the released data make it possible to infer the characteristics of an individual data source more accurately than would have otherwise been possible.[8, 9] The usual way to achieve attribute disclosure is through identity disclosure. First, one identifies an individual through some combination of variables and then learns about the values of additional variables included in the released data. Attribute disclosure may occur, however, without identity disclosure, such as when all people from a population subgroup share a characteristic and this quantity becomes known for any individual in the subgroup.

Inferential disclosure relates to the probability of identifying a particular attribute of a data source. Because almost any data release can be expected to increase the likelihood of an attribute being associated with a data source, the only way to guarantee protection is to release no data at all. It is for this reason that researchers use certain methods not to prevent disclosure, but to limit or control the nature of the disclosure. These methods are known as disclosure limitation methods or statistical disclosure control.[11]

Disclosure under the HIPAA Privacy Rule means the release, transfer, provision of, access to, or divulging in any other manner, of information outside of the entity holding the information.[12]

2.3 Linking Records and Probabilistic Matching

Computer-assisted record linkage goes back to the 1950s, and was put on a firm statistical foundation by Fellegi and Sunter.[13] Most common techniques for record linkage either rely on the existence of unique identifiers or use a structure similar to the one Fellegi and Sunter described with the incorporation of formal statistical modeling and methods, as well as new and efficient computational tools.[14, 15] The simplest way to match records from separate databases is to use a so-called "deterministic" method of linking databases in which unique identifiers exist for each record. In the United States, when these identifiers exist they might be names or Social Security numbers; however, these particular identifiers may not in fact be unique.[16] As a result, some form of probabilistic approach is typically used to match the records. Thus, there is little actual difference between methods using deterministic versus probabilistic linkage, except for the explicit representation of uncertainty in the matching process in the latter.

The now-standard approach to record linkage is built on five key components for identifying matching pairs of records across two databases:[13]

1. Represent every pair of records using a vector of features (variables) that describe similarity between individual record fields. Features can be Boolean, discrete, or continuous.
2. Place feature vectors for record pairs into three classes: matches (M), non-matches (U), and possible matches (P). These correspond to "equivalent," "nonequivalent," and "possibly equivalent" (e.g., requiring human review) record pairs, respectively.
3. Perform record-pair classification by calculating the ratio $(P(\gamma \mid M)) / (P(\gamma \mid U))$ for each candidate record pair, where γ is a feature vector for the pair and $P(\gamma \mid M)$ and $P(\gamma \mid U)$ are the probabilities of observing that feature vector for a matched and non-matched pair, respectively. Two thresholds based on desired error levels—$T\mu$ and $T\lambda$—optimally separate the ratio values for equivalent, possibly equivalent, and nonequivalent record pairs.
4. When no training data in the form of duplicate and nonduplicate record pairs are available, matching can be unsupervised; that is, conditional probabilities for feature values are estimated using observed frequencies in the records to be linked.
5. Most record pairs are clearly nonmatches, so one need not consider them for matching. This situation is managed by "blocking," or partitioning the databases based on geography or some other variable in both databases, so that only records in comparable blocks are compared. Such a strategy significantly improves efficiency.

The first four components lay the groundwork for accurate record-pair matching using statistical or machine-learning prediction models such as logistic regression. The fewer identifiers used in steps 1 and 2, the poorer the match is likely to be. Accuracy is well known to be high when there is a 1–1 match between records in the two databases, and deteriorates as the overlap between the files decreases and the measurement error in the feature values consequently increases.

The fifth component provides for efficient processing of large databases, but to the extent that blocking is approximate and possibly inaccurate, its use decreases the accuracy of record-pair matching. The less accurate the matching, the more error (i.e., records not matched or matched inappropriately) there will be in the merged registry files. This *error* will impede the quality of analyses and findings from the resulting data.[17-19]

This standard approach has problems when (1) there are lists or files with little overlap, (2) there are undetected duplications within files, and (3) one needs to link three or more lists. In the latter case, one essentially matches all lists in pairs, and then resolves discrepancies. Unfortunately, there is no single agreed-upon way to do this, but some principled approaches have recently been suggested.[20] Record linkage methodology has been widely used by statistical agencies, especially the U.S. Census Bureau. The

methodology has been combined with disclosure limitation techniques such as the addition of "noise" to variables in order to produce public use files that the agencies believe cannot be linked back to the original databases used for the record linkage. Another technique involves protecting individual databases by stripping out identifiers and then attempting record linkage. This procedure has two disadvantages: first, the quality of matches is likely to decrease markedly; and second, the resulting merged records will still need to be protected by some form of disclosure limitation. Therefore, as long as there are no legal restrictions against the use of identifiers for record linkage purposes, it is preferable to use detailed identifiers to the extent possible and to remove them following the matching procedure.

Currently there are no special features of registry data known to enhance or inhibit matching. Registry data may be easier targets for re-identification because the specifics of diseases or conditions usually help to define the registries. In the United States, efforts are often made to match records using Social Security numbers. There are large numbers of entry errors for these numbers in many databases, and there are problems associated with multiple people using one number and some people using multiple numbers.[16] Lyons and colleagues describe a very large-scale matching exercise in the United Kingdom linking multiple health care and social services data sets using National Health Service numbers and various alternative sets of matching variables in the spirit of the record linkage methods described above. They report achieving accurate matching at rates of only about 95 percent.[21]

2.4 Procedural Issues in Linking Data Sets

It is important to understand that neither *data* nor *link* can be unambiguously defined. For instance, a data set may be altered by the application of tools for statistical disclosure limitation, in which case it is no longer the same data set. Linkage need not mean, as it is customarily construed, "bringing the two (or more) data sets together on a single computer." Many analyses of interest can be performed using technologies that do not require literal integration of the data sets.

Even the relationship between data sets can vary. Two data sets can hold the same attributes for different individuals (*horizontal partitioning*); for example, one data set may contain information for individuals born before a certain date, while a second data set contains the same information for individuals born after that date. Or, two data sets may contain different attributes for the same individuals (*vertical partitioning*); for example, one data set may contain clinician-reported information for a set of individuals, while a second data set contains laboratory data for the same individuals. Finally, some data sets may contain a complex combination of different attributes for different individuals.

The process of linking horizontally partitioned data sets engenders little incremental risk of re-identification. There is, in almost all cases, no more information about a record on the combined data set than was present in the individual data set containing it. Moreover, any analysis requiring only data summaries (i.e., in technical terms, sufficient statistics) that are additive across the data sets can be performed using tools based on the computer science concept of secure summation.[22] Examples of analyses for which this approach works include creation of contingency tables, linear regression, and some forms of maximum likelihood estimation.

Only in a few cases have comparable techniques for vertically partitioned data been well enough understood to be employed in practice.[23] Instead, it is usually necessary to actually link individual subjects' records that are contained in two or more data sets. This process is inherently and unavoidably risky because the combined data set contains more information about each subject than either of the components.

Suppose that each of the two data sets to be linked contains the same unique identifiers (for individuals, an example is Social Security numbers) in all of the records. In this case, techniques based on cryptography (e.g., homomorphic encryption[24] and hash functions) enable secure determination of individuals common to both data sets and assignment of unique but uninformative identifiers to the shared records. The combined data set can then be purged

of individual identifiers and altered to further limit re-identification. These alterations will of necessity reduce the accuracy of standard statistical analyses compared with an unaltered data set.

Such linkage techniques are computationally very complex, and may need to involve trusted third parties without access to information in either data set other than the common identifier.[25] Therefore, in many cases the database custodian may prefer to remove identifiers and carry out statistical disclosure limitation prior to linkage. It is important to understand that this latter approach compromises, perhaps irrevocably, the linkage process, and may introduce substantial errors into the linked data set that later— perhaps dramatically—alter the results of statistical analyses.

Many techniques for record linkage depend at some level on the presence of combinations of attributes in both databases that are unique to individuals but do not lead to re-identification—a combination that may be difficult to find. For instance, the combination of date of birth, gender, and ZIP Code of residence might be present in both databases. It is estimated that this combination of attributes uniquely characterizes a significant portion of the U.S. population—somewhere between 65 and 87 percent, or even higher for certain subpopulations—so that re-identification would only require access to a suitable external database.[26, 27] Other techniques such as the Fellegi-Sunter record linkage methods described above are more probabilistic in nature. They can be effective, but they also introduce data quality effects that cannot readily be characterized, and the intrinsic error associated with the matching will need to be accounted for in some fashion when the linked data set is analyzed. Simulations and sensitivity analyses may help clarify the extent of the issues here, but will rarely be sufficient.

No matter how linkage is performed, a number of other issues should be addressed. For instance, comparable attributes should be expressed in the same units of measure in both data sets (e.g., English or metric values for weight). Also, conflicting values of attributes for each individual common to both databases need reconciliation.

Another issue involves the management of patient records that appear in only one database; the most common decision is to drop them. Data quality provides another example; it is one of the least understood statistical problems and has multiple manifestations.[28] Even assuming some limited capability to characterize data quality, the relationship between the quality of the linked data set and the quality of each component should be considered. The linkage itself can produce quality degradation. For example, there is reason to believe that the quality of a linked data set is strictly less than that of either component, and not, as might be supposed, somewhere between the two.

Finally, it is important to understand that there exist endemic risks to data linkage. Anyone with access to one of the original data sets and the linked data set may learn, even if imperfectly, the values of attributes in the other. It may not be possible to determine what knowledge the linkage will create without actually executing the linkage. For these reasons, strong consideration should be given to forms of data protection such as licensing and restricted access in research data centers, where both analyses and results can be controlled.

3. Legal Aspects of Data Linkage Projects

3.1 Risks of Identification

The HIPAA Privacy Rule describes two methods for de-identifying health information.[29] One method requires a formal determination by a qualified expert (e.g., a qualified statistician) that the risk is very small that an individual could be identified. The other method requires the removal of 18 specified identifiers of the individual and of the individual's relatives, household members, and employers, as well as no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual. (See Chapter 7 for more information.) For more information about methods of de-identification under the HIPAA Privacy Rule, see the recent HHS guidance published on this topic.[30]

The data removal process alone may not be sufficient to remove risks of re-identification.

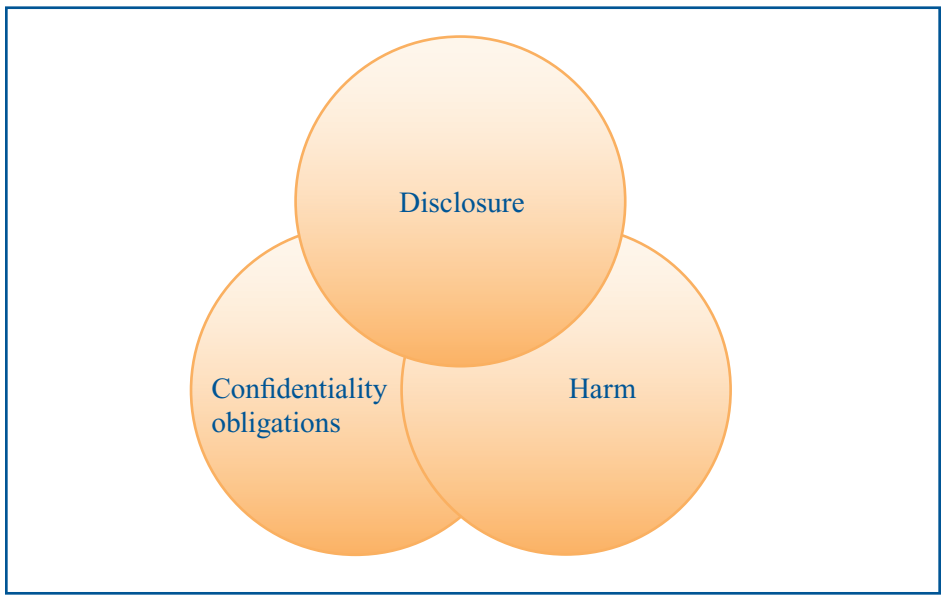
Residual data especially vulnerable to disclosure threats include (1) geographic detail, (2) longitudinal information, and (3) extreme values (e.g., income). In addition, variables that are available in other accessible databases pose special risks.

Statistical organizations such as the National Center for Health Statistics have traditionally focused on the issue of identity disclosure and thus refused to report information in which individuals or institutions can be identified. Concerns about identity disclosure arise, for example, when a data source is unique in the population for the characteristics under study, and is directly identifiable in the database to be released. But such uniqueness and subsequent identity disclosure may not reveal any information other than the association of the source with the data collected in the study. In this sense, identity disclosure may only be a technical violation of a promise of confidentiality. Thus, uniqueness only raises the issue of possible confidentiality problems resulting from identification. A separate issue is whether the release of information is one that is permitted by the HIPAA Privacy Rule or is authorized by the data source.

The foregoing discussion implicitly introduces the notion of "harm," which is not the same as a breach of confidentiality. For example, it is possible for a pledge of confidentiality to be technically violated, but produce no harm to the data source because the information is "generally known" to the public. In this case, some would argue that additional data protection is not required. Conversely, information on individuals or organizations in a release of sample statistical data may well increase the information about characteristics of individuals or organizations not in the sample. This information may produce an inferential disclosure for such individuals or organizations and cause them harm, even though there was no confidentiality obligation. Skinner[31] suggests the separation of assessment of disclosure potential from harm.

Figure 16–1 depicts the overlapping relationships among confidentiality, disclosure, and harm.

Figure 16–1. Relationships among confidentiality, disclosure, and harm



Some people believe that the way to ensure confidentiality and prevent identity disclosure is to arrange for individuals to participate in a study anonymously. In many circumstances, such a belief is misguided, because there is a key distinction between collecting information anonymously and ensuring that personal identifiers are not inappropriately made available. Moreover, clinical health care data are simply not collected anonymously. Not only do patient records come

with multiple identifiers crucial to ensuring patient safety for clinical care, but they also contain other information that may allow the identification of patients even if direct identifiers are stripped from the records.

Moreover, health- or medicine-related data may also come from sample surveys in which the participants have been promised that their data will not be released in ways that would allow them to be individually identified. Disclosure of such data can produce substantial harm to the personal reputations or financial interests of the participants, their families, and others with whom they have personal relationships. For example, in the pilot surveys for the National Household Seroprevalence Survey, the National Center for Health Statistics moved to make responses during the data collection phase of the study anonymous because of the harm that could potentially result from information that an individual had an HIV infection or engaged in high-risk behavior. But such efforts still could not guarantee that one could not identify a participant in the survey database.

The question about the confidentiality of registry data persists after an individual's death, in part because of the potential for harm to others. The health information of decedents is subject to the HIPAA Privacy Rule until 50 years after their death (see Chapter 7 for more information), and several statistical agencies explicitly treat the identification of a deceased individual as a violation of their confidentiality obligations.

3.1.1 Examples of Patient Re-Identification

For years, the confidentiality of health information has been protected through a process of "de-identification." This protection entails the removal of person-specific features such as names, residential street addresses, phone numbers, and Social Security numbers. However, as discussed above, de-identification does not guarantee that individuals may not be identified from the resulting data. On multiple occasions, it has been shown that de-identified health information can be "re-identified" to a particular patient without hacking or breaking into a private health information system. For instance, before the HIPAA de-identification standards were created, Latanya Sweeney, a graduate student at the Massachusetts Institute of Technology in the mid-1990s, showed that de-identified hospital discharge records, which were made publicly available at the State level, could be linked to identifiable public records in the form of voter registration lists. Her demonstration received notoriety because it led to the re-identification of the medical status of the then-governor in the Commonwealth of Massachusetts.[32] This result was achieved by linking the data resources on their common fields of patient's date of birth, gender, and ZIP Code. As noted earlier, this combination identifies unique individuals in the United States at a rate estimated at somewhere between 65 and 87 percent or even higher in certain subpopulations.[27]

3.1.2 High-Risk Identifiers

One response to the Sweeney demonstration was the HIPAA Privacy Rule method for de-identification by removal of data elements. This process requires the removal of 18 explicit identifiers from patient information before it is considered de-identified, including dates of birth and ZIP Codes. (See Chapter 7.)[33] Nonetheless, even the removal of these data elements may fail to prevent re-identification, as there may be residual features that can lead to identification. The extent to which residual features can be used for re-identification depends on the availability of relevant data fields. Thus, one can roughly partition identifiers into "high-risk" and relatively "low-risk" features. The high-risk features are documented in multiple environments and publicly available. These features could be exploited by any recipient of such records. For instance, patient demographics are high-risk identifiers. Even de-identified health information permitted under the HIPAA Privacy Rule may leave certain individuals at risk for identification if the data are combined with public data resources containing similar features, such as public records containing birth, death, marriage, voter registration, and property assessment information.[30, 34-36]

3.1.3 Relatively Low-Risk Identifiers

In contrast, lower risk data elements do not appear in public records and are less available. For instance, clinical features, such as an individual's

diagnosis and treatments, are relatively static because they are often mapped to standard codes for billing purposes. These features might appear in de-identified information, such as hospital discharge databases, as well as in identified resources such as electronic medical records. While combinations of diagnostic and treatment codes might uniquely describe an individual patient in a population, the identifiable records are available to a much smaller group than the general public. Moreover, these select individuals, such as the clinicians and business associates of the custodial organization for the records, are ordinarily considered to be trustworthy, because they owe independent ethical, professional, and legal duties of confidentiality to the patients.

3.1.4 Special Issues With Linkages to Biospecimens

Health care is increasingly moving towards evidence-based and personalized systems. In support of this trend, there is a growing focus on associations between clinical and biological phenomena. In particular, the decreasing cost of genome sequencing technology has facilitated a rapid growth in the volume of biospecimens and derived DNA sequence data. As much of this research is sponsored through Federal funding, it is subject to Federal data sharing requirements. However, biospecimens, and DNA in particular, are inherently unique and there are a number of routes by which DNA information can be identified to an individual.[37] For instance, there are over 1 million single nucleotide polymorphisms (SNPs) in the human genome; these little snippets of DNA are often used to make genetic correlations with clinical conditions. Yet it is estimated that fewer than 100 SNPs can uniquely represent an individual.[38] Thus, if de-identified biological information is tied to sensitive clinical information, it may provide a match to the identified biological information—as, for example, in a forensic setting.[39]

Biospecimens and information derived from them are of particular concern because they can convey knowledge not only about the individual from whom they are derived, but also about other related individuals. For instance, it is possible to derive estimates about the DNA sequence of relatives.[40] If the genetic information is predictive or diagnostic, it can adversely affect the ability of family members to obtain insurance and employment, or it may cause social stigmatization.[41-43] The Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits health insurers from using genetic information about individuals or their family members, whether collected intentionally or incidentally, in determining eligibility and coverage, or in underwriting and setting premiums.[44] Insurers, in collaboration with external research entities, may request that policyholders undergo genetic testing, but a refusal to do so cannot be permitted to affect the premium or result in medical underwriting.

4. Risk Mitigation for Data Linkage Projects

4.1 Methodology for Mitigating the Risk of Re-Identification

The disclosure limitation methods briefly described in this section are designed to protect against identification of individuals in statistical databases, and are among the techniques that data linkage projects involving registries are most likely to use. One problem these methods do not address is the simultaneous protection of individual and institutional data sources. The discussion here also relates to the problems addressed by secure computation methodologies, which are explored in the next section.

4.1.1 Basic Methodology for Statistical Disclosure Limitation

Duncan[45] categorizes the methodologies used for disclosure limitation in terms of disclosure-limiting masks, i.e., transformations of the data where there is a specific functional relationship (possibly stochastic) between the masked values and the original data. The basic idea of masking involves data transformations. The goal is to transform an n x p data matrix Z through pre- and post-multiplication and the possible addition of noise, such as depicted in Equation (1):

$$Z \longrightarrow AZB+C \quad (1)$$

where A is a matrix that operates on cases, B is a matrix that operates on variables, and C is a matrix

that adds perturbations or noise to the original information. Matrix masking includes a wide variety of standard approaches to disclosure limitation:

- Addition of noise
- Release of a subset of observations (deleting rows from *Z*)
- Cell suppression for cross-classifications
- Inclusion of simulated data (addition of rows to *Z*)
- Release of a subset of variables (deletion of columns from *Z*)
- Switching of selected column values for pairs of rows (data swapping)

This list also omits some methods, such as micro-aggregation and doubly random swapping, but it provides a general idea of the types of techniques being developed and applied in a variety of contexts, including medicine and public health. The possibilities of both identity and attribute disclosure remain even when a mask is applied to a data set, although the risks may be substantially diminished.

Duncan suggests that we can categorize most disclosure-limiting masks as suppressions (e.g., cell suppression), recodings (e.g., collapsing of rows or columns, or swapping), or samplings (e.g., release of subsets), although he also allows for simulations as discussed below. Further, some masking methods alter the data in systematic ways (e.g., through aggregation or through cell suppression), whereas others do it through random perturbations, often subject to constraints for aggregates. Examples of perturbation methods are controlled random rounding, data swapping, and the post-randomization method (PRAM) of Gouweleeuw,[46] which has been generalized by Duncan and others. One way to think about random perturbation methods is as restricted simulation tools. This characterization connects them to other types of simulation approaches.

Various authors pursue simulation strategies and present general approaches to "simulating" from a constrained version of the cumulative, empirical distribution function of the data. In 1993, Rubin asserted that the risk of identity disclosure could be eliminated by the use of synthetic data (in his case using Bayesian methodology and multiple imputation techniques) because there is no direct function link between the original data and the released data.[47] Said another way, the data remain confidential because simulated individuals have replaced all of the real ones. Raghunathan, Reiter, and Rubin[48] provide details on the implementation of this approach. Abowd and Woodcock (in their chapter in Doyle et al., 2001)[49] describe a detailed application of multiple imputation and related simulation technology for a longitudinally linked individual and work history data set. With both simulation and multiple-imputation methodology, however, it is still possible that the data values of some simulated individuals remain virtually identical to those in the original sample, or at least close enough that the possibility of both identity and attribute disclosure remain. As a result, checks should be made for the possibility of unacceptable disclosure risk.

Another important feature of the statistical simulation approach is that information on the variability of the data set is directly accessible to the user. For example, in the Fienberg, Makov, and Steele[50] approach for categorical data, the data user can begin with the reported table and information about the margins that are held fixed, and then run the Diaconis-Sturmfels Monte Carlo Markov chain algorithm to regenerate the full distribution of all possible tables with those margins. This technique allows the user to make inferences about the added variability in a modeling context that is similar to the approach to inference in Gouweleeuw and colleagues.[46] Similarly, Raghunathan and colleagues proposed the use of multiple imputations to directly measure the variability associated with the posterior distribution of the quantities of interest.[48] As a consequence, Rubin showed that simulation and perturbation methods represent a major improvement in access to data over cell suppression and data swapping without sacrificing confidentiality. These methods also conform to the statistical principle allowing the user of released data to apply standard statistical operations without being misled.

There has been considerable research on disclosure limitation methods for tabular data, especially in the form of multidimensional tables of counts

(contingency tables). The most popular methods include a process known as cell suppression, which systematically deletes the values in selected cells in the table and collapses categories. This process is a form of aggregation. While cell suppression methods have been very popular among the U.S. Government statistical agencies, and are useful for tables with nonnegative entries rather than simple counts, they also have major drawbacks. First, good algorithms do not yet exist for the methodology when it is associated with high-dimensional tables. More importantly, the methodology systematically distorts the information about the cells in the table for users, and, as a consequence, makes it difficult for secondary users to draw correct statistical inferences about the relationships among the variables in the table. For further discussion of cell suppression, and for extensive references, see the various chapters in Doyle et al.,[49] notably the one by Duncan and his collaborators.

A special example of collapsing categories involves summing over variables to produce marginal tables. Instead of reporting the full multidimensional contingency table, one or more collapsed versions of it might be reported. The release of multiple sets of marginal totals has the virtue of allowing statistical inferences about the relationships among the variables in the original table using log-linear model methods (e.g., see Bishop, Fienberg, and Holland).[51] With multiple collapsed versions, statistical theory makes it clear that one may have highly accurate information about the actual cell entries in the original table. As a result, the possibility of disclosures still requires investigation. In part to address this problem, a number of researchers have recently worked on the problem of determining upper and lower bounds for the cells of a multi-way table given a set of margins; however, other measures of risk may clearly be of interest. The problem of computing bounds is in one sense an old one, at least for two-way tables, but it is also deeply linked to recent mathematical developments in statistics and has generated a flurry of new research.[52, 53]

4.1.2 The Risk-Utility Tradeoff

Common to virtually all the methodologies discussed in the preceding section is the notion of a risk-utility tradeoff, in which the risk of disclosure is balanced with the utility of the released data (e.g., see Duncan,[45] Fienberg,[54] and their chapter with others in Doyle et al.[49]). To keep this risk at a low level requires applying more extensive data masking, which limits the utility of what is released. Advocates for the use of simulated data often claim that this use eliminates the risk of disclosure, but still others dispute this claim. See also the recent discussion of risk-utility paradigms by Cox and colleagues.[55]

4.1.3 Privacy-Preserving Data Mining Methodologies

With advances in data mining and machine learning over the past two decades, a large number of methods have been introduced under the banner of privacy-preserving computation. The methodologies vary, and many of them focus on standard tools such as the addition of noise or data swapping of one sort or another. But the claims of identity protection in this literature are often exaggerated or unverifiable. For a discussion of some of these ideas and methods, see Fienberg and Slavkovic[53] and El Emam and colleagues.[34] For two recent interesting examples explicitly set in the context of medical data, see Malin and Sweeney[56] and Boyens, Krishnan, and Padman.[57]

The common message of this literature is that privacy protection has costs measured in the lack of availability of research data. To increase the utility of released data for research, some measure of privacy protection, however small, needs to be sacrificed. It is nonetheless still possible to optimize utility, subject to predefined upper bounds on what is considered to be acceptable risk of identification. See a related discussion in Fienberg.[58]

4.1.4 Cryptographic Approaches to Privacy Protection

While the current risks of identification in modern databases are similar for statistical agencies and biomedical researchers, there are also new challenges: from contemporary information repositories that store social network data (e.g., cell phone, Twitter, and Facebook data), product preferences data (e.g., Amazon), Web search data, and other sources of information not previously archived in a digital format. A recent literature emanating from cryptography focuses on

algorithmic aspects of this problem with an emphasis on automation and scalability of a process for conferring anonymity. Automation, in turn, presents a fundamentally different perspective on how privacy is defined and provides for both a formal definition of privacy and proofs for how it can be protected. By focusing on the properties of the algorithm for anonymity, it is possible to formally guarantee the degree of privacy protection and the quality of the outputs in advance of data collection and publication.

This new approach, known as differential privacy, limits the incremental information a data user might learn beyond that which is known before exposure to the released statistics. No matter what external information is available, the differential privacy approach guarantees that the same information is learned about an individual, whether or not information about the individual is present in the database. The papers by Dwork and colleagues[59, 60] provide an entry point to this literature. Differential privacy, as these authors describe it, works primarily through the addition of specific forms of noise to all data elements and the summary information reported, but it does not address issues of sampling or access to individual-level microdata. While these methods are intriguing, their utility for data linkages with registry data remains an open issue.[61]

4.1.5 Security Practices, Standards, and Technologies

In general, people adopt two different philosophical positions about how the confidentiality associated with individual-level data should be preserved: (1) by "restricted or limited information," that is, restrictions on the amount or format of the data released, and (2) by "restricted or limited access," that is, restrictions on the access to the information itself.

If registry data are a public health good, then restricted access is justifiable only in situations where the confidentiality of data in the possession of a researcher cannot be protected through some form of restriction on the information released. Restricted access is intended to allow use of unaltered data by imposing certain conditions on users, analyses, and results that limit disclosure risk. There are two primary forms of restricted access. The first is through licensing, whereby users are legally bound by certain conditions, such as agreeing not to use data for re-identification and to accept advance review of publications. The licensure approach allows users to transfer data to their sites and use the software of their choice. The second approach is exemplified by research data centers, discussed in more detail below, and remote analysis servers, which are conceptually similar to data centers: users, and sometimes analyses, are evaluated in advance. The results are reviewed, and often limited, in order to limit risk of disclosure. The data remain at the holder's site and computers; the difference between a research data center and a remote analysis server is whether access is in person at a data center or using a remote analysis center via the Internet.

4.1.6 Registries as Data Enclaves

Many statistical agencies have built enclaves, often referred to as research data centers, where users can access and use data in a regulated environment. In such settings, the security of computer systems is controlled and managed by the agency providing the data. Such environments may maximize data security. For a more extensive discussion of the benefits of restricted access, see the chapter by Dunne in Doyle et al.[49]

These enclaves incur considerable costs associated with their establishment and upkeep. A further limitation is that the enclave may require the physical presence of the data user, which also increases the overall cost to researchers working with the data. Moreover, such environments often prevent users from executing specialized data analyses, which may require programming and other software development beyond the scope of traditional statistical software packages made available in the enclave.

The process for granting access to data in enclaves or restricted centers involves an examination of the research credentials of those wishing to do so. In addition, these centers control the physical access to confidential data files and they review the materials that data users wish to take from the centers and to publish. Researchers who are accustomed to reporting residual plots and other information that allows for a partial reconstruction of the original data, at least for some variables,

will encounter difficulties, because restricted data centers typically do not allow users to remove such information.

4.1.7 Accountability

To limit the possibility of re-identification, data can be manipulated by the above techniques to mitigate risk. At the same time, it is important to ensure that researchers are accountable for the use of the data sets that are made available to them. Best practices in data security should be adopted with specific emphasis on authentication, authorization, access control, and auditing. In particular, each data recipient should be assigned a unique login identification, or, if the data are made available online, access may be provided through a query response server. Prior to each session of data access, data custodians should authenticate the user's identity. Access to information should be controlled either in a role-based or information-based manner. Each user access and query to the data should be logged to enable auditing functions. If there is a breach in data protection, the data custodian can investigate the potential cause and make any required notifications.

4.1.8 Layered Restricted Access to Databases

In many countries, the traditional arrangement for data use involves restrictions on both information and access, with only highly aggregated data and summary statistics released for public use.

One potential strategy for privacy protection for the linkage of registries to other confidential data is a form of layered restrictions that combines two approaches with differing levels of access at different levels of detail in the data. The registry might function as an enclave, similar to those described above, and in addition, public access might be limited to only aggregate data. Between these two extremes there might be several layers of restricted access. An example is licensing that includes privacy protection, requiring greater protection as the potential for disclosure risk increases.

5. Legal and Technical Planning Questions

The questions in Tables 16–1 and 16–2 are intended to assist in the planning of data linkage projects that involve using registry data plus other files. Registry operators should use the answers to these questions to assemble necessary information and other resources to guide planning for their data linkage projects. Like the preceding discussion, this section considers regulatory and technical questions.

Several assumptions underlie the regulatory questions that follow in Table 16–1. Their application to the proposed data linkage project should be confirmed or determined. These assumptions are listed here:

- The HIPAA Privacy Rule applies to the entities that first collect data from individuals/subjects.
- Other laws may restrict access or use of the initial data sources.
- The Common Rule or FDA regulations may or may not apply to data linkage.
- The Common Rule or FDA regulations may or may not apply to the original data sets.

Different regulatory concerns arise depending on the answers to each category of the following questions. Consult as necessary with experienced health services, social science, or statistician colleagues; and with regulatory personnel (e.g., the agency Privacy Officer) or legal counsel to clarify answers for specific data linkage projects.

Table 16–1. Legal planning questions

1. Purpose(s) for data linkage	• Research? • Public health? • Quality improvement? • Required for postmarketing safety studies? • Determining effectiveness of a product or service? • Other purpose? • Combination of purposes?
2. Conditions under which data (plus or minus biospecimens) were originally collected	• Collection required by law (e.g., Federal regulatory mandate, State public health mandate)? • For treatment, payment, or health care operations, as defined by the HIPAA Privacy Rule? • With documented consent from each individual to research participation and authorization for research use of PHI? • With an IRB alteration or waiver of consent and authorization? • With permission of health care provider or plan? • With contractual conditions or limitations on future use or disclosure (release)? • What are the reasonable expectations, held by the subjects of the information and the entities that first collected individuals' information, of privacy or confidentiality for future uses of the data?
3. Data	• Is sensitive information involved (e.g., about children, infectious disease, mental health conditions)? • Do the data contain direct identifiers? Indirect identifiers? • Is PHI involved? • Is a limited data set (LDS), and thus a data use agreement (DUA), involved? • Are the data de-identified in accordance with the HIPAA Privacy Rule? • Do the data contain a code to identifiers? • Who holds the key to the code? • Is a neutral third party (an honest broker) involved? • Does the code to identifiers conform to the re-identification standard in the HIPAA Privacy Rule? • Is re-identification needed prior to performing the data linkage? • Will the data linkage increase the risk that the data may be identifiable? • What is the minimally acceptable cell size to avoid identifying individuals?
4. Person or institution holding the data for the linkage	• Is this person or institution a covered entity or a business associate of a covered entity under the HIPAA Privacy Rule?
5. Person or institution performing data linkage	• Is this person or institution a covered entity or a business associate of a covered entity under the HIPAA Privacy Rule or the American Recovery and Reinvestment Act of 2009?
6. Other laws or policies that may apply to data use or disclosure (release)	• Are government data involved? • Are NIH data sharing policies involved? • Does State law apply? Which State?
7. Terms and conditions that apply to data disclosure (release) and use	• Are there consent and authorization documents that contain limitations on data use—unless the data have been sufficiently de-identified? • Is there a DUA or other contract that applies to data use by any subsequent holder of the data?

Table 16–1. Legal planning questions (continued)

8. Anticipated needs for data validation and verification	• Initially for the data linkage processes? • In the future?
9. Future need to protect the privacy and security of the data	• What will happen to data resulting from the linkage once the analyses have been completed? How will the data be stored? • What measures will be in place to protect the security of the data?
10. Anticipated future uses of the linked data	• Will the data resulting from the linkage be maintained for multiple analyses? For the same or different purposes? • Will the data resulting from the linkage be used for other linkages? • What permissions are necessary for, or restrictions apply to, planned future uses of the data? • Are there currently requirements for tracking uses and disclosures of the data?

DUA = data use agreement; HIPAA = Health Insurance Portability and Accountability Act; IRB = institutional review board; LDS = limited data set; NIH = National Institutes of Health; PHI = protected health information.

Table 16–2. Technical planning questions

• Who is performing the linkage? Are the individuals performing the linkage permitted access to identifiers or restricted sets of identifiers? Are they neutral agents ("honest brokers") or the source of one of the data sets to be linked?
• Is there a common feature or pseudonym (sets of attributes in both databases that are unique to individuals but do not lead to re-identification) available across the data sets being linked?
• Is the registry a flat file or a relational database?* The latter is more difficult to manage unless a primary key is applied.
• Is the registry relatively static or dynamic? The latter is harder to manage if data are being added over time, because the risk of identification increases.
• How many attributes are included in the registry? The more attributes, the harder it will be to manage the risk of identification associated with the registry.
• How will conflicting values of attributes common to both databases be resolved? (Comparable attributes such as weight should be converted to the same units of measurement in data sets that will be linked.)
• Does the registry contain information that makes the risk of identification intrinsic to the registry? Direct identifiers such as names and Social Security numbers are problematic, as is fine-scale geography.
• Is there a sound data dictionary?
• How many external databases will be linked to the registry data? How readily available and costly is each external database?
• How will records that appear in only one database be managed?
• How will the accuracy of the linked data set relate to the accuracy of its components? The accuracy is only as good as that of the least accurate component.

*In a relational database, information is presented in tables with rows and columns. Data within a table may be related by a common concept, and the related data may be retrieved from the database. (From A Relational Database Overview. http://docs.oracle.com/javase/tutorial/jdbc/overview/database.html. Accessed July 16, 2013).

6. Summary

This chapter describes technical and current legal considerations for researchers interested in creating data linkage projects involving registry data. In addition, the chapter presents typical methods for record linkage that are likely to form the basis for the construction of data linkage projects. It also discusses both the hazards for re-identification created by data linkage projects, and the statistical methods used to minimize the risk of re-identification. Two topics not covered in this chapter are (1) considerations about linking data from public and private sectors, where different, perhaps conflicting, ethical and legal restrictions may apply, and (2) the risks involved in identifying the health care providers that collect and provide data.

Data set linkage entails the risks of loss of reliable confidential data management and of identification or re-identification of individuals and institutions. Recognized and developing statistical methods and secure computation may limit these risks and allow the public the health benefits that registries linked to other data sets have the potential to contribute.

Case Examples for Chapter 16

Case Example 36. Linking registries at the international level

Description	Psonet is an investigator-initiated, international scientific network of coordinated population-based registries; its aim is to monitor the long-term effectiveness and safety of systemic agents in the treatment of psoriasis.
Sponsor	Supported initially by a grant from the Italian Medicines Agency (AIFA); supported since 2011 by a grant from the European Academy of Dermato Venereology (EADV) and coordinated by the Centro Studi GISED.
Year Started	2005
Year Ended	Ongoing
No. of Sites	9 registries across Europe and an Australasian registry
No. of Patients	27,800

Challenge

The number of options for systemic treatment of psoriasis has greatly increased in recent years. Because psoriasis is a chronic disease requiring lifelong treatment, data on long-term effectiveness and safety are needed for both old and new treatments. Several European countries have established patient registries for surveillance of psoriasis treatments and outcomes. However, these registries tend to have small patient populations and little geographic diversity, limiting their strength as surveillance tools for rare or delayed adverse events.

Proposed Solution

Combining the results from nation-based registries would increase statistical power and may enable investigators to conduct analyses that would not be feasible at a single-country level. Psonet was established in 2005 as a network of European registries of psoriasis patients being treated with systemic agents. The goal of the network is to improve clinical knowledge of prognostic factors and patient outcomes, thus improving treatment of psoriasis patients. An International Coordinating Committee (ICC), including representatives of the national registries and some national pharmacovigilance centers, oversees the network activities, including data management, publications, and ethical or privacy issues. The ICC has appointed an International Safety Review Board, whose job is to review safety data, prepare periodic safety reports, and set up procedures for the prompt identification and investigation of unexpected adverse events. Informed consent for data sharing is obtained before patients are enrolled in participating registries.

Case Example 36. Linking registries at the international level (continued)

Proposed Solution (continued)

When drafting the registry protocol, member registries agreed to a common set of variables and procedures to be included and implemented in the national registries. However, some registries were already active at the time the draft was written, and harmonization is not perfect. Although inclusion criteria, major outcomes, and followup schedules are quite similar among registries, there are some differences. There are also differences in terms of software used, data coding, and data ownership arrangements. These factors made sharing individual patient data complicated, and an alternate solution was identified: meta-analysis of summary measures from each registry. As summary measures (or effect measures) are calculated, the methods used to obtain them are decided in advance, including methods used to control for confounding and methods used to temporarily link exposures and events.

Results

Ten national and local registries at different stages of development are associated with the registry to date, contributing a total of about 27,800 patients. While the registry is too new to have published results, planned activities and analyses include comparative data on treatment strategies for psoriasis in Europe, rapid alerts on newly recognized unexpected events, regular reports on effectiveness and safety data, and analyses of risk factors for lack of response as a preliminary step to identifying relevant biomarkers.

Key Point

Data from multiple registries in different countries may be combined to provide larger patient populations for study of long-term outcomes and surveillance for rare or delayed adverse events. Meta-analysis of prospectively calculated summary measures can be a useful tool.

For More Information

Psonet: European Registry of Psoriasis. http://www.psonet.eu/cms/.

Lecluse LLA, Naldi L, Stern RS, et al. National registries of systemic treatment for psoriasis and the European 'Psonet' initiative. Dermatology. 2009;218(4):347–56.

Naldi L. The search for effective and safe disease control in psoriasis. Lancet. 2008;371:1311–2.

Case Example 37. Linking a procedure-based registry with claims data to study long-term outcomes

Description	The CathPCI Registry measures the quality of care delivered to patients receiving diagnostic cardiac catheterizations and percutaneous coronary interventions (PCI) in both inpatient and outpatient settings. The primary outcomes evaluated by the registry include the quality of care delivered, outcome evaluation, comparative effectiveness, and postmarketing surveillance.
Sponsor	American College of Cardiology Foundation through the National Cardiovascular Data Registry. Funded by participation dues from catheterization laboratories.
Year Started	1998
Year Ended	Ongoing
No. of Sites	1,450 catheterization laboratories
No. of Patients	12.7 million patient records; 4.5 million PCI procedures

Challenge

The registry sponsor was interested in studying long-term patient outcomes for diagnostic cardiac catheterizations and PCI, but longitudinal data are not collected as part of the registry. Rather than create an additional registry, it was determined that the most feasible option was linking the registry data with available third-party databases such as Medicare.

Before the linkage could occur, however, several legal questions needed to be addressed, including what identifiers could be used for the linkage and whether institutional review board (IRB) approval was necessary.

Proposed Solution

The registry developers explored potential issues relating to the use of protected health information (under the Federal HIPAA [Health Insurance Portability and Accountability Act] law) to perform the linkage; the applicability of the Common Rule (protection of human subjects) to the linkage; and the contractual obligations of the individual legal agreement with each participating hospital with regard to patient privacy. The registry gathers existing data, including direct patient identifiers collected as part of routine health care activities. Informed consent is not required. The registry sponsor has business associate agreements in place with participating catheterization laboratories for which the registry conducts the outcomes evaluations.

After additional consultation with legal counsel, the registry sponsor concluded that the linkage of data could occur under two conditions: (1) that the data sets used in the merging process must be in the form of a *limited data set* (see Chapter 7), and (2) that an IRB must evaluate such linkage. The decision to implement the linkage was based on two key factors. First, the registry participant agreement includes a data use agreement, which permits the registry sponsor to perform research on a limited data set but also requires that no attempt be made to identify the patient. Second, since there was uncertainty as to whether the proposed data linkage would meet the definition of research on human subjects, the registry sponsor chose to seek IRB approval, along with a waiver of informed consent.

Results

The registry data were linked with Medicare data, using probabilistic matching techniques to link the limited data sets. A research protocol describing the need for linkage, the linking techniques, and the research questions to be addressed was approved by an IRB. Researchers must reapply for IRB approval for any new research questions they wish to study in the linked data.

Results of the linkage analyses were used to develop a new measure, "Readmission following PCI," for the Centers for Medicare & Medicaid Services' hospital inpatient quality pay-for-reporting program.

Case Example 37. Linking a procedure-based registry with claims data to study long-term outcomes (continued)

Key Point

There are many possible interpretations of the legal requirements for linking registry data with other data sources. The interpretation of legal requirements should include careful consideration of the unique aspects of the registry, its data, and its participants. In addition, clear documentation of the way the interpretation occurred and the reasoning behind it will help to educate others about such decisions and may allay anxieties among participating institutions.

For More Information

https://www.ncdr.com/webncdr/cathpci/

Case Example 38. Linking registry data to examine long-term survival

Description	The Yorkshire Specialist Register of Cancer in Children and Young People is a population-based registry that collects data on children and young adults diagnosed with a malignant neoplasm or certain benign neoplasms, living within the Yorkshire and Humber Strategic Health Authority (SHA). The goals of the registry are (1) to serve as a data source for research at local, national, and international levels on the causes of cancer in children, teenagers, and young people, and (2) to evaluate the delivery of care provided by clinical and other health service professionals.
Sponsor	Primary funding is provided by the Candlelighters Trust, Leeds.
Year Started	1974
Year Ended	Ongoing
No. of Sites	18 National Health Service (NHS) Trusts
No. of Patients	7,728

Challenge

In 2002, approximately 1,500 children in the United Kingdom were diagnosed with cancer. Previous estimates of malignant bone tumors in children have been approximately 5 per million person-years in the United Kingdom. The registry collects data on individuals younger than 30 living within the Yorkshire and Humber SHA, and diagnosed with a malignant neoplasm or certain benign neoplasms by pediatric oncology and hematology clinics or teenage and young adult cancer clinics. Primary patient outcomes of the registry include length of survival, access to specialist care, late effects following cancer treatment, and hospital activity among long-term survivors. While bone cancer is ranked as the seventh most common malignancy in the United Kingdom, the relative rarity of this type of childhood cancer makes it difficult to gather sufficient data to evaluate incidence and survival trends over time.

Proposed Solution

The registry participated in a collaborative effort to combine its data with three other population-based registries—the Northern Region Young Persons' Malignant Disease Registry, the West Midlands Regional Children's Tumour Registry, and the Manchester Children's Tumour Registry. Together, the four population-based registries represented approximately 35 percent of the children in England.

Results

In a 20-year period from 1981 to 2002, 374 cases of malignant bone tumors were identified in children ages 0 to 14 years. The age-standardized incidence rate for all types of bone cancers (i.e., osteosarcoma, chondrosarcoma, Ewing sarcoma, and "other") was reported to be 4.84 per million per year. For the two most common types of bone cancer, osteosarcoma and Ewing sarcoma, the incidence rates were 2.63 cases per million person-years (95% confidence interval [CI], 2.27

Case Example 38. Linking registry data to examine long-term survival (continued)

Results (continued)

to 2.99) and 1.90 cases per million person year (95% CI, 1.58 to 2.21), respectively. While an improvement in survival was observed in patients with Ewing sarcoma, no survival improvement was detected in patients with osteosarcoma. The 5-year survival rate for children with all types of diagnoses observed in the study was an estimated 57.8 percent (95% CI, 52.5 to 63).

Key Point

In the analysis of rare diseases, the number of cases and deaths included in the study determines the statistical power for examining survival trends and significant risk factors, and the precision in estimating the incidence rate or other parameters of disease. In cases where it is difficult to obtain a large enough sample size within a single study, considerations should be given to combining registry data collected among similar patient populations.

For More Information

Eyre R, Feltbower RG, Mubwandarikwa E, et al. Incidence and survival of childhood bone tumours in Northern England and the West Midlands, 1981. Br J Cancer. 2002;2009(s100):188–93.

Case Example 39. Linking longitudinal registry data to Medicaid Analytical Extract files

Description	The Cystic Fibrosis Foundation (CFF) Patient Registry is a rare-disease registry that collects data from clinical visits, hospitalizations, and care episodes to track national trends in morbidity and mortality, assess the effectiveness of treatments, and drive quality improvement in patients with cystic fibrosis (CF).
Sponsor	Cystic Fibrosis Foundation
Year Started	1986
Year Ended	Ongoing
No. of Sites	110 CFF-accredited care centers in the United States
No. of Patients	More than 26,000

Challenge

Clinical services and health information generated outside of clinic visits and hospitalizations at accredited care centers may or may not be captured in the CFF Patient Registry. Therefore, administrative claims data such as Medicaid Analytical Extract (MAX), with comprehensive information on reimbursed health services, are necessary to completely evaluate drug exposure for epidemiological studies. To protect patient information, the CFF Patient Registry only collects the last four digits of the Social Security number, gender, and date of birth as direct patient identifiers. Since these identifiers are largely non-unique, linkage of the registry data to other data sources presents a challenge.

Proposed Solution

A deterministic patient matching algorithm, or linkage rule, between the CFF Patient Registry and MAX data using non-unique patient identifiers was developed to link the two data sources. MAX patients (with at least two in- or outpatient claims with diagnosis for CF) and CFF registry patients born between January 1, 1981, and December 31, 2006, were included. We examined the following variables for linking plausibility: date of birth, last four digits of the Social Security number, Zip Code, gender, date of sweat test, date of gene testing, and date of hospital admission. Specifically, we determined the percentage of unique records for each selected variable or combination of variables in the MAX data set and the registry data set. Only variable combinations with a 99 percent level of uniqueness (99 percent of records unique) were considered for the deterministic rule definitions. We then examined the linkage performance of

Case Example 39. Linking longitudinal registry data to Medicaid Analytical Extract files (continued)

Proposed Solution (continued)

each rule and the validation parameters (i.e., sensitivity, specificity, and positive predictive value [PPV]) of these rules were compared against the selected gold standard (defined as the rule with the highest linkage performance).

Results

We assessed 14,515 and 15,446 patient records in MAX and CF registry data sets, respectively. A total of nine linkage rules were established. The linkage rule including gender, date of birth, and Social Security number had the highest performance with 32.04 percent successfully linked records and was considered the gold standard. Linkage rule performance ranged from 1.4 percent (95% CI, 1.2 to 1.6) to 32.0 percent (95% CI, 31.3 to 32.8). As expected, rules with lower linkage performance had fewer or no matching records. Compared with the selected gold standard, the sensitivity of the other linkage rules ranged from 4.3 percent (95% CI, 3.8 to 4.9) to 73.3 percent (95% CI, 72.0 to 74.6); the specificity ranged from 88.2 percent (95% CI, 87.6 to 88.9) to 99.9 percent (95% CI, 99.8 to 99.9); and the PPV ranged from 68.2 percent (95% CI, 62.6 to 73.4) to 99.0 percent (95% CI, 96.5 to 99.8).

Key Point

The defined linkage rules exhibited varying operational characteristics of sensitivity, specificity, and PPV. When using deterministic linkage methods to link registry data with administrative claims data, relying on multiple linkage rules may be necessary to optimize linkage performance. Applying probabilistic record linkage methods should be considered when deterministic linkage methods are likely to fail; however, the absence of a set criterion for establishing probability weights could pose a challenge for its implementation.

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Chapter 17. Managing Patient Identity Across Data Sources

1. Introduction

Electronic health care data are increasingly being generated and linked across multiple systems, including electronic health records (EHRs), patient registries, and claims databases. In general, every system assigns its own identifier to each patient whose data it maintains. This makes it difficult to track patients across multiple systems and identify duplicate patients when different systems are linked. Efforts to address this challenge are complicated by the need to protect patient privacy and security.

Patient identity management (PIM) has been defined as the "ability to ascertain a distinct, unique identity for an individual (a patient), as expressed by an identifier that is unique within the scope of the exchange network, given characteristics about that individual such as his or her name, date of birth, gender [etc.]."[1] For the purposes of this chapter, the scope of this definition will be expanded to refer to PIM as the process of accurately and appropriately identifying, tracking, managing, and linking individual patients and their digitized health care information, often within and across multiple electronic systems.[2] A related idea is the concept of patient identity integrity, which is defined as "the accuracy and completeness of data attached to or associated with an individual patient."[3] Efficient patient identity management leads to high patient identity integrity.

The need for PIM strategies in the realm of health care data is rising, primarily because of the continued increase in the quantity and linkage of electronic health care data. The quantity of electronic health care data continues to grow. EHRs are increasingly being used to generate electronic health care data—72 percent of office-based physicians in the United States now use some form of EHR.[4] This number is likely to increase significantly in response to the EHR incentive programs enacted by the Centers for Medicare & Medicaid Services (CMS), which "provide a financial incentive for the 'meaningful use' of certified EHR technology to achieve health and efficiency goals."[5] In addition to office-based EHRs, electronic health care data may be created by hospital EHRs, billing systems, insurance claims systems, pharmacy record systems, medical devices, and even by patients themselves via electronic patient health record systems. Large amounts of electronic health care data are also being generated from clinical research. Patient registries, for example, often use electronic data capture tools to collect and manage their data.

This increase in the quantity of electronic health care and research data creates new opportunities and need for data linkage. Pharmaceutical companies conducting clinical trials on specific genetic markers are seeking ways to more easily identify and recruit potential patients. EHRs and patient registries are interfacing with each other to minimize the burden of data entry on participating centers and practices (see Chapter 15). Data from patient registries and other electronic sources are being pooled together to form larger, more statistically powerful data sets for research and analysis (see Chapters 16 and 18 and Case Examples 42 and 43).

As more electronic health care data are generated and linked together, PIM has become crucial in order to (1) enable health record document consumers to obtain trusted views of their patient subjects, (2) facilitate data linkage projects, (3) abide by the current regulations concerning patient information–related transparency, privacy, disclosure, handling, and documentation,[2] and (4) make the most efficient use of limited health care resources by reducing redundant data collection. To address this growing need, a number of standards development organizations are involved in the development of PIM strategies and standards. Several major organizations currently include: Integrating the Healthcare Enterprise[6]; Health Level Seven International[7]; and The Regenstrief Institute, Inc.[8] See Appendix C for a more complete list.

2. PIM Strategies

The challenge of PIM is not a new one, and it has existed since health care information was first digitized. In general, PIM is conducted in one of two environments: either shared identifiers are present or they are absent. When shared identifiers exist, the main PIM strategy that has emerged is to assign a unique patient identifier (UPI) to each patient. In situations where shared identifiers do not exist, the most common PIM strategy is to use patient-matching algorithms to determine whether two sets of information belong to separate patients or the same patient.

2.1 When Shared Identifiers Are Present—UPI

2.1.1 Definition and Context

One of the most straightforward PIM strategies is the creation of a unique health identifier for individuals, or a UPI. Generally, a UPI is defined as a "unique, non-changing alphanumeric key for each patient"[9] in a health care system, which is associated with each medical record or instance of health care data for that patient. Some proposed desirable characteristics of a UPI include that it be unique, nondisclosing, invariable, canonical, verifiable, and ubiquitous.[10] In this context, "nondisclosing" means that the UPI does not contain any personal information about the patient, such as date of birth or Social Security number.

The concept of a *universal* UPI (i.e., a UPI that is assigned to a patient for life and is consistent across all electronic health care systems in the United States) has been discussed and debated for a number of years. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 called for the adoption of "standards providing for a standard unique health identifier for each individual, employer, health plan, and health care provider for use in the health care system."[11] Since the passage of HIPAA, the concept of a UPI has generally been welcomed by the health care industry, which views it as a tool to reduce administrative workload and increase efficiency in exchanging electronic health data.[12] Other groups, including private citizens and experts attending a National Committee on Vital and Health Statistics hearing in July 1998, have expressed serious concerns about the effects that a universal UPI might have on patient privacy and data security.[12] These concerns have halted further efforts at creating a UPI in the United States until appropriate privacy legislation is in place[13, a] even though recent research has argued that adoption of a universal UPI would actually strengthen patient privacy and security (by limiting the number of access points to patient health care data) and, while requiring a significant upfront cost, could pay for itself in cost savings from error reduction and administrative efficiency.[14] The adoption of a universal UPI is also viewed by some as the logical next step in strengthening and developing the national health information network.[9]

2.1.2 Current Uses of UPIs

UPIs have long been used within individual patient registries and data sets, especially those with prospective data collection, to track and link a particular patient's data over time. One of the most familiar types of UPI is a medical record number—a unique number assigned by a hospital or physician practice that links a patient with their medical record at that institution. Some hospitals have multiple electronic health information systems (e.g., EHRs, administrative/billing systems, lab systems, pharmacy dispensing systems) that assign UPIs to the patients within their domains, and a patient may not necessarily have the same UPI from system to system. Many patient registries also assign a UPI to patients upon screening or enrollment, and UPIs remain the simplest and most straightforward way to uniquely identify patients in a controlled data set.

[a]Privacy and security concerns did not prevent CMS from developing the National Plan & Provider Enumeration System (NPPES) to assign unique identifiers to health plans and health care providers. The National Provider Identifier (NPI) has been implemented since 2006, and a standard identifier has not yet been implemented for health plans. (https://nppes.cms.hhs.gov/NPPES/Welcome.do. Accessed June 28, 2012.)

UPIs have also been used on a slightly larger scale in aggregated data sets and to link existing databases with administrative data sets. For example, the National Database for Autism Research aggregates data from many different collections of autism data and biospecimens and generates a global unique identifier for each patient represented in the aggregated data set.[15] Similarly, in 2008 the Society of Thoracic Surgeons Database began collecting unique patient, surgeon, and hospital identifier fields to facilitate long-term patient followup via linking to the Social Security Death Master File and the National Cardiovascular Data Registry.[16]

Outside the United States, UPIs have been used on a wider scale. In Sweden, for example, the personal identity number (PIN) is a unique administrative identifier assigned to all permanent residents in Sweden since 1947. The PIN is used to track vital statistics and also link patients between several national-scale patient registries, including the Patient Register (containing inpatient and outpatient data), Cancer Register, Cause of Death Register, Medical Birth Register,[17] and Knee Arthroplasty Register.[18] In England, a new health identifier was introduced in 1996—the NHS number is a 10-digit unique identifier used solely for the purpose of patient identification.[19]

2.1.3 Future Directions for UPIs

Recently, interest has increased in expanding the use of existing administrative identifiers (such as the Social Security number in the United States) to serve as UPIs in the health care arena. In 2009, the U.S.–based nonprofit Global Patient Identifiers proposed the Voluntary Universal Healthcare Identifier project, which aims to make unique health care identifiers available to any patient who uses the services of a regional health information organization or health information exchange (HIE).[20] In May 2011, production deployment on the system began. The voluntary nature of this project and its capacity for patients to have both an "open" voluntary identifier and a "private" voluntary identifier (which can be used to control which caregivers have access to clinically sensitive information) make it an interesting alternative to a mandated universal UPI that would likely be assigned and administered by a Federal Government agency. In March 2011, the eCitizen Foundation began requirements-gathering work on the Patient Identity Service Project, an open-source, open standards–based patient identity service that will be able to identify and authenticate a patient across multiple systems to gain access to their health records and services.[21] The project is funded by the OpenID Foundation of Japan, and future goals include research and development, design, implementation, and testing of the service.

2.1.4 Registries and UPIs

UPIs offer a straightforward way to identify specific patients within a particular registry. However, the implementation of a universal UPI in the United States has been halted by concerns over patient privacy, security, and confidentiality, which are unlikely to be resolved soon.

In Sweden, the ability to link data from separate national patient registries using the PIN has allowed researchers to pull from a pool of millions of Swedish residents to address difficult epidemiological questions. Concerns about patient privacy and confidentiality have been addressed by requiring that an ethical review board review and approve the planned study before any data are released to researchers. Past precedent has been that the review boards allow most PIN-based registry linkages, on the condition that the PINs are removed from the combined data set and replaced with different, unique serial numbers. Researchers also sign a legal agreement ensuring secure storage of the data and agreeing not to attempt to re-identify the patients in the de-identified data set they are given.[17]

2.2 When Shared Identifiers Are Not Present—Patient-Matching Algorithms

2.2.1 Definition and Context

In the absence of a national UPI in the United States, most researchers and hospital administrators have turned to patient-matching algorithms and other statistical matching techniques as a way to manage patient identities within the confines of a specific patient registry, research project, institution, or other grouping of health care data. This method of PIM involves

comparing identifiable patient attributes (often demographics such as date of birth, gender, name, and address, but sometimes other individually identifiable information) using a logic model that then classifies each pair as a match, a non-match, or a possible match that may require manual review.

In the realm of patient and record matching, algorithms can be either deterministic or probabilistic. Deterministic algorithms are more straightforward and classify a pair of records as a match if they meet a specified threshold of agreement. The definition of agreement can vary depending on which data elements are available, the quality of the data (including the level of missing data), and the desired sensitivity and specificity of the algorithm. Probabilistic algorithms treat the match status of individual data elements as observable variables and the match status of the record pair as a latent variable, and model the observable variables as a pattern mixture. This method characterizes the uncertainty in the matching process, making it a more sophisticated (and less straightforward) method than deterministic matching.[22]

One major consideration in choosing an appropriate matching algorithm is the accuracy with which it matches patients. Matching accuracy is affected by the number of patients being compared, the number and type of common data elements being compared, and the mathematical validity of the algorithm itself. An algorithm that returns close to 100-percent matching in a pool of few patients with many data elements may perform less accurately in a pool of many patients with fewer data elements. Importantly, an algorithm that does not perform accurately may limit the conclusions and results able to be drawn from a particular data set.

2.2.2 Current Uses of Patient Matching Algorithms

Patient-matching algorithms are widely used when disparate health care data sources are combined and no unique, common patient identifier is available. The two main options are to use an existing record linkage software program or to develop a new matching algorithm independently. Commercial software options, such as Link Plus and The Link King, apply probabilistic algorithms that have been found to provide a higher sensitivity than matching using a basic deterministic algorithm.[23] As described in Case Example 40, an open-source product (Febrl) was used to combine data from 11 different data sources into KIDSNET, a computerized registry that gives providers an overall view of children's use of preventive health services.[24] Case Example 41 describes a different approach to patient matching.

Many patient-matching algorithms have been developed to meet the needs of specific projects. For example, a group at Partners HealthCare developed an algorithm to compare data in the Social Security Death Master File with demographic data in the Partners EHR system to identify patient deaths that may have occurred outside of Partners institutions (and therefore were not recorded in the patients' medical record). They then developed another algorithm using clinical data to identify false-positives resulting from the first algorithm (e.g., if clinical data for a supposedly deceased patient is recorded as more than 30 days after the date of death in the Social Security Death Index [SSDI], that patient must have been falsely matched to an SSDI entry).[25] In another example, researchers at the University of Alabama Birmingham used matching algorithms to link emergency medical services data with hospital EHRs and a statewide death index to characterize the medical conditions and comorbidities of patients who received out-of-hospital endotracheal intubation.[26]

New and innovative algorithms that are unrelated to specific projects also continue to be developed, with the goal of advancing patient matching algorithm science. Recent examples include algorithms proposed by groups at Vanderbilt University in Nashville, Tennessee,[27] John Radcliffe Hospital in the United Kingdom,[28] and the University of Duisburg-Essen in Germany.[29]

2.2.3 Future Directions of Patient-Matching Algorithms

Any statistical matching approach is dependent on three factors, listed below:

1. *The quality of the data it is comparing*: Are the data entered correctly, without mistakes? Are the data complete, or is there a high level of missing data? The quality of data within a particular registry will always be a factor of the practices employed by that registry. See Chapter 11 for recommended best practices.
2. *The comparability of the data it is comparing*: Are the data from the different sources collected in the same format and in the same way? There are a number of current initiatives to improve the standardization of data elements being used in patient registries,[30] but the area with the most need for future work is the testing and standardization of the algorithms themselves.
3. *The accuracy of the matching algorithm*: What is the likelihood of the algorithm returning a false positive match or missing true matches? While there has been some scientific research validating specific matching algorithms,[31-33] the Health Information Technology Policy Committee recently called for increased standards around patient matching, including standardized formats for demographic data fields; internal evaluation of matching accuracy within institutions and projects; accountability to acceptable levels of matching accuracy; the development, promotion, and dissemination of best practices in patient matching; and supporting the role of the patient.[34]

Another emerging trend in patient matching algorithms is privacy-preserving record linkage, or "finding records that represent the same individual in separate databases without revealing the identity of the individuals."[29] This concept was expanded upon by researchers at University of Duisburg-Essen in Germany, mentioned in the previous section, who propose a method that encrypts patient identifiers while allowing for errors in identifiers. Given the concerns about patient privacy and confidentiality surrounding patient identity management, this method may be increasingly used in the future.

2.2.4 Registries and Patient Matching Algorithms

As mentioned above, patient matching algorithms have become the default PIM strategy for registries that link with outside data sources, due to the lack of a universal UPI in the United States. As a result, many different algorithms have been developed—some commercially available, some open-source, some developed for specific projects, and some developed with broader applications in mind. The performance and effectiveness of matching algorithms can impact the results produced by the registries that are using them. The type of registry also impacts the type of patient-matching algorithm needed. Registries used for direct patient care may require an algorithm with different sensitivity, specificity, and timeliness than those used for population-based research efforts. Registry owners and operators would benefit from standards surrounding patient-matching algorithms, which would allow them to more confidently and effectively use appropriate algorithms for linking projects.

3. Emerging Strategies and Related Ideas

In addition to a universal patient identifier and patient matching algorithms, other strategies are emerging to manage patient identities in disparate electronic health care data sources, including biometrics and master patient indices. In the technical realm of patient-centric document exchange, HIEs are becoming increasingly important in providing the interoperability infrastructure for successful EHR implementations within and across affinity domains.

3.1 Biometrics

One new option in the PIM field is the use of biometrics—that is, "automated methods of recognizing an individual based on measurable biological (anatomical and physiological) and behavioral characteristics."[35] Some examples of biometric measurements are: fingerprint, palm print, hand geometry, DNA, handwriting, finger or hand vascular pattern, iris/retina, facial shape, voice pattern, and gait.

Biometrics are attractive because of their difficulty to fabricate, their resistance to change over time (unlike demographic information such as name and address), and their high degree of uniqueness—making them effectively biological

UPIs. For biometrics to be used as UPIs, though, there would need to be agreement on which biometric to use and the format in which it should be collected. Also, some biometric measurements are more unique than others. For example, a fingerprint is highly unique to an individual, while a person's hand geometry is not as unique. Hand geometry therefore is often used to confirm a person's identity (i.e., in combination with another identifier) rather than as a sole identifier.

One drawback to using biometrics is the investment in specialized technology and equipment required to capture many of these measurements. There is also concern about the privacy and security implications surrounding the use of biometrics, connected with their history of use in law enforcement and their potential misuse to derive information other than identity (e.g., analyzing DNA for genetic diseases).[36]

Some hospitals have begun using biometrics to verify provider identity and restrict access to EHRs. Biometrics are also being used in some hospitals to verify patient identity upon hospital admission[37] and identify critically injured, unconscious patients presenting to an emergency room.[38]

Many registries, particularly those with biobanks associated with them, already collect biometric data (e.g., DNA). However, the data are often used for purposes other than PIM, including investigating genetic components of disease[39] and risk factors for disease.[40]

Biometrics remains an attractive option for PIM; the largest obstacle to its use in patient registries is likely the investment in technology and equipment that it requires, although this would vary depending on where registry data are collected. A multisite, practice-based registry would probably be less able to accommodate the collection of biometric data, while a registry based out of a single hospital that already collects biometric data for other purposes would be able to begin collecting biometrics for a registry more easily, since the initial investment in technology has already been made. Registries using biometrics would also be subject to the same concerns about privacy and security as biometric use in other disciplines.

3.2 Master Patient Index

A master patient index (MPI) facilitates the identification and linkage of patients' clinical information within a particular institution. The term "enterprise master patient index" (EMPI) is sometimes used to distinguish between an index that serves a single institution (i.e., MPI) and one that contains data from multiple institutions (EMPI). MPIs are not themselves patient identity management strategies, but rather informational infrastructures within which those strategies are applied. Most MPIs use a patient matching algorithm to identify matches and then assign a UPI that is associated with that patient record going forward. MPIs and EMPIs are created for the purpose of assigning a UPI to each patient treated within a certain health care system—providers can then use that identifier to have a global view of the patient's care across multiple institutions within that system.

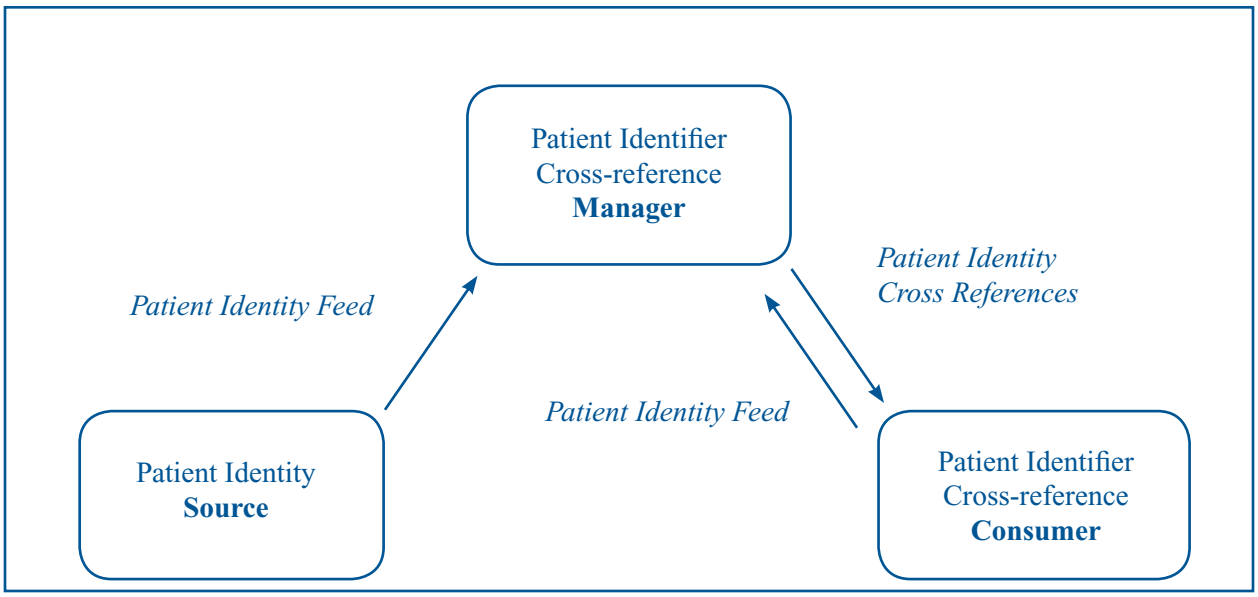
Several leading software companies have released commercially available MPI and EMPI products. Oracle has published a thorough description of the design and functionality of their EMPI product.[41] Open-source options are also available, including one developed by Project Kenai called OpenEMPI.[42]

EMPIs are used as supplemental tools to apply PIM strategies for data sharing efforts such as HIEs, described more fully in the next section. For example, the Michigan Clinical Research Collaboratory at the University of Michigan created the "Honest Broker" system, which serves three functions: facilitating the actual exchange of data between members of the collaboratory for research, maintaining an MPI to manage patient identities within that data, and de-identifying data sets in conformance with HIPAA standards.[43]

Figure 17–1 is adapted from the Integrating the Healthcare Enterprise integration profile[44] and illustrates the actors that participate in the Patient Identifier Cross-referencing profile. The entity often called an MPI is represented by the combination of the Patient Identity Source ("Source") and the Patient Identity Cross-reference Manager ("Manager"). The Source provides patient identity information (Patient Identity Feed) to the Manager. It is common to have multiple

patient identity sources that provide patient ID feeds to the Manager. The Manager is responsible for managing patient identities by detecting matches and creating and maintaining cross-references of patient identifiers across these various sources. The Patient Identifier Cross-reference Consumer ("Consumer") retrieves Patient Identity Cross References or aliases. This allows patients to be linked across multiple systems or domains that use different patient identifiers to represent the same patient.

Figure 17–1. Basic process flow with patient identifier cross-referencing



Illustrating how users may interact with an MPI in daily practice may be helpful. In one possible scenario, an emergency room physician sees a patient presenting at the emergency room with vague and poorly defined pain who specifically asks to be prescribed narcotics. A new quality improvement program being implemented in this emergency room requires the physician to check the patient's history of filling prescriptions before issuing a prescription for a narcotic drug. The emergency room's EHR system and the hospital pharmacy's electronic dispensing record system each assign their own patient IDs to patients within their systems, and send patient feeds to the hospital's MPI (the Manager in this scenario) each time a new patient ID is assigned. The MPI creates and maintains cross-references of all identifiers for patients and provides the cross-references to consumers who seek that information. The consumer in this scenario would be the emergency room system, which sends the MPI a patient identity cross-reference or demographic query with information about the patient in question. The MPI notifies the emergency room system that the patient identified in the emergency room as "ER703" matches the patient whose pharmacy records are under the pharmacy system identifier "012." The emergency room system then queries the pharmacy system for the identifier "012," and presents the dispensing record data to the emergency room physician.

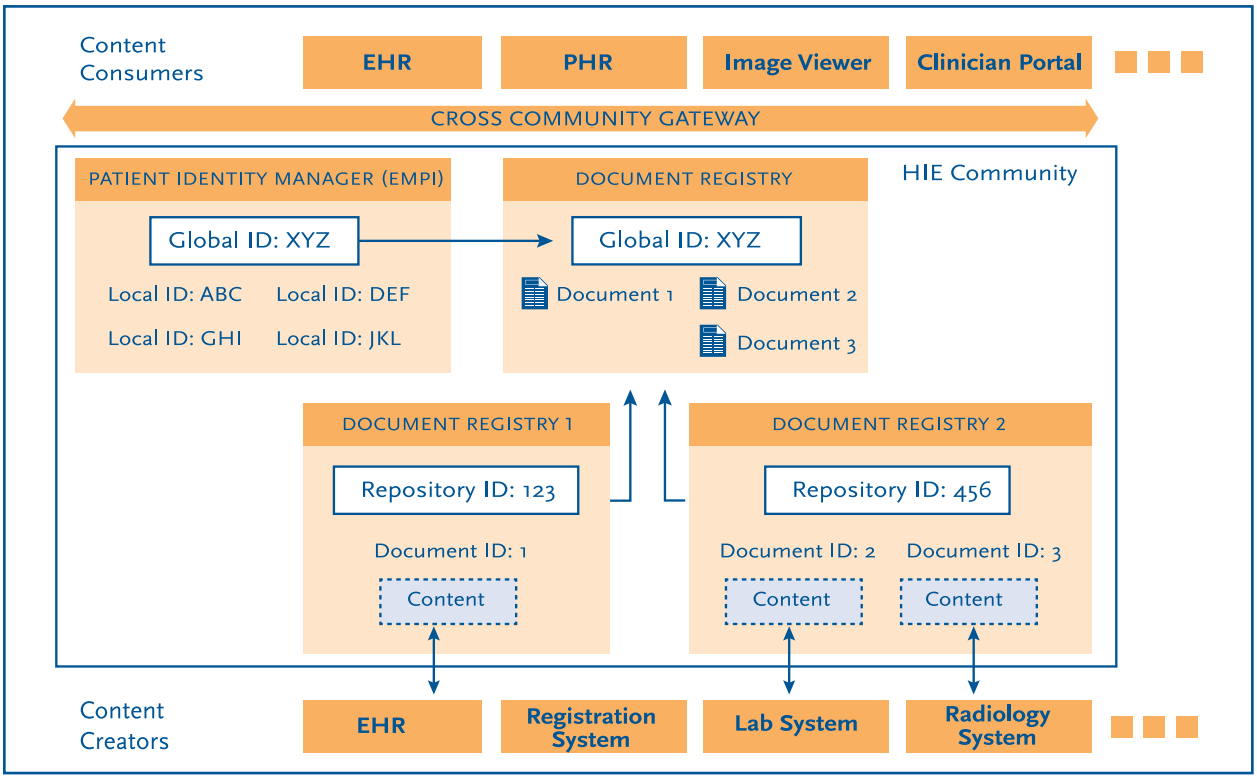
Health care institutions that use MPIs to manage patient identities across their multiple data sources (e.g., EHRs, pharmacy records, administrative and billing records) are desirable partners for data linkage projects and for inclusion in patient registries, since they are able to draw from a broader pool of data than any one of the data sources alone. By addressing PIM needs upfront, they minimize the work needed for outside sources to link to their data for research uses.

In the relational infrastructure shown in Figure 17–1, registries can act as Patient Identity Sources, Patient Identifier Cross-reference Consumers, or both. Registries that contain patient identifiers and other demographic information can act as Patient Identity Sources and send patient identity feeds to a Manager. Registries can also act as Patient Identifier Cross-reference Consumers, if they request and receive patient identity cross references from an MPI or other Patient Identity Cross-reference Manager. This may be done to add new patients to a registry or to augment existing data in a registry with additional information on the same patients.

3.3 Health Information Exchange

An HIE is an integrated open standards–based solution to enable information sharing across disparate health care applications. (See Case Example 34, which describes the Oakland Southfield Physicians HIE.) HIEs are interoperability platforms that provide the means to share patient data produced by health care applications with other applications that consume and use the data, such as EHRs. HIEs implement standards-based health care messages and provide the requisite authentication and auditory services for data governance. HIEs are not themselves patient identity management strategies, but they implement those strategies to manage their data. Most HIEs achieve this by incorporating an MPI to manage and cross-reference the identity of patients within the HIE. See Figure 17–2 for a graphical representation of the relationship between HIEs, MPI/EMPIs, and data creators and consumers.

Figure 17–2. Data flow through a health information exchange[a]



EHR = Electronic Health Record; PHR = Personal Health Record; EMPI = Enterprise Master Patient Index; HIE = Health Information Exchange; ID = Identifier

[a]Copyright 2010 Health Information and Management Systems Society. Figure reprinted with permission.

Key components of an HIE include:

- *Patient Identity Cross-Reference Manager*: An implementation of an MPI that cross-references multiple identifiers and serves the linked identifiers, global patient identifier, and unified patient demographics to information consumers and other HIE components.
- *Document Repository*: Clinical document repository for storing patient records and documents.
- *Document Registry*: Registry of patient's documents located in various document repositories.
- *Cross Community Gateway*: Serves as the entry point for communications between HIE communities.

Content creators who create new patient identifiers provide patient feeds to the Identity Manager, which in turn cross-references it to a global patient identifier. Content consumers and creators can query the Identity Manager for the global identifier by providing a subset of patient demographics or one of their local identifiers. This global identifier is used by the document registry to keep track of patient clinical documents. This infrastructure facilitates an interoperable environment that respects data ownership demands but also provides a complete view of the patient's clinical records from multiple sources.

HIEs can be powerful research tools. A group at the Swansea University School of Medicine has developed the Secure Anonymized Information Linkage (SAIL) databank, containing more than 500 million records from multiple health and social care service providers in the United Kingdom.[45] The SAIL databank has already been used to demonstrate the feasibility of identifying potential clinical trial participants at the primary care level, which may be especially useful for disease areas in which recruitment of clinical trial participants is historically difficult (e.g., chronic conditions such as diabetes).[46]

Because they contain patient data, HIEs are subject to the same privacy and security concerns and regulations as patient registries. A white paper published in April 2011 by the American Health Information Management Association/Healthcare Information Management and Systems Society (AHIMA/HIMSS) HIE Privacy & Security Joint Work Group provides a summary of these considerations.[47]

A patient registry may contribute data to an HIE, but registries and HIEs are distinct and separate endeavors. Data contained in HIEs are not necessarily collected using observational study methods, as patient registry data are; rather, they are often collected and aggregated by linking to existing databases (which may be, for example, registries, administrative databases, or public health surveillance systems). The purpose of an HIE is not just to evaluate specified outcomes in a defined patient population or even to serve any one predetermined scientific, clinical, or policy purpose, but to provide an aggregated database that can be used for a variety of purposes (which may include identifying patients to recruit for clinical trials, or conducting ecological studies, for example).

4. Major Challenges and Barriers

The process of patient identity management introduces several technical, ethical, and operational challenges, including selecting the appropriate PIM strategy, discussed earlier in this chapter. Additional challenges include the obligation to protect the privacy and security of patient data and the technical interoperability (or lack thereof) of disparate health care data sources.

4.1 Protecting Patient Privacy and Security

One of the most pressing challenges in PIM is addressing the tension between linking patient data in order to manage patients' identities and protecting the privacy and security of those data. This challenge has inherent ethical, regulatory, and technical considerations.

4.1.1 Ethical and Regulatory Considerations

The concepts of protecting patient privacy and security and PIM have always been intertwined. Managing patient identities is essential for

protecting the privacy and security of those patients. Conversely, regulations and ethical considerations compel the protection of patients' privacy and security when managing their identities (i.e., it is not enough to know who they are and which information is theirs; one must also protect this information).

Many stakeholders in the health information technology field recognize this relationship. The Health Information Security and Privacy Collaboration counts patient and provider identification as one of its nine domains of privacy and security.[48] The Commission on Systemic Interoperability released a report in 2005 in which it recommended that Congress authorize the Department of Health and Human Services to "develop a national standard for determining patient authentication and identity," and "develop a uniform federal health information privacy standard for the nation, based on HIPAA and pre-empting state privacy laws […]." These recommendations were made simultaneously, "to advance progress of the connectivity of health information technology."[49] Thus, it is widely recognized that PIM and patient privacy and security are closely related, but there continues to be disagreement about *how they should* relate.

The regulatory framework that guides this discussion in the United States is HIPAA, enacted in 1996. As mentioned previously in this chapter, HIPAA mandated the implementation of a nationwide unique patient identifier, but in 1999 concerns about patient privacy and security prompted the barring of any funding for this endeavor. While HIPAA has not led to the implementation of a standard PIM method, it does set forth a framework for the protection of patient privacy and health information security. This framework is summarized in Table 7–1 in Chapter 7.

In Europe, recently proposed data protection regulations may have a profound impact on the regulatory environment in which registries conduct PIM activities. The directive proposed by the European Commission in January 2012 includes a provision for the "right to be forgotten," essentially giving individuals the power to remove their personal data from third party data holders at any time they choose.[50] If adopted by the European Parliament and European Union member states, the directive will take effect within two years. The implications that this may have for health care research and registries operating in Europe remain to be seen.

4.1.2 Technical Considerations

Data holders employ three main technical methods of ensuring the privacy and security of patient data: anonymization, encryption, and pseudonymization:

- *Anonymization* is the practice of removing information that is identifiable to an individual or that may enable an individual's identity to be deduced. This is a viable option in some data use situations (e.g., conducting a research study that does not require patient followup), but not an option in others (e.g., maintaining comprehensive health records for patients in an EHR). It is also not a reversible process—once identifiers are removed from data, they cannot be reinserted.
- *Encryption* involves applying a mathematical calculation or algorithm to transform a patient's original data (plain text) into coded data (cypher text). In order to read the cypher text, a user or system must have access to a key that decrypts the data back into plain text. This is an attractive option because it does not involve deleting or removing patient data, and because the coded data is not in a readable format if it falls into the wrong hands. However, encryption requires robust data management policies and resources to be implemented successfully.[51]
- *Pseudonymization* is a more sophisticated approach to patient privacy protection. It involves two steps: depersonalization, in which identifiable data are separated from other clinical data and stored in a separate location, and pseudonymization, in which a unique identifier is generated and applied to the depersonalized data set. The unique identifier, or pseudonym, does not change for a given patient over time, and is not derived from any identifiable attributes of the patient. Pseudonymization can be reversible, if the

relationship between the pseudonym and the identifiable data is maintained in a secure way and can facilitate re-identification of the patient under specific circumstances (e.g., a trusted third party maintains the relationship, and only discloses that relationship if the requestor has knowledge of a particular key or password). Pseudonymization can also be irreversible, if a situation arises in which the relationship between the pseudonym and the identifiable data is not maintained, and re-identification is not possible.[52, 53]

4.2 Interoperability

In the same way that health care enterprises such as hospitals, clinics, and physician offices require patient identifier cross-referencing, that is the linking of patients across different domains, it is necessary to consider how registries may fit within this model and the challenges that level of interoperability may impose. Separate patient registries may use the same PIM infrastructure to register their patient identifiers within a shared patient identifier cross-reference manager, allowing the identifiers to be linked back to relevant health care and related systems. This approach may represent a possible solution whereby registries can more easily and securely be linked to other systems across known domains such as an HIE, but challenges still remain in terms of how this approach could successfully be used more broadly across nonparticipating health care enterprises.

5. Summary

Patient identity management is a fast-growing and evolving field, influenced by emerging technologies, regulations, and opportunities to use electronic health care data. The current status of PIM in the United States is primarily a factor of the provision in HIPAA for "standards providing for a standard unique health identifier for each individual […] for use in the health care system,"[11] the debate this provision has generated over implications for patient privacy and security, and the subsequent blocking of any funding being allocated to the pursuit of a national UPI. As a result, most PIM endeavors in the United States (including attempts to link patient registries with other health care data sources) use patient-matching algorithms to identify duplicates and manage patient identities. The lack of standards in this area means that the accuracy and effectiveness of these algorithms can vary widely.

Debate continues around how to best address the challenge of PIM, and stakeholders generally hold one of two views. Some view a national UPI as the best solution, provided the long-standing concerns about protecting patient privacy and security can be adequately addressed in the future. Others believe that resources would be better spent developing and standardizing the PIM methods that have grown organically in the absence of a national UPI; namely, EMPIs and patient matching algorithms. These two endeavors are not necessarily mutually exclusive, and patient registries and data linkage projects would benefit from the advancement of either or both.

Case Examples for Chapter 17

Case Example 40. Integrating data from multiple sources with patient ID matching

Description	KIDSNET is Rhode Island's computerized registry to track children's use of preventive health services. The program collects data from multiple sources and uses those data to help providers and public health professionals identify children in need of services. The purpose of the program is to ensure that all children in the State receive appropriate preventive care measures in a timely manner.
Sponsor	State of Rhode Island, Centers for Disease Control and Prevention, and others
Year Started	1997
Year Ended	Ongoing
No. of Sites	216 participating practice sites and more than 150 other groups of authorized users
No. of Patients	314,211

Challenge

In the 1990s, the Rhode Island Department of Health recognized that its data on children's health were fragmented and program specific. The State had many children's health initiatives, such as programs for hearing assessment and lead poisoning prevention, but these programs collected data separately and did not attempt to link the information. This type of fragmented structure is common in public health agencies, as many programs receive funding to fulfill a specific need but no funding to link that information with other programs. This type of linkage would benefit the Department's activities, as children who are at risk for one health issue are often at risk for other health issues. By integrating the data, the Department would be able to better integrate services and provide better service.

To integrate the data from these multiple sources and to allow new data to be entered directly into the program, the Department implemented the KIDSNET computerized registry. The registry consolidates data from eight electronic data sources, in addition to immunization and online data entry from four more public health programs to provide an overall picture of a child's use of preventive health care services. The sources are newborn developmental risk screening; the immunization registry; lead screening; hearing assessment; the Women, Infants, and Children (WIC) program; home visiting; early intervention; blood spot screening; foster care; birth defects; vital records data; asthma environmental inspection referrals, early child developmental screening, and audiology results. The goals of the registry are to monitor and assure the use of preventive health services, provide decision support for immunization administration, give providers reporting capacity to identify children who are behind in services, and provide recall services and quality assurance.

After being launched in 1997, the registry began accumulating data on children who were born in the State or receiving preventive health care services in the State. Some of the data sources entered data directly into the registry, and some of the data sources sent data from another database to the registry. The registry then consolidated data from these sources into a single patient record for each child by matching the records using simple deterministic logic. As the registry began importing records, the system held some records as questionable matches, since it could not determine if the record was new or a match to an existing record. These records required manual review to resolve the issue, which was time consuming, at approximately 3 minutes per record.

Due to lack of resources to devote to the manual review, the number of records held as questionable matches increased to 48,685 by 2004. The time to resolve these records manually was estimated at 17 months, and the registry did not have the resources to devote to that task.

Case Example 40. Integrating data from multiple sources with patient ID matching (continued)

Challenge (continued)

However, the incomplete data resulting from so many held records made the registry less successful at tracking children's health and less used by providers.

Proposed Solution

To resolve the issue of patient matching, the sponsor implemented an automated solution to the matching problem after evaluating several options, including probabilistic and deterministic matching strategies and commercial and open-source options for matching software. Since the State had limited funds for the project, an open-source product, Febrl, was selected.

A set of rules to process incoming records was developed, and an interface was created for the manual review of questionable records. Using the rules, the software determines the probability of a match for each record. The registry then sets probability thresholds above which a record is considered a certain match and below which a record is considered a new record. All of the records that fall into the middle ground require manual review.

Results

After considerable testing, the new system was launched in spring 2004. Immediately upon implementation, 95 percent of the held records were processed and removed from the holding category, resulting in the addition of approximately 11,000 new patient records to the registry. The new interface for manual review reduced the time to resolve an error from 3 minutes to 40 seconds. With these improvements, the registry now imports 95 percent of the data sent to the database and is able to process the questionable records through the improved interface.

Key Point

Many strategies and products exist to deal with matching patients from multiple data sources. Once a product has been selected, careful consideration must be given to the probability thresholds for establishing a match. Setting the threshold for matches too high may result in an unmanageable burden of manual review. However, setting the threshold too low could affect data quality, as records may be merged inappropriately. A careful balance must be found between resources and data quality in order for matching software to help the registry. In addition, matching quality should be monitored over time, as matching rules and probability thresholds may need to be adjusted if the underlying data quality issues change.

For More Information

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Case Example 41. Using patient identity management methods to combine health system data

Description	The clinical breast program at Providence Health & Services—Oregon provides screening, diagnosis, and treatment of breast conditions for women in seven hospitals within a regional health care system. The Providence Regional Breast Health Registry integrates patient data from multiple sources to improve patient care and outcomes, conduct research, and collaborate on national quality initiatives.
Sponsor	Providence Health & Services—Oregon; Safeway Foundation
Year Started	2008
Year Ended	Ongoing
No. of Sites	7 health system hospitals in Oregon
No. of Patients	265,130 encounters as of December 2011

Challenge

Leaders of the clinical breast program at Providence Health & Services—Oregon are interested in collecting patient-level data for reporting performance and outcome measures related to health care quality (e.g., biopsy rates); health services (e.g., screening volumes over time); research questions; and accreditation with the National Accreditation Program for Breast Centers (NAPBC). However, patient data reside in numerous information systems, including the hospital electronic health record, administrative billing systems, imaging systems (e.g., mammography, MRI, ultrasound), and the pathology system. The health system uses a patient corporate number (PCN), assigned to each patient in the health system as a patient identifier. Each hospital assigns its own medical record number (MRN) to each patient and a separate encounter number for each visit.

Meeting the reporting and research needs of the breast clinic program requires integrating data from all of these multiple systems as well as managing the identities of patients whose data could be contained in one or all systems.

Proposed Solution

In 2008, the Providence Regional Breast Health Registry was created. Registry data are housed in a structured query language (SQL) database that imports data from the various systems and applies matching algorithms to appropriately group data from the same patient. To make the match, the algorithms take into account the PCN, MRN, and encounter numbers for patients with breast health encounters based on a breast-specific ICD-9 and CPT procedure query. Transformation of data from different systems is sometimes necessary to allow matching (e.g., changing the patient corporate number from 12 to 10 digits).

Results

As of December 2011, the registry contained data on 265,130 patient encounters. It continues to collect and integrate data, and is expanding across the health system to accommodate data from affiliated clinics. Registry data are used to create quarterly updates on quality and outcomes measures identified by program leadership. For the two hospitals in the health system that are NAPBC-accredited, registry data are used to create their required annual reports on outcomes and benchmarks. Registry data have also been used for research purposes, such as identifying factors related to progression from premalignant to invasive lesions.

Key Point

Registries can take advantage of patient identity management solutions to link data from health information systems, regardless of whether a common patient identifier is present. Such linked data provide opportunities for quality improvement, research, and accreditation.

Case Example 41. Using patient identity management methods to combine health system data (continued)

For More Information

http://oregon.providence.org/patients/healthconitionscare/breast-health/Pages/askanexpertland.aspx?TemplateName=Providence+Breast+Health+Care+Registry&Templatetype=FormsandInstructions

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Soot L, Weerasinghe R, Wang L, et al. Core Needle vs. Surgical Excision Breast Biopsy in a Community-based Health System. Poster presented at: 13th Annual Meeting of the American Society of Breast Surgeons. Phoenix, AZ; May 2–6 2012.

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Chapter 18. Analysis of Linked Registry Data Sets

1. Introduction

This chapter provides a review and discussion of the analytic challenges faced by studies that use existing administrative databases and patient registries. We provide additional detail and examples of the issues raised in Chapter 13. While that chapter focused on the analysis of registry data in accordance with the registry's purpose and objectives, this chapter tackles the issues and opportunities that arise when using registry data, often in combination with other data sources, to investigate hypotheses or questions that are secondary to the original reason for data collection. Case Examples 42 and 43 provide real-world examples of the analysis of linked registry data sets.

The use of administrative databases and medical registries to provide data for epidemiologic research has blossomed in the last decade,[1] fulfilling prophecies that date to the mid-1970s.[2] Studies that use data collected for a primary purpose other than research (e.g., administrative databases) or collected for research purposes but used to support secondary studies (e.g., patient registries) have contributed substantial information to the understanding of the incidence, prevalence, outcomes, and other descriptive characteristics of many diseases. For simplicity, this chapter will refer to all such studies as "retrospective database studies." Retrospective database studies have also contributed information to the understanding of disease etiology, patterns of treatment and disparities in care, adverse effects and late events associated with disease treatments, and the comparative effectiveness of some therapies. Despite these achievements, retrospective database studies sometimes receive criticism because of their potential to yield invalid results.[1, 3] Weiss, for example, points out the potential for retrospective database studies to ascertain exposures, outcomes, and potential confounding variables with poor accuracy, or to provide an invalid reference group (the unexposed in a cohort design or controls in a case-control design). Ray[1] provides a table of potential pitfalls in "automated database studies," which includes a similar warning about inaccurate measurement of exposure, outcomes, and covariates, the potential for unmeasured confounding and missing data, and the potential to include immortal person-time.

While these examples and lists of pitfalls provide valuable guidance, none of them is unique to retrospective database studies. Nonrandomized studies of all designs are susceptible to systematic errors arising from mismeasurement of analytic variables,[4] unmeasured confounding,[5] and poor choice of reference group.[6, 7] Also, immortal person-time bias is not limited to retrospective database studies; it has even plagued a secondary analysis of data gathered in a randomized trial.[8, 9] Taking a different approach, this chapter begins with a review of the fundamentals of sound study design and analysis. These fundamentals apply to epidemiologic research nested in any study population, but the chapter will focus on and illustrate the topics with examples that use retrospective database studies. In the subsequent sections, important considerations in retrospective database studies will be discussed, with the recognition that studies nested in other study populations may have the same considerations, but perhaps less often or to a lesser degree than retrospective database studies.

2. Fundamentals of Design and Analysis in Retrospective Database Research

2.1 Statement of Objective

Most productive epidemiologic research begins with a clear statement of objective. This objective might be descriptive; for example, to measure the incidence of a particular disease in some population, to characterize the patterns or costs of treatment for a particular disease in some population, or to measure the occurrence of outcomes among patients with a particular disease.

The objective might also involve a comparison; for example, to compare the incidence of a particular disease in two or more subgroups defined by common characteristics (e.g., etiologic research), to compare the cost or quality of care for a particular disease in two or more subgroups (e.g., health services research or disparities research), or to compare the rate of outcomes among two or more subgroups of patients (often defined by different types or levels of treatment) with a particular disease (e.g., clinical research). In all cases, the overarching objective is to obtain an accurate (valid and precise) and generalizable estimate of the frequency of an outcome's occurrence, or its relative frequency compared across groups.[10] A valid estimate is one that can be interpreted with little influence by systematic error. A precise estimate is one that can be interpreted with little influence by random error. A generalizable estimate is one that provides information pertinent to the target population, the population for which the study's information provides a basis for potential action, such as a public health or medical intervention. Often times the objective will be accompanied by a specific hypothesis (see Chapter 13), although that is less important than the statement of objective.

2.2 Selection of a Study Population

Once the study's objectives have been stated, the next step in the research plan is to select a study population. Selection of a study population requires identifying potential participants in time and place, including inclusion/exclusion (admissibility) criteria related to the study's objectives and feasibility. Admissibility criteria related to the study's objectives include focusing on a clinically relevant study population of individuals in whom sufficient events will occur to provide adequate precision for the estimates of disease frequency, and in whom the exposure categories will occur with sufficient frequency to provide adequate precision for the estimates of association. These criteria are also used to exclude people with characteristics that can introduce significant bias into the estimates of disease frequency or estimates of association, and that cannot be controlled easily or adequately in the analysis. Precision and validity criteria for admissibility pertain to all studies, regardless of whether they are nested in a health database.

Admissibility criteria related to feasibility center on access to the data. Many ongoing cohort studies have established procedures for data sharing. Similarly, most publicly funded health databases have established procedures for data access. Investigators must ordinarily provide a statement of the study's objective, a protocol for data collection from the database and for data analysis, a list of individuals who will have access to the data, and a study timeline. Some databases charge a fee for data access, although many do not.

An advantage of retrospective database studies is the potential to study associations between rare exposures and rare outcomes in a population large enough to provide sufficient precision, with nearly complete followup, and with few exclusion criteria pertaining to age, comorbidity, or other factors that sometimes limit participation in clinical trials.[11, 12] For example, surveillance databases that monitor adverse events potentially associated with pharmaceuticals identified signals suggesting that use of HMG CoA-reductase inhibitors (statins) might increase the risk of amyotrophic lateral sclerosis (ALS).[13, 14] The only available epidemiologic evidence came from pooling 41 randomized trials, in which ten ALS cases occurred among 56,352 individuals assigned to placebo and nine ALS cases occurred among 64,602 individuals assigned to the statins arm.[14] Using Danish databases, a case-control study identified 556 cases of ALS or other motor neuron syndromes and 5,560 population controls.[15] The odds ratio associating disease occurrence with statins use was 0.96 (95% CI, 0.73 to 1.28), thereby rapidly and cost-efficiently providing evidence to counter the drug-monitoring studies and with far greater precision than provided by the pooled clinical trials.

Selection of a study population inevitably involves balancing accuracy and generalizability concerns, as well as cost and feasibility considerations. For example, restriction is one of the most effective strategies for control of confounding through study design.[16] If one is concerned about confounding by sex, a simple and effective strategy to control that confounding is to restrict the study population

to a single sex. However, such restriction reduces the study's precision by decreasing the sample size, and may also reduce the generalizability of the results (only applicable to half of the target population). An alternative would be to include both sexes and to stratify the analysis by sex. While this approach would improve the generalizability of the results, and allow an evaluation of confounding, the precision of the estimated association would be reduced, and perhaps substantially reduced, if the estimate of effect in men was substantially different from the estimate of effect in women. In this circumstance, the study becomes effectively two studies.

2.3 Definition of Analytic Variables

The protocol for an epidemiological study should provide a clear, unambiguous definition of the outcome being studied, a description of how it will be measured, and a discussion of the accuracy of that measurement. When sensitivity of a dichotomous disease classification is nondifferential and independent of any errors in classification of exposure categories, and there are expected to be few false positives (near perfect specificity), there will usually be little bias of a ratio measure of association.[4] This exception to the rule that "nondifferential misclassification biases towards the null" has important design implications. It suggests that retrospective database studies should be designed to optimize specificity; in fact, to ideally make the specificity perfect so there will be no false positives. Such a design might require more stringent criteria applied to the outcome definition than are ordinarily applied in a clinical setting, and therefore more stringent than might be found in a disease registry. For example, the estimated prevalence of dementia in a cohort of men and women aged 65 years or older varied by a factor of 10 depending on the diagnostic criteria that were applied.[17] Strategies to reduce inclusion of false-positive cases can include requiring evidence in the patient record of medical procedures (e.g., cholecystectomy for gallstone disease or podiatry examination for diabetes) or interventions (e.g., insulin or glucose lowering medications for diabetes) that provide greater confidence in the validity of the case-finding definition.[18] Such an approach often results in fewer included cases and reduced precision, but improved validity.[19]

If the study objective is to compare the frequency of outcome across subgroups, then the protocol should provide a definition of the exposure contrast(s). It is critical that both the index condition (i.e., the "exposed" or "treated" group) and the reference condition (i.e., the "unexposed" or "untreated/placebo" group) are well defined.[6, 20] One frequent shortcoming of epidemiologic research is to compare the occurrence of disease in an index group with the occurrence of disease in all others who do not satisfy the index group definition. Studies of this design are easily constructed with retrospective database research, because of the abundance of participants who do not meet the index group definition. This "all others" reference group is therefore usually a poorly defined mixture of individuals.[21] For example, if one uses a pharmaceutical registry to compare the incidence of a disease in statins users with the incidence of disease in those who do not use statins, the reference group of nonusers will contain individuals with indications for statin use but who have not been prescribed statins, as well as individuals without indications for statins use. Nonusers also differ from users in the frequency of contact with medical providers, which raises the potential for differential accuracy of ascertainment of health outcomes. It is therefore preferable to first ensure that the reference group of nonusers contains individuals who have indications for use of the treatment,[18] and who, if possible, are receiving alternative therapies for the same indication.[22] If one has a biologic basis to separate statins into categories, such as hydrophilic and hydrophobic statins, then a comparison of users of hydrophilic statins with users of hydrophobic statins would often be more valid. With these definitions, only individuals with indications for statins, and treated with statins, are included in the analysis, thereby reducing the potential for confounding by indication and differential followup.[23]

Finally, considerable attention should be given to identifying and accurately measuring potential confounders and effect modifiers.[4, 24] The opportunity to examine important etiologic

questions with considerable precision has expanded significantly with the availability of large databases, but systematic error due to confounding by unmeasured or poorly measured confounders remains a central concern. Fortunately, databases generally capture inpatient and outpatient clinical events and medication use that can characterize comorbidities and health care resource utilization, which can aid in the control of confounding. As discussed further below, information on behavioral and lifestyle factors (e.g., cigarette smoking, alcohol use, diet) is infrequently captured or is poorly measured in many databases. Thus, retrospective database researchers should carefully consider the available information on confounders before initiating studies. When data on critical confounders cannot be obtained in a database, and cannot be obtained by linking to another data source, an alternative data set might be better suited to accomplish the study's objectives. Alternatively, in the presence of unmeasured confounding, researchers can use bias analysis[5, 25] to assess the potential impact of residual confounding on their observed findings.[26, 27]

2.4 Validation Substudies

The goal of quality study design and analysis is to reduce the amount of error in an estimate of association. With this goal in mind, investigators have an obligation to quantify how far they are from this goal, and bias analysis is one method by which to achieve this goal.[5, 25] Bias analysis methods require data to inform the bias model, and these data are obtained from internal or external validation substudies. Retrospective database research is often amenable to collection of internal validation data, for example by medical record review. In addition, many databases have internal protocols that constantly validate at least some aspects of the data. The validation data generated by these protocols can provide an initial indication of the data quality. To facilitate data collection for study-specific internal validation studies, investigators should consider the important threats to the validity of their research while designing their study, and should allocate project resources accordingly. This consideration should immediately suggest the corresponding bias analyses, which will then inform the data collection required to complete the bias modeling.

For example, in the study of statin use related to ALS and neurodegenerative diseases described above,[15] the ICD-10 code used to identify cases (G12.2) corresponded to diagnoses of ALS or other motor neuron syndromes. The investigators therefore selected a random sample of 25 individuals from among all those who satisfied the case definition, and a clinician investigator reviewed their discharge summaries. The proportion of these 25 who did not have ALS (32 percent) was used to inform a bias analysis to model the impact of these false-positive ALS diagnoses. Assuming a valid bias model, the bias analysis results showed that the null association was unlikely to result from the nondifferential misclassification of other diseases as ALS.

In this example, there was no effort to validate that non-cases of ALS were truly free of the disease. Non-cases are seldom validated, because false-negative cases, especially of rare diseases, occur very rarely. Furthermore, validating the absence of disease often requires a study-supported medical examination of the non-case patients, an expensive, time-consuming, and invasive procedure. Prevalent diseases with a lengthy preclinical period and relatively simple diagnostic tests, such as diabetes, are more amenable to validation of non-cases. The ALS example also illustrates that an internal validation study requires protocol planning and allocation of study resources to collect the validation data. A protocol should be written that specifies how participants in the validation sample will be selected from the study population. Participation in the validation substudy might require informed consent to allow medical record review, whereas the database data itself might be available without individual informed consent. These aspects should be resolved in the planning stage, and the analytic plan should include a section devoted to bias modeling and analysis.[5]

3. Important Considerations

Once an investigator decides to pursue a research objective using a retrospective database study, there are a number of important considerations to evaluate before undertaking the study. These considerations mostly pertain to the quality and completeness of the database,[28, 29] and especially to the potential for systematic errors in the database to affect the validity of the study's result.

3.1 Structural Framework for Data Collection

Health databases collect data for various primary purposes[30] and can be categorized as follows: (1) data collected for the purpose of reimbursing health care providers; (2) data collected for the purpose of monitoring care provided to beneficiaries of an integrated health care system; (3) data collected for the purpose of surveillance regarding a particular disease or disease category; (4) data collected for the purpose of surveillance for individuals with a specific exposure; and (5) data collected on individuals with a single admission-defining disease or medical procedure. Each type has strengths and limitations (presented in Table 18–1) to consider when evaluating the database for use in studies.

Databases that collect information for reimbursement (e.g., Medicare, Medicaid, or Ingenix), which are sometimes called "claims" or "administrative" databases, are quite useful for understanding health care costs and can provide important surveillance information on clinical practices and outcomes. However, they may be susceptible to systematic errors if data entries are manipulated by the data generators to affect (likely increase) their reimbursement. For instance, certain clinical conditions with high reimbursement rates may be preferentially reported on claims for patients who have those conditions but who present in the hospital or outpatient setting with other clinical issues, particularly if the presenting conditions are reimbursed at lower rates. The accuracy of some claims data sets have been questioned for diagnoses and procedures including dialysis,[31] weight management,[32] neutropenia,[33] heart failure,[34] diabetes,[35] and functional outcomes after prostatectomy,[36] as examples. On the other hand, the accuracy of registered diagnoses can be quite good.[37] The accuracy of the claims data for its intended objective should therefore be considered, and preferably estimated quantitatively by an internal validation substudy.[38, 39] Alternatively, estimates of the data's accuracy may be available from an analogous study population from the same or a similar claims data set; an example is an external validation study. Claims data often lack important information on laboratory parameters, diagnostic test results, and behavioral and lifestyle characteristics, which may limit their utility for research in some topic areas.

The second type of database collects information on the health care provided to beneficiaries within an integrated health care system. This system can be a health insurer (e.g., Kaiser Permanente), a benefits program provided to selected individuals (e.g., Veteran's Health Administration), or a national health care system (e.g., the United Kingdom's Clinical Practice Research Database[40]). These databases typically use an integrated electronic health records system to capture health care information directly from physicians' offices, hospitals, pharmacies, and other sites where care is provided (e.g., infusion centers, surgical centers). The granularity and quality of data captured in these databases is quite good and includes demographic and clinical characteristics, medication use, major clinical events including death, and importantly, results of diagnostic tests and laboratory assays. As with many epidemiological studies, some databases are limited in their geographic coverage and in the demographic characteristics of their patient populations. This lack of representativeness may affect the generalizability of results from studies nested in them.

The intended purpose of a third set of databases is surveillance of the incidence and outcomes related to a particular disease or disease category. These databases, or surveillance registries, often pertain to infectious diseases, cancer, and end-stage renal disease (ESRD). Surveillance for infectious diseases sometimes recognizes that only a proportion of cases will be reported, but assumes that the sensitivity and specificity of reporting

remain constant over time, so that changes in the relative frequency of reported incidence provides a signal regarding the true incidence in the population. Thus, although the data quality is high, the completeness may be low. In contrast, both the data quality and completeness in most cancer registries are quite high, and the motivation for manipulation to influence reimbursement does not exist because the registry data are not used for that purpose. For example, the U.S. Cancer Surveillance, Epidemiology, and End Results (SEER) registry has a history of quality control and improvement dating to its inception in 1973 and has been linked to the Medicare administrative database to provide data on cancer treatments and outcomes. In the United States and some other countries, patients with ESRD (patients receiving chronic dialysis or who are transplant recipients) are guaranteed coverage of all dialysis services including medications, procedures, and hospitalizations. These benefits extend throughout the patient's life and require significant resources. Consequently such countries have established surveillance programs like the United States Renal Data System to monitor the health care provided to these patients and the costs associated with their health care.

The fourth type of database collects data on patients with a common exposure, and is commonly used as part of a postmarketing pharmacovigilance program related to a biologic or pharmaceutical product or a medical device. This type of database is typically designed to monitor the incidence of adverse events related to the exposure. These databases are often patient registries.

A last type of database is a clinical patient registry of individuals with a single admission-defining disease or medical procedure. In fact, the first known health-related registry was the Leprosy Registry in Norway, initiated in 1856. In keeping with this history, many of the current clinical registries are found in Scandinavia. For example, the Danish government supports clinical databases used for quality assurance and research (e.g., breast cancer, colorectal cancer, hip arthroplasty, and rheumatologic diseases), as well as disease registries (e.g., the multiple sclerosis registry) used for monitoring and research.[41] In fact, a central objective of disease-specific registries may be to provide an infrastructure for clinical trials pertaining to treatments for the disease. The main advantage of these registries and databases is the quality of data on disease characteristics, received treatments, and outcomes related to the disease. The main disadvantage is that they are difficult to use for studies of the etiology of the disease that initiates membership in the registry, since the registry includes only individuals with the disease.

Table 18–1. Types of databases used for retrospective database studies, and their typical advantages and disadvantages

Database Type	Strengths	Limitations	Examples
Reimbursement purposes ("claims" data)	• Population-based • Captures inpatient and outpatient clinical events • Captures mortality data • Captures oral and injectable medication use • All claims are adjudicated	• Specific patient populations (65+ yrs old/disabled; employed) • Limited information on subject characteristics (e.g., lifestyle factors) • Does not capture laboratory or test results • Missing medication use in the hospital • Reflects regional practices	• Medicare • Ingenix • Marketscan
Monitoring of health care provided to beneficiaries	• Population-based • Captures inpatient and outpatient clinical events • Captures oral and injectable medication use • Captures subject characteristics (e.g., body mass index, smoking, blood pressure)	• Limited racial and ethnic diversity • Specific health care practices (e.g., selected formulary)	• Nordic Hospital Registries (Denmark, Sweden, Finland) • Kaiser Permanente, Group Health Cooperative • Clinical Practice Research Database (CPRD)
Disease or disease category surveillance	• Population-based • Captures granular disease-specific data (e.g., cancer stage) • Captures outcome events	• Variable amounts of health care utilization information • Limited information on subject characteristics (e.g., lifestyle factors)	• SEER, SEER-Medicare • USRDS
Exposure surveillance	• Prospectively designed • Typically collects granular information on relevant covariates • Designed to capture all potential drug-related adverse events	• Limited information on comparator treatments.	
Quality assurance or research regarding patients with a single admission-defining disease or procedure	• High-quality data on the index disease or procedure • High quality data on the treatment and outcomes associated with the index disease or procedure • Potential to link with other data sources to obtain more complete data	• Absence of an equivalent comparison group without the index disease or procedure • Limited data on health conditions and treatments not related to the index disease or procedure • Limited data on behavioral health (tobacco, diet, exercise, and alcohol consumption)	• Danish Breast Cancer Cooperative Group • Danish Multiple Sclerosis Registry • Danish Hip Arthroplasty registry

SEER = United States Cancer Surveillance, Epidemiology, and End Results Registry; USRDS = United States Renal Data System.

3.2 Changes in Coding Conventions Over Time

A common problem with retrospective database research is the impact of changes in coding conventions over the lifetime of the database. These changes can take the form of diagnostic drift,[42] changes in discharge coding schemes, changes in the definition of grading of disease severity, or even variations in the medications on formulary in one region but not others at different points in time. For example, the Danish National Registry of Patients (DNRP) is a database of patient contacts at Danish hospitals. From 1977 to 1993, discharge diagnoses were coded according to ICD-8, and from 1994 forward discharge diagnoses were coded according to ICD-10. ICD-10 included a specific code for chronic obstructive pulmonary disease (J44), whereas ICD-8 did not [ICD-8 496 (COPD not otherwise specified) did not appear in the DNRP]. In addition, from 1977 to 1994 the DNRP registered discharge diagnoses for only inpatient admissions, but from 1995 forward discharge diagnoses from outpatient admissions and emergency room contacts were also registered. COPD patients seen in outpatient settings before 1995 were therefore not registered; this excluded patients who likely had less severe COPD on average. The change in ICD coding convention in 1994 and the exclusion of outpatient admissions before 1995 presented a barrier to estimating the time trend for incidence of all admissions for COPD in any period that overlapped these two changes to the DNRP.[43]

The General Practice Research Database (GPRD) was a medical records database capturing information on approximately 5 percent of patients in the United Kingdom[44] (as of March 2012, the GPRD became the Clinical Practice Research Database). Information was directly entered into the database by general practitioners trained in standardized data entry. When the GPRD was initiated in 1987, diagnoses were recorded using Oxford Medical Information Systems (OXMIS) codes, which were similar to ICD-9 codes. In 1995, the GPRD adopted the Read coding system, a more detailed and comprehensive system that groups and defines illnesses using a hierarchical system. Without knowledge of this shift in coding and how to align codes for specific conditions across the different coding schemes, studies using multiple years of data could produce spurious findings.

3.3 Other Data Quality Considerations

3.3.1 Selection of Registered Population

An important advantage of some retrospective database research is that it is population based, and therefore provides good representativeness for the target population. However, not all retrospective database research provides this advantage. For example, the U.S. Veterans Health Administration databases provide an important resource retrospective database research. A recent analysis of individuals receiving Veterans Health Administration services in fiscal years 2004 and 2005 reported a mortality rate due to accidental poisoning of about 20 per 100,000 person-years.[45] However, this database includes only U.S. military veterans, a selected subpopulation of the U.S. population, with a higher proportion of men than the overall population, and probably an unrepresentative proportion of other characteristics as well. The rate of accidental poisonings was thus almost twice that of the U.S. general population, after adjusting for differences in the age and sex distributions. Similarly, the Medicare administrative database provides an important resource for retrospective database research, including its links with the SEER cancer registry mentioned above. However, the former includes only Medicare recipients, almost all of whom are 65 years of age or older, and many variables are unavailable for members of this population who participate in managed health care plans. Whether the lack of representativeness in these two examples, and others like them, affects inference made to the target population depends on the particular topic.

3.3.2 Probability of Registration in Relation to Disease Severity

A second type of incomplete data arises at the level of registered individuals, rather than afflicting the whole database. In an earlier example, cases of COPD were registered in the Danish National Registry of Patients in reference

to ICD-8 before 1994 and in reference to ICD-10 thereafter. Only inpatient diagnoses of COPD were registered in the DNRP before 1995; inpatient, outpatient, and emergency department contacts were registered thereafter. At no time has the DNRP registered COPD cases diagnosed and treated only by a Danish General Practitioner. The least severe cases of this progressive disease are, therefore, missing from the DNRP throughout its history,[46] and patients treated as outpatients are missing from the DNRP before 1995. Similar problems occur with hospital databases of other progressive diseases such as diabetes, Alzheimer's disease, or Parkinson's disease. Patients treated by their general practitioners will often eventually appear in the hospital database with the proper discharge diagnosis, since these progressive diseases become more severe over time. The less severe cases do not appear in hospital discharge databases, and their absence presents a barrier to studies of population-based incidence or prevalence, as well as to the accurate determination of whether exposure to a potential etiologic agent preceded the disease diagnosis,[47] since neither the date of first diagnosis by the general practitioner nor the date of symptom onset is recorded.

Databases often lack accurate measurements of lifestyle and behavioral factors, such as tobacco use, alcohol drinking, exercise habits, and diet. Some databases can provide proxy measurements of these behavioral factors. For example, poor lung function or diagnosis of COPD is a proxy marker for tobacco smoking history, alcohol-related diseases such as cirrhosis or prescriptions for disulfiram can be used as proxy markers for alcohol abuse, and medically diagnosed obesity may be a proxy marker for poor diet and lack of exercise. None of these proxies provides a reliable measure of the actual concept, however.

Other methods of estimation may add information. For diseases that can be identified by use of specific medications, one could compare the incidence of that medication use with the incidence in the hospitalization database to estimate the proportion of total cases that are registered. Comparison of the date of onset of the medication use with the date of first outpatient or inpatient diagnosis of the disease would provide an estimate of the typical delay between diagnosis by a general practitioner and progression of the disease to a severity level treated in the outpatient or inpatient setting.

3.3.3 Missing Data

Item nonresponse and missing data at the level of an individual record are often less of a problem for retrospective database research than for comparable cohort studies. Cohort studies that rely on participation by study subjects are subject to attrition and nonresponse. Attrition occurs when participants early in the cohort's followup stop replying to regularly mailed surveys, telephone interviews, or emailed data collection instruments. These losses to followup are sometimes related to exposure characteristics and health outcomes, which introduces a form of selection bias,[48] even if subjects rejoin the study at a later time.[49] Item nonresponse occurs when a participant answers a survey or interview, but does not provide a response for one or more of the data fields. Item nonresponse can also occur when data on an exposure or outcome are collected by other methods, such as when a biospecimen is unavailable to provide tissue for an assay of a genetic or protein biomarker. This missing data may also be related to exposure and disease characteristics, and can introduce a bias, although reliable methods have been developed to resolve bias from item non-response (missing data) in many circumstances.[50] Likewise, inverse probability weighting can sometimes be used to address selection bias and loss to followup,[51] although it has seldom been implemented to date.

Retrospective database research ordinarily uses data collected for a primary purpose other than research. Item nonresponse (one form of missing data) is also often less of a concern, since the databases often have inherent quality control methods to assure high data completeness. Other forms of missing data can, however, plague retrospective database research in other ways. For example, left truncation is sometimes an important problem in retrospective database research, and is basically a missing data problem (although it can also be conceptualized as an information bias).[52]

Left truncation occurs when information required to characterize prevalent exposures, covariates, or diseases precedes the establishment of the database. With left truncation, unexposed individuals (e.g., nonusers of a medication) may have been users before the database was established, and apparently incident cases of a disease may have been diagnosed before the database was established, which would make them prevalent cases. Furthermore, covariate information collected at the inception of the database might have been affected by the medical history before the database was established. For example, blood pressure measured soon after a database began might be affected by blood pressure medications prescribed before the database began. Characterizing this initial measurement as baseline (i.e., preceding the first recorded prescription for blood pressure medications) would fail to account for the effect of the prevalent prescription for blood pressure medications, which was prescribed during the left truncation period.

As a second example, in a study of the association between metformin use and the occurrence of breast cancer, the prescription database used to ascertain use of metformin among diabetic patients was not established until after the medication came to market.[53] Data on use of metformin were therefore left-truncated, which can be conceptualized as a missing data problem for time-varying characterization of metformin use in the years preceding the database. (See Ibrahim and colleagues[54] for a review of methods to model time-varying data.) Alternatively, this distortion can be conceptualized as the more general problem of having poor sensitivity of ever/never classification of metformin use.

Left truncation is a common problem whenever prevalent conditions may have preceded the establishment of a database. For example, many etiologic epidemiology and clinical epidemiology studies exclude prevalent cases of the outcome at the inception of followup. However, some cases of disease may have occurred before followup began and even before the database's inception, and these prevalent cases would be impossible to identify unless they also appeared in the database after its inception but before the followup time began. For many prevalent diseases with good survival, contact with the medical system is frequent, so most prevalent cases should be identifiable after the database is 5 to 10 years old. However, the potential for left truncation to mask some prevalent cases of the disease under study should be considered as a question specific to the research topic.

Right censoring can also occur in retrospective database research. For example, studies that use birth registries to ascertain congenital defects usually fail to detect defects that are diagnosed later in life, such as congenital heart anomalies. These defects are usually never recorded in the birth registry, so must be ascertained by some other method. Without such continued followup, the measurement of the outcome is right censored at the date of last followup by the birth registry.

Left truncation and right censoring are specific examples of the more general problem of data gaps. Data gaps occur when databases pertain only to a particular subgroup of the larger population,and membership in that subgroup is dynamic. Examples include individuals covered by Medicaid and members enrolled in managed care plans. In both examples, the databases pertain to participants in a health insurance program, and membership in those programs can change frequently. Data are collected only while the participants are members. If membership is lost and restored again later, there will be a data gap. Importantly, membership in these plans might be related to other characteristics that affect health, such as socioeconomic status or employment.[55] Similar problems can arise when there are gaps in residency and the database is based on national health care data, or when individuals have health insurance from more than one source.

Data gaps in retrospective database research can also arise when medications are dispensed in the hospital, since many databases do not capture in-hospital medication use, leading to a form of information bias. In drug safety studies examining mortality risk related to the use of a particular medication, missing in-hospital medication use can result in spurious estimates of treatment effects.[56] This bias was illustrated in a case-control

study examining mortality risk related to inhaled corticosteroid use from the Saskatchewan, Canada, database. Analyses that failed to account for missed corticosteroid use during hospitalization events preceding death or the matched date for controls showed a beneficial effect (RR=0.6; 95% CI, 0.5 to 0.73). The RR estimates changed markedly once the missing in-hospital corticosteroid use was included (RR=0.93; 95% CI, 0.76 to 1.14 and RR=1.35; 95% CI, 1.14 to 1.60).[56] This bias has also been observed in studies of injectable medications in dialysis patients where hospitalization events preceding death resulted in spuriously low effect estimates.[57]

3.4 Confounding by Indication

Confounding by indication may occur in nonrandomized epidemiologic research that compares two treatments (or treatment with no treatment).[58] In the absence of randomization, the indications for selecting one treatment in preference to another (or in preference to no treatment) are often also related to the outcome meant to be achieved or prevented by the treatment.[59] For example, randomized trials in younger breast cancer patients have shown that chemotherapy prevents breast cancer recurrence.[60] However, in a nonrandomized study of older breast cancer patients, those who received chemotherapy had a higher rate of recurrence than those who did not, probably because chemotherapy was offered only to the women with the most aggressive cancers.[61] This example is a classic illustration of confounding by indication. Importantly, this study collected complete detailed data on every prognostic marker of recurrence and all of the other breast cancer treatments, yet adjustment for this detailed suite of variables did not resolve the confounding by indication, even using more advanced methods.[23]

Retrospective database research is as susceptible to confounding by indication as any other design. However, strategies to reduce the strength of this confounding have been proposed[21] and may be most successful when used in the large study populations often achievable only in databases.[62] Explained here is a special class of confounding by indication, which might arise especially in retrospective database research: time-dependent confounding by indication generated by dynamic dosing.[63] Dynamic dosing refers to the clinical situation in which a medication's dose is titrated (increased or decreased) in response to a changing biomarker or clinical measurement on which the medication acts (i.e., a clinical intermediate).[63] Examples include diabetes medications titrated in reaction to hemoglobin A1c (HbA1c) measurements, erythropoiesis stimulating agents (ESAs) titrated in reaction to hemoglobin levels, blood pressure medications titrated in reaction to systolic and diastolic blood pressure values, and antiretroviral therapy titrated in reaction to CD4 counts. The clinical intermediate is therefore both a consequence of therapy and a predictor of future therapy. Time-dependent confounding arises when the clinical intermediate is also a prognostic indicator.[64] For example, hemoglobin concentration is a time-dependent confounder of the effect of ESA therapy on survival because it is a risk factor for mortality, it predicts future ESA dose, and past ESA therapy predicts future hemoglobin concentration. Dynamic dosing therefore introduces time-dependent confounding of the treatment's association with outcomes in the presence of this structure of confounding by indication.[63]

It is important to recognize that the structure requires the clinical intermediate to be both a causal intermediate and a confounder. If it is only a confounder, such as baseline comorbidity or time-dependent comorbidity, the confounding can be addressed by conventional analytic methods. However, when the causal structure indicates that the clinical intermediate is both a causal intermediate and a confounder, inverse probability of treatment weighting (IPTW) with marginal structural models (MSMs) has been proposed as one method for valid adjustment.[65] Pharmacoepidemiological studies that have used MSMs to address time-dependent confounding have shown significant improvements in confounding control relative to traditional time-dependent analysis.[66-68] In a study of the effect of highly active antiretroviral therapy (HAART) on time to AIDS, the hazard ratio using standard time-dependent Cox regression to adjust for time-varying covariates such as CD4 count and HIV

RNA level was 0.81 (95% CI, 0.61 to 1.07). Using an MSM, this effect was strengthened substantially (HR=0.54, 95% CI, 0.38 to 0.78), providing stronger evidence of the benefit of HAART.[66] Studies examining the effect of titrated ESA doses on mortality risk in dialysis patients that have used MSMs have found hazard ratio estimates at or below the null,[67, 68] whereas results from traditional models found substantially elevated hazard ratio estimates.[67]

3.5 Precision Considerations When Standard Errors Are Small (Over-Powered)

The large size of the study population that can often be included in retrospective database study is both a strength and a limitation. The sample size allows adjustment for multiple potential confounders with little potential for over-fitting or sparse data bias,[69] and allows design features such as comparisons of different treatments for the same indication (comparative effectiveness research) to reduce the potential for confounding by indication.[21] Nonetheless, systematic errors remain a possibility, and these systematic errors dominate the uncertainty when estimates of association are measured with high precision as a consequence of a large sample size.[70] When confidence intervals are narrow, systematic errors remain, and/or inference or policy action will potentially result, investigators have been encouraged to employ quantitative bias analysis to more fully characterize the total uncertainty.[25] Bias analysis methods have been used to address unmeasured confounding,[27] selection bias,[71] and information bias[27, 72] in retrospective database research.

A second potential problem is the possibility of overweighting results from retrospective database–based research in a quantitative meta-analysis of an entire body of research on a particular topic. In such meta-analyses, weights are in proportion to the inverse of variance, so large studies carry most of the weight. The variance, however, measures only sampling error; it does not measure systematic error. This problem of large studies dominating the weights pertains to any meta-analysis that includes one or two studies much larger than the others. However, given the large sample sizes often achieved by retrospective database research, the high-weight studies may often come from studies nested in these databases. For example, in a 2004 quantitative meta-analysis of 11 prospective studies of the association between pregnancy termination and incident breast cancer,[73] the two retrospective database studies[74, 75] accounted for 54 percent of the weight in the meta-analysis, but only 18 percent (2 of 11) of the studies. Random effects meta-analyses[76] and other weighting methods[77] provide only a partial solution to this potential overweighting, and only in some circumstances. Meta-analysts should therefore consider the potential for retrospective database research to be overweighted in their quantitative summary estimates. A plot of the inverse-normal of rank percentile against the corresponding study's estimate of association and confidence interval provides a visual depiction of the distribution of study results,[78] without undue influence by overpowered studies. (See, for example, the aforementioned meta-analysis of the association between pregnancy termination and breast cancer risk.[73])

4. Special Opportunities

As noted earlier, retrospective database research runs the gamut of research topics. There are, however, several research areas to which retrospective database research studies are particularly well suited.

4.1 Rapid Response to Emerging Problems, With Prospective Data

Retrospective database research is ordinarily secondary to another primary purpose. While the collected data may not be optimized to a particular research topic, it is often possible to use the collected data for rapid response to emerging research problems.[79] The study mentioned above of the association between statins medication and incident ALS is also a suitable example here. Drug surveillance databases had identified a higher-than-expected prevalence of statins medications associated with reports of ALS. A pooled analysis of trials data revealed no association, but was limited by the small number of ALS cases, short duration of followup, and potential for crossover

from the placebo arm to statins treatment after the trial finished.[80] Thus, there was little evidence to evaluate the potential causal association between this highly effective drug class—which prevents cardiovascular morbidity and mortality[81, 82]—and the incidence of ALS, a progressive, neurodegenerative, terminal disease.[83]

The precisely measured null association reported in the case-control study15 provided a rapid and reliable basis to assuage concerns about an etiologic association between statin use and ALS occurrence. Imagine what would have been required for a purposefully designed study to evaluate the association. The pooled trials result had included nearly 120,000 individuals observed over more than 400,000 person-years, yet included only 19 cases of this rare disease. Few existing cohort studies would have had sufficient person-time to expect substantially more cases, and a cohort study designed to evaluate the association would have required a substantial investment of time and financial support.

A case-control study might have been feasible, but imagine the resources required to enroll and interview an equivalent number of ALS cases as were included in the database study (~550) and their matched controls. Furthermore, a case-control study of this design would likely have been susceptible to recall bias and selection bias.[4, 7] The retrospective database research study avoided both of these biases.[15] Recall bias was avoided by ascertaining statins use from a prescription database. These prescriptions were recorded before the ALS incidence, so could not have been affected by the subsequent disease occurrence. Selection bias was avoided because all ALS cases in the region during the followup period were included, and controls were selected from the Civil Registration System. Neither case/control status nor use of statins was likely to be associated with participation. Thus, the retrospective database research study on this topic provided a rapid, cost-efficient, and precise result on an important public health topic, which otherwise would have gone unevaluated or would have required a substantial investment of time and finances to achieve an equivalent, or possibly more biased, result. This study provides a good example of the value of retrospective database research in such circumstances.

4.2 Cost-Efficient Hypotheses-Scanning Analyses

Retrospective database research can sometimes evaluate multiple associations with only a marginal increase in cost over the evaluation of a single association. The U.S. Food and Drug Administration's (FDA) Sentinel Initiative will use an active surveillance system within electronic data from health care information holders to monitor the safety of all FDA-regulated products.[84] Similarly, the EU-ADR project aims to use clinical data from health databases, combined with prescription databases, to detect adverse drug reactions.[85, 86] The project uses text mining, epidemiological, and computational techniques to analyze electronic health records, with the goal of detecting combinations of drugs and adverse events that merit further investigation.

As a second example, Latourelle and colleagues used retrospective database research to evaluate the association between estrogen-related diseases, such as osteoporosis or endometriosis, and the occurrence of Parkinson's disease.[87] To be categorized as "exposed" to these diseases, cases or controls had to have them appear as discharge codes in the hospital database before the first discharge code for Parkinson's disease. For relatively little additional cost, the investigators also evaluated the association between 200 other diseases and the subsequent diagnosis of Parkinson's disease as a hypothesis scanning study, with the objective of suggesting new ideas regarding Parkinson's disease etiology.[87] The analysis adjusted for multiple comparisons using empirical Bayesian methods designed to reduce the emphasis on potentially false-positive associations.[88] This potential for cost-effective hypotheses-scanning studies as an explicit objective of retrospective database research should be viewed as a strength of such research, not a limitation, so long as the objective is appropriately labeled as such. Hypotheses suggested by these types of studies are often further investigated using studies designed specifically for the topic.

4.3 Hybrid Designs

Retrospective database research does not necessarily have to be limited to data collection from secondary data sources. Hybrid designs allow the use of database research for some aspects of data collection, and primary data collection for others. For example, a study of drug-drug and gene-drug interactions that might reduce the effectiveness of tamoxifen therapy began by identifying eligible breast cancer patients using the Danish Breast Cancer Cooperative Group's clinical registry.[89] This clinical registry also provided data on prognostic factors such as tumor diameter and lymph node evaluation, and on treatments such as chemotherapy and radiation therapy. Linkage with the Danish Civil Registration System provided data on vital status; linkage with the Danish National Patient Registry provided data on comorbid diseases; and linkage with the Danish National Registry of Medicinal Products provided data on use of prescription medications. Thus, for relatively low cost, a cohort of breast cancer patients with complete medical, prognostic, and breast cancer treatment data was assembled. A case-control study was then nested in this cohort by identifying cases of breast cancer recurrence and then matching controls to them by risk-set sampling.[7] Once cases and controls had been identified, their tumor blocks were collected from the Danish National Pathology Registry,[90] and these were used for the necessary bioassays. Thus, retrospective database research allowed identification of the source population and selection of cases and controls, and provided all but the bioassay data. These data, which are expensive to collect, were only obtained for about 13 percent of the members of the total cohort. This hybrid design demonstrates that retrospective database research will remain an important contributor, even in the era of personalized medicine.

In a second example of a hybrid design, survey data collected over the Internet were linked to retrospective database research.[91, 92] The objectives of the study were to assess the feasibility and validity of studies that use the Internet to recruit and follow participants, evaluate the relationship between lifestyle and behavioral factors and delayed time to pregnancy among women attempting to conceive, and evaluate the relationship of several exposures to risk of miscarriage and infant birth weight among women who conceived. Participants were recruited by advertisements on Web sites likely to be visited by women who intended to become pregnant. They were directed to the study's Web site, where they completed an enrollment screening questionnaire followed by an interview covering socio-demographics, reproductive and medical history, lifestyle, and other factors. Enrolled participants were then contacted every 2 months by email for 12 months or until they reported that conception had occurred. Data obtained from the Web-based questionnaires were linked to nationwide databases, which allowed collection of additional data on confounders and outcomes, as well as an assessment of the validity of some of the self-reported data, such as prescription drug use. This study again demonstrated that retrospective database research, in combination with primary data collection, can provide a cost-efficient resource for collecting some aspects of the study data. In contrast to the previous cancer treatment example, the cohort in this pregnancy study was enrolled following more typical cohort study strategies, and not by using the databases to identify a source population.

Hybrid designs have also been used to collect data by medical record review for data fields that are available for a subset of participants in a database.[93] Thus, the database provides a cost-efficient resource for initial data collection, which is then supplemented as necessary by medical record review or another primary data collection method to complete the data set. Once an investigator is open to the potential for hybrid designs and there are retrospective database resources suitable to the research topic, the opportunities for combining the databases with primary data collection are limited only by the investigator's creativity.

4.4 Ample Data Allows for Novel Designs

As mentioned above, the ample data often available from retrospective database research can lead to overweighting of such studies in quantitative meta-analyses. While this problem may be disadvantageous, a compensating advantage is the opportunity to use retrospective database research to implement novel study designs. For example, confounding by indication and other biases often plague clinical epidemiology,[3, 23] even in the era of comparative effectiveness research. However, the ample study size often provided by retrospective database research can overcome these threats to validity in some situations. The large sample size might allow a design with carefully restricted exposure groups,1 for example, new users of a pharmaceutical only,[94] whereas conventionally sized cohort studies would not always have sufficient study size to implement such a design. The new user design in turn facilitates other advanced designs, such as propensity score matching and instrumental variable analyses,[21] which are intended to further counteract these threats to validity. These and other novel designs can be implemented in studies of any size, but are likely most effective when the study size is large.[95]

4.5 Data Pooling Methods

Although retrospective database research often provides relatively large study size within a research topic area, a study's power may still be insufficient if the study must be restricted to rare exposure subgroups or if the study outcome is rare. In these cases, data pooling across similar databases may allow sufficient sample size to provide adequate power. Data pooling also provides advantages over conventional meta-analyses because it allows simultaneous and consistent data analyses. However, such pooling projects face substantial challenges.

First among these challenges is harmonization of the data elements. To accommodate a pooled analysis, data collected from different databases must provide analytic variables (exposure, confounders, modifiers, and outcomes) with equivalent categorizations and definitions. Such data harmonization can be quite challenging. Harmonization of data elements categorized differently or differentially available in two or more databases may pose an insurmountable barrier to pooling. For example, one database might include data on behaviors like alcohol and tobacco use, whereas a second database might not. The pooling project would then face the unenviable decision of controlling for these behaviors for some, but not all, data centers (in which case the analysis becomes comparable to a conventional meta-analysis), or abandoning control for these variables at all centers in order to achieve the data harmonization goal. Differences in the conceptual underpinnings of data elements may be more common. Even a variable as conceptually simple as the Charlson comorbidity index[96] can present surprising challenges when subject to harmonization considerations. The Charlson index includes 19 comorbid conditions (e.g., diabetes). As mentioned above, some databases might be able to ascertain diabetes diagnosed in all medical settings (e.g., general practitioner, outpatient, and inpatient), whereas others might be able to ascertain diabetes diagnosed in only a subset (e.g., only general practitioner or only outpatient specialty clinics). Diabetes is defined differently in the different databases, which are not strictly harmonious, and therefore contribute differently to the Charlson index. While the definition of the Charlson variable may be harmonious across the pooled databases, the underlying conceptualization is different, and this difference could result in differences in the strength of confounding by the comorbidity variable or in the degree to which it modifies the association between an exposure contrast and outcome.

Ethical and legal constraints, which are often placed on data sharing, present a second important challenge to pooling projects. Pooling of de-identified data sets can sometimes be arranged through data use agreements, but even these arrangements can be quite challenging and time-consuming. Rassen and colleagues compared four methods of pooling de-identified data sets:[97] (1) full covariate information, which may violate privacy concerns; (2) aggregated data methods,

which aggregate patients into mutually stratified cells with common characteristics, but usually delete cells with low frequency counts that might defeat the privacy protections of large frequency counts; (3) conventional fixed or random effects meta-analysis, which provides only summary estimates of association for pooling; and (4) propensity score-based pooling, for which a propensity score summarizes each individual's covariate information. They reported that the last alternative provided reasonable analytic flexibility and also strong protection of patient privacy, and advocated its use for studies that require pooling of databases, multivariate adjustment, and privacy protection.[97]

More recently, Wolfson and colleagues proposed a pooling method that requires no transfer of record-level data to a central analysis center.[98] Rather, the central analysis center implements statistical computing code over a secure network, accessing record-level data maintained on servers at the individual study centers. Data aggregation occurs through return of anonymous summary statistics from these harmonized individual-level databases, and even iterative regression modeling can be implemented. The advantage is a reduced burden to comply with ethical and legal requirements to protect privacy, since no record-level data are ever transferred. The disadvantages include requirements for strong data harmonization, secure networks that satisfy regulatory oversight, and assurances that no record-level data are transmitted. It is possible that some summary statistics could violate standards for de-identification, but safeguards can be implemented to prevent transmission of such summary statistics.

These new methods for pooling provide exciting opportunities for pooled projects. At the time of this writing, investigators who choose to undertake them should expect delays required to explain these methods to regulators responsible for oversight of data protection, who are not yet familiar with them. In addition, it is likely that implementing the methods for the first few projects will be challenging. With those caveats in mind, the path should be blazed, because once the methods are familiar and reliable, new research opportunities and efficiencies will inevitably arise. Investigator teams without the time, resources, or patience to implement these new methods can ordinarily rely on conventional meta-analysis methods,[99] which solve the privacy protection concerns but also have some important disadvantages by comparison.[97, 98]

5. Summary

Retrospective database research has made important contributions to descriptive epidemiology, public health epidemiology targeted at disease prevention, and clinical epidemiology targeted at improving disease outcomes or estimates of disease prognosis. Investigators who conduct retrospective database research should first focus on the fundamentals of epidemiologic design and analysis, with the goal of achieving a valid, precise, and generalizable estimate of disease frequency or association. Beyond the fundamentals, retrospective database research presents special challenges for design and analysis, and special opportunities as well; researchers should be aware of both in order to optimize the yield from their work.

Case Examples for Chapter 18

Case Example 42. Combining de-identified data from multiple registries to study long-term outcomes in a rare disease

Description	Four independent, prospective, observational, and multicenter disease registries participate in an ongoing systematic review of their aggregated data to study pediatric pulmonary arterial hypertension (PAH). The review is intended to describe disease course and long-term outcomes of pediatric PAH in real-world clinical settings.
Sponsor	Actelion Pharmaceuticals Ltd.
Year Started	2009
Year Ended	Ongoing
No. of Sites	4 multicenter registries
No. of Patients	Approximately 500

Challenge

PAH is a rare disease that is poorly described in pediatric populations. Newly developed PAH therapies used in the pediatric population have recently led to improved survival, and patients are now likely to reach adulthood. This increased attention on pediatric PAH patients presents new challenges in both data needs and methodology to evaluate disease history and progression, general development, and clinical and treatment experience.

In 2009, the European Medicines Agency (EMA) approved Actelion's product bosentan for an expanded indication of pediatric PAH. The sponsor then began working with the EMA to determine how best to collect longitudinal treatment and outcomes data on this population.

Proposed Solution

Four existing registries already collected data on pediatric PAH patients: one is global and three are national in scope (in the United States, France, and the Netherlands). The sponsor and the EMA recognized that a compilation of results from these multiple registries within a common systematic review protocol would allow them to examine data from a large number of patients representing a significant proportion of global pediatric PAH patients. After the EMA approved the systematic review study design, the individual registries reviewed the protocol and agreed to participate.

The sponsor contacted the individual registries to evaluate their data collection and analysis practices. As it was not feasible to pool the data due to differences in data collection elements used by the registries, analyses were done by the respective registry data owners using similar methods under the guidance of a common statistical analysis plan. The de-identified summary tables were sent separately to the sponsor to be included in the systematic review reports.

The outcomes of interest are disease course and long-term outcome (e.g., clinical worsening, hospitalization, death) and general development (e.g., height, body mass index, sexual maturation, onset of puberty). The protocol and statistical analysis plan define the study population (all patients enrolled in one of the four registries aged ≤18 years at the time of diagnosis with PAH), observation period, appropriate statistical methods, and standardized procedures for data extraction (including data quality assurance).

Results

Analyses are performed on an annual basis and the same data cutoff date is applied to all registries to define the observation times of analysis (i.e., from Oct 2009 to the annual report's data cut-off date). This effectively creates a new cohort for each annual report, which is a stand-alone document.

The first annual report was sent to the EMA in 2010. For this first analysis, the sponsor had to address technical challenges related to differences between the registries. For example, three of the registries used the SAS software package to conduct their analysis, and one used SPSS, which

Case Example 42. Combining de-identified data from multiple registries to study long-term outcomes in a rare disease (cotinued)

Results (continued)

produces a slightly different output. For subsequent reports, the sponsor also spent time in dialogue with the registries to clarify the detailed requirements, definitions, and analyses of the statistical analysis plan to ensure that each registry understood and interpreted it the same way.

Longitudinal analyses will be examined for evidence of improvement or deterioration over the followup period. The method of analysis respects correlations of within-patient measurements and is based on all patients with at least two measurements during the followup period.

Key Point

For rare disease populations where registries already exist, systematic review of registry data sets may be a more feasible way to analyze outcomes data rather than creating a new patient registry. When planning and conducting such a study, close collaboration between the parties is important to develop a detailed statistical analysis plan and clarify expectations for registry-level analyses.

For More Information

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Case Example 43. Understanding baseline characteristics of combined data sets prior to analysis

Description	The Kaiser Permanente Anterior Cruciate Ligament Reconstruction (KP ACLR) Registry was established to collect standardized data on ACLR procedures, techniques, graft types, and types of fixation and implants. The objectives of the registry are to identify risk factors that lead to degenerative joint disease, graft failure, and meniscal failure; determine outcomes of various graft types and fixation techniques; describe the epidemiology of ACLR patients; determine and compare procedure incidence rate at participating sites; and provide a framework for future studies tracking ACLR outcomes.
Sponsor	Kaiser Permanente
Year Started	2005
Year Ended	Ongoing
No. of Sites	42 surgical centers and 240 surgeons
No. of Patients	17,000

Challenge

The KP ACLR Registry aimed to collaborate with the Norwegian Ligament Reconstruction Registry on a series of studies to proactively identify patient risk factors as well as surgical practices and techniques associated with poor surgical outcomes. The Norwegian registry has been operating since 2004 and contains data on 14,232 patients. Combining data from these two registries would allow for faster identification of certain risk factors and evaluation of low frequency events.

Proposed Solution

The first step was to compare the patient cohorts of the registries and the surgical practices of the two countries. Aggregate data were shared between the registries in tabular form. Analysis was conducted to identify differences that would be important to consider when making inferences about a population other than that covered by the registry. Commonalities were also identified to determine when inferences could be made from each other's analysis and when data do not need to be adjusted.

Results

The analysis found that the registries generally have similar distributions of age, gender, preoperative patient-reported knee function, and knee-related quality of life. Differences were observed between the two registries in race, sports performed at the time of injury, time to surgery, graft use, and fixation type. While these differences should be accounted for in future analyses of combined data sets from both registries, the results indicate that analyses of the combined data sets are likely to produce findings that can be generalized to a wider population of ACLR patients.

Since this comparison was conducted, two hypothesis-driven analyses have begun, investigating questions using the combined registry data sets. Future plans include further collaboration with ACLR registries in additional countries.

Key Point

Combining or pooling registry data can be a valuable approach to achieving a larger sample size for data analysis. However, it is important to identify cohort and practice differences and similarities between registries before making generalizations of registry findings to other populations or sharing data for collaboration projects.

For More Information

http://www.kpimplantregistries.org/Registries/acl.htm

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Section V

Special Applications in Patient Registries

Chapter 19. Use of Registries in Product Safety Assessment

1. Introduction

Once a drug or device is approved for use by a regulatory authority, the product 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 postapproval (also called postmarketing) safety assessment as it exists today was, for the most part, born out of well-publicized product safety issues that were initially detected by clinicians recognizing a pattern of rare serious events, such as phocomelia caused by prenatal exposure to thalidomide[1] and rare vaginal cancers that occurred in young women who had in utero exposure to diethylstilbestrol.[2] The detection of serious adverse drug reactions after authorization has led to much debate about the adequacy of both industry and regulatory approaches to preauthorization assessment and testing. However, the decision to authorize a medicine is a balance between wanting to know as much as possible about the safety of a product and the need to make new drugs available for patients.[3] The implication is that authorization cannot mean that a medicine is completely safe; rather, it is an assessment that at the time of authorization, the known benefits for the average patient in the approved indication outweigh the known risks. But the degree to which the known risks represent the actual safety profile of a product will depend upon the size, duration, representativeness, and thoroughness of the clinical trial program, which, in turn, is related to the complexity of the patients and the state of knowledge of the disease being targeted. Trials conducted as part of clinical development are, by necessity, of limited duration and size and generally focus on a narrowly defined population that represents only a small segment of the population with the disease or product use of interest. Clinical trial populations tend to be restricted to those who have limited concurrent disease and who are on few, if any, concomitant medications. Typically, trial protocols include lengthy lists of inclusion and exclusion criteria that further restrict the trial population. Unless a drug or a product is intended for a very narrow indication or a very rare disease, it is not feasible to require clinical trials to be inclusive of all types of patients likely to ever be exposed to it. Even in the case of a narrow indication, the potential long-term and delayed effects of a product are unlikely to be established during most clinical trial development programs.

To address the acknowledged limitations of what is known about the safety profile of a product at the time of authorization, postmarketing pharmaco- and medical device vigilance is traditionally, and by regulation, performed through spontaneous adverse event (AE) reporting. The exact requirements for spontaneous reporting to the regulatory authorities vary internationally and depend on 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 that, while it is useful for identifying rare and potentially significant events,[4, 5] 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 postmarketing surveillance is reactive in that one waits for AEs/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 the events of interest. There is some evidence that clinicians who report AEs are not typical of clinicians 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.[6-8]

The current methods available for AE reporting are seen by many as burdensome and not amenable to

incorporation into a clinician'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 nonserious as well as serious AEs that could potentially overwhelm established systems.

To overcome some of the difficulties associated with managing large databases of spontaneous AEs, many investigators employ statistical methods to identify signals of disproportionate reporting (SDRs). These methods identify AEs that are reported more frequently with a drug or device than would be expected compared with other event/product pairs in the database, and do not imply any kind of causal relationship.[9] It is important to be precise as to what is meant when using the term "signal" or "signal detection" since the terms are ambiguous; in the context of automated methods of detecting statistical anomalies, the term "SDR" should be used.[9] However, these statistical methods may not be reliable in certain situations, such as when there is major confounding or when the increased risk is small compared with the background incidence of the event.[9] All these above-mentioned limitations mean that there are situations when spontaneous reporting may not be adequate as the sole method of postmarketing surveillance.

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 to further address unresolved safety concerns, some products are approved subject to postmarketing 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 a European Union–risk management plan (EU-RMP) when seeking a marketing authorization 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 characterized, and what risk minimization activities will be undertaken. While many products will require only routine pharmacovigilance, for others more proactive methods of pharmacovigilance will be necessary to supplement the use of spontaneous adverse reaction reporting and periodic safety update reports. Although additional clinical trials may occasionally be mandated, it is more common for observational pharmacoepidemiological 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 the prescription event monitoring (PEM) systems used in the United Kingdom (Drug Safety Research Unit),[10] New Zealand (NZ Intensive Monitoring Programme), Japan (J-PEM), and elsewhere, targeting new products; and the retrospective use of administrative claims data. In the United Kingdom, 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 U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, an effort to create an integrated electronic system in the United States for AE monitoring, incorporating multiple existing data sources including claims data and electronic medical record systems.[11]

Medical devices in the United States have surveillance programs different from those for drugs. The Safe Medical Devices Act of 1990 requires that high-risk medical devices be tracked after marketing, and that product corrections and removals be reported to FDA if actions were taken to reduce health risks. Most medical device safety tracking is accomplished through reports submitted to 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 FDA whenever they believe that a device caused or contributed to the death of a patient, though this reporting is a voluntary requirement and not enforceable or audited.[12]

Whether to comply with a postmarketing requirement or out of 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 postapproval 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 comorbidities, as well as 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 a product or undergoing a procedure, since the inclusion criteria are usually broad and may potentially include all patients exposed regardless of age, comorbidities, or concurrent treatments. Data collection may lead to insights about provider prescribing practices or off-label use and information regarding the potential for studying new indications within the expanded patient population. Followup 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, to assist the medical community with developing recommendations for monitoring patient safety and product usage, and/or to contribute to the understanding of the natural history of the disease.

There are also many challenges to the utility of 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 specific products do so through cooperation from physicians who prescribe (or implant) these products. Depending on the setup and legal constraints of the registry, sometimes only a subsection of prescribing physicians may be involved in entering patients, a situation that raises questions about the representativeness of the physicians and their patients. However, the registry approach has the potential to be very useful for studying products that are used according to their labeled indications; it also allows for effective surveillance of products that are used off label but by the same practitioners who would use it for the labeled indication. For example, a product might be approved for people with moderate to severe asthma and used off label in patients with mild asthma, yet the prescribing 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 a medical product is used by a wide variety of medical care providers; for example, drugs that promote wakefulness or are thought to increase a patient's ability to concentrate, acting as immunomodulators. The legal, regulatory, and ethical aspects of registry sponsors also affect whether they are required to report any AEs that may be observed, since only those legal entities that market (or distribute) a medical product are required to report AEs. For all other parties, such reporting is ethical and desirable, but not enforceable or required.

The purpose of this chapter is to examine the role of registries as one of the available tools for enhanced understanding of product safety through AE detection and evaluation. The examination will include both the role of registries created specifically for the purposes of safety assessment and of those in which the collection of safety data is ancillary to the registry's primary objectives. The legal obligations of regulated industries are discussed by others and are only mentioned briefly here. Similarly, issues to consider in the design and analysis of registries are covered in Chapters 3 and 13, respectively. Chapter 12 discusses practical and operational issues with reporting AE data from registries. The potential ethical obligations, technical limitations, and resource constraints that face registries with multiple different purposes in considering their role in AE detection and reporting are also discussed in this chapter. Case Examples 44 and 45 offer descriptions of how some registries have provided data for product safety assessments.

2. 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 who are not just different from but more complicated than those included in clinical trials, in terms of the complexity of their underlying disease, their comorbidities, and their concomitant medications.

2.1 Design Considerations: Disease Registries Versus Product Registries

Product registries, by definition, focus on patients treated with a particular medical product. To be useful, the registry should record specific information about the products of interest, including route of administration, dose, duration of use, start and stop date, and, ideally, information about whether a generic or branded product was used (and which brand) and/or specific information about the product. Biologic medicines and devices have their own challenges, ideally requiring information about device identifiers, production lots, and batches. Disease registries include information not only on products or procedures of interest, but also on similar patients who receive other treatments, other procedures, or no treatment for the same clinical indications. By characterizing events in the broad population with conditions of interest, disease registries can make a meaningful contribution to the understanding of AE rates by providing 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, they 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. The utility of this information, of course, depends on these registries' capturing relatively specific and clear information about the events of interest among "typical" patients, and the ability of readers and reviewers to gauge how well the registries cover information about the target population of interest. Generating this kind of real-world data as part of disease registries can be informative either for the design of subsequent product registries (e.g., to establish appropriate study size estimations) or for the incorporation of new treatments into the data collection as they become available, since the data can provide useful benchmarks against which to assess the importance of any signals. Some would argue that disease registries, rather than specific product registries, are more likely to be successful in systematically collecting interpretable long-term safety data, thereby allowing legitimate comparisons, to the extent possible, across types and generations of drugs, devices, and other interventions.[13]

Consideration should be given during the registry design phase to inclusion/exclusion criteria, appropriate comparator groups, definitions of the exposure and relevant risk window(s), and analysis planning (see Chapter 3). Registries involving products new to the market must be cognizant of selection bias, channeling bias, and unmeasured confounding by indication. Channeling bias occurs when patients prescribed the new product are not comparable to the general disease population. For example, channeling bias occurs when sicker patients receive new treatments because they are nonresponsive to existing treatments; conversely, patients who are doing well on existing treatments are unlikely to be switched to new treatments. Unmeasured confounding can also be introduced by frailty; for example, vaccine effectiveness studies can be misleading if only healthy people get vaccinated.

In some countries, cost constraints imposed by reimbursement status (whether dictated by government agencies or private insurance) mean that new therapies are restricted to narrower populations than indicated by the approved indication. For new devices or procedures, provider learning curves and experience are additional factors that must be considered in analysis planning. Since bias is inherent in observational research, the key is to recognize and control it to the extent possible. In some cases, the

potential for bias may be reduced through inclusion/exclusion criteria or other design considerations (e.g., enrollment logs) (see Chapter 3). In other cases, additional data may be collected and analytic techniques used to help assess bias (see Chapter 13). Any recognized potential for bias should be discussed in any publications resulting from the registry.

In some settings, registries are used to collect specific AEs or events of interest. Once the types of AEs and/or other special events of interest have been identified, the registry must be designed to collect the data efficiently. 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 AEs.

Upon registry inception, clinicians or other health care professionals who may encounter patients participating in the registry should be educated about what AEs 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. They should also be reminded about the need to follow up on events that may not obviously be of immediate interest. For example, if a clinician asked a patient how he was feeling and the patient replied that he just returned from the hospital, it would be incumbent on the clinician to obtain additional information to determine whether this hospitalization 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 AEs. Such an active role by participants as well as their treating clinicians can contribute to a robust safety database. In addition to identifying events known to be of interest, the systematic collection of followup data can also 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 followup of all registry patients for key AEs, as well as vital status and patient contact and enrollment information at prespecified visits or intervals, to ensure that analyses of the occurrence of AEs among the registry population are not hampered by extensive missing data. Otherwise, the possibility that patients "lost to followup" may differ from those with repeat visits, with regard to risk of AEs, cannot be excluded.

It is also important to keep in mind that it may be necessary to revisit the registry design if it becomes apparent that the initial plan will not meet expectations. For example, the original criteria for defining the target population (patients and/or health care providers) may not yield enough patients, such as when a treatment of interest is only slowly coming into use for the intended population.

2.1.1 Health-Care Provider– and Patient-Reported Outcomes

Registries and other prospective data collection approaches have the advantage of incorporating both health care provider– and patient-reported data. Although patients and their advocates may spontaneously report postmarketing AEs to manufacturers (e.g., via inquiries directed to medical information departments) and directly to regulatory bodies, this is relatively uncommon. Furthermore, spontaneous reports received directly from patients that lack health care provider confirmation may fall outside of standard aggregating processes by regulatory bodies. In Europe, there are schemes in some countries to encourage patients to report directly to regulatory authorities; throughout Europe, manufacturers have an obligation to follow up patient reports with their health care provider. However, significant events that are not clinically recognized may be substantially underreported.

In addition, registries may collect health care provider–level data, such as training level, number of patients seen annually, and practice type and locations, that may contribute to an understanding of differences in event rates and reporting. This, along with the patient-reported data not routinely

or consistently captured in the medical record (such as concomitant environmental and lifestyle exposures and adherence to prescribed regimes), differentiates registries from other electronic data sources, and in many cases allows for improved assessment of confounding and ability to assess the potential of a signal internally, prior to further signal evaluation or action.

2.1.2 Effects Observed in a Larger Population Over Time

Registries, including those used to follow former clinical trial participants, are well suited to the identification of effects that can only be observed in a large and diverse population over an extended period of time. They make it possible to follow patients longitudinally, and thereby identify long-term device failures or consequences or delayed drug safety issues or benefits; for example, failures of orthopedic implants increasingly placed in more active, younger patients. Similarly, such long-term followup facilitates evaluation of drug-drug interactions (including interactions with new drugs as they come to market and are used) and differences in drug metabolism related to genetic and other patient characteristics.

One of the most consistent risk factors for AEs is the total number of medications taken by a patient.[14] Polypharmacy is commonplace, especially in the elderly, and health care providers are often unaware of over-the-counter, herbal, and other complementary (alternative) medications their patients take. Registries that collect data directly from patients can seek information about use of these products. In the case of registries used solely by health care practitioners, data collection forms can be designed specifically to request that patients be asked about such use.

When designing a registry for safety, the size of the registry, the enrolled population, and the duration of followup are all critical to ensure applicability of the inferences made from the data. If the background rate of the AE 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 AE rate. In addition, the broad inclusion criteria typical of registries make it likely that subgroups of exposed patients may be identified and analyzed separately. Such stratified analyses may require larger sample sizes to achieve rate estimations with confidence intervals narrow enough to allow meaningful interpretation within strata.

As is also true for clinical trials, which often do not have a sufficient sample size for safety, but rather, for efficacy endpoints, describing safety outcomes from observational studies in statistical terms is not always straightforward. Postmarketing 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 is often identified as part of ongoing risk assessment, and these events usually continue to be events of interest after approval. An 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 the fact that a specific event is *not* being observed in a finite population (i.e., that the numerator of its rate of occurrence is zero). Using asymptotic risk estimation, the rule posits that in a large enough study (i.e., >30 patients), if no event occurs, and if the study were repeated over and over again, there can be 95-percent confidence that the event (or events) would not actually occur more often than one in n/3 people, where n is the number of people studied.[15] The rule, originally described by Hanley and Lippman-Hand in 1983, is probably summarized best as a means for "estimating the worst case that is compatible with the observed data."[16] For the purposes of registries, this rule must be carefully applied, since it assumes that reporting of all events occurring in the study population is complete and that the study population is an accurate representation of the intended population. Nonetheless, this rule of thumb provides some guidance regarding registry size and interpretation of results.

2.1.3 Challenges

In planning a registry for safety, it is essential to consider how patients will be identified and recruited in order to understand which types of patients will be included, and equally, if not more importantly, what types of patients will likely *not* 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, practical challenges include the difficulty of 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 AEs and other events of interest without causing undue concern about product safety.

Drawing attention to the registry among health care providers who use the treatments off label is especially challenging, due to competing concerns about being inclusive enough to capture all use (on-label or not) versus the need, especially if the sponsor of the registry is also a manufacturer, to avoid the appearance of promoting off-label use when contacting physicians in specialties known to use the product off label. In addition, diseases targeted for off-label use may be markedly different from indicated uses and may pose different safety issues. In Europe, when there is limited knowledge about the safety of a product prior to its authorization and when a registry is part of a risk management plan, manufacturers may be required, prior to launch of the product, to notify all physicians who may possibly prescribe the product about the existence of a registry (sometimes also called in this context a postauthorization safety study or PASS), including details of how to register patients.

It is more challenging to evaluate the utility of a registry when the entire population at risk has not been included; however, this situation merits careful consideration, since it is far more common than one where a registry captures every single treated patient. Registries organized for research purposes are typically voluntary by design, a situation that does not promote full 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 (1) whether the patients in the registry are representative of typical patients, and (2) 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 recruited only from tertiary referral hospitals? In the latter case the patients can be expected to be more complicated or have more advanced disease than other patients with a similar diagnosis. Are there competing activities in the target population, such as large registration trials or other observational studies, that may skew participation of sites or patients? Are patients in late stages of the disease or with greater disease severity more likely to participate? (See Chapters 3 and 13 for more information on representativeness.)

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 can demonstrate that the actual population (the population enrolled) is representative of the target population through other means (e.g., by comparison to external data sources) can nevertheless be tremendously informative and may be the only feasible way that data can be collected.

Consider, for example, the National Registry for Myocardial Infarction (NRMI), one of the first cardiac care registries.[17] 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 AEs for specific products and comparative information on safety events. Although this registry was quite large in terms of hospitals and patients, it included neither all MI patients nor all patients using the product for

which it described safety information. It was nevertheless considered to be broadly representative of typical MI patients who presented for medical care.

2.1.4 Defining Exposure and Risk Windows

Patients will enter a registry at various stages in the course of their disease or its medical management. 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 prespecified clinical data recorded on standardized forms at scheduled assessments, a practice that 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 returns for followup care, whether or not the visit corresponds to a prespecified data collection schedule). The more haphazard schedule is more reflective of "real-world" settings, yet results in nonuniform data collection for all subjects.

Rather than being discarded, these nonuniform data can be analyzed both by categorizing patient visits in terms of time windows of treatment duration (e.g., considering data from all visits occurring within 30 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 AEs in terms of their induction period and patient time at risk. When the collection of AE data is completed through an ongoing active process and is expected to be continued over the long term, periodic analysis and reporting should be structured around specified time points (e.g., annually, semiannually, or quarterly) and may align with the periodic safety update reports. The rigor of prespecified reporting schedules requires periodic assessment of safety and can support systematic identification of delayed effects.

In addition to variability in the timing of followup, consideration must be given to other recognized aspects of product use in the real world; for example, switching of therapies during followup, use of multiple products in combination or in sequence, dose effects, delayed effects, and failures of 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—practices that make it difficult to determine exposure-outcome relationships. Switching between biologics may lead to problems with immunogenicity because even products that are clinically the same, as in the case of the 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 to treatment—or lack thereof—during registry followup is an important potential 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 followup 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, related to 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.[18] 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 followup, consideration must be given to how long is long enough to appreciate these effects.

Noncompliance can have a substantial effect on the assessment of AEs, particularly 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. With products used to treat chronic diseases it is possible to estimate compliance via electronic health records, by first estimating when repeat prescriptions should be issued, and then measuring the observed versus expected frequency. Although registries may be directly designed to track compliance through patient diaries and other methods of direct reporting, capturing compliance accurately and minimizing recall bias remain challenges.

2.1.5 Special Conditions: Pregnancy Registries

The use of specially designed registries for specific safety monitoring has a long history. 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 collects information on a broad class of products to determine the risk of teratogenesis.[19] (See Case Examples 49 through 52.) 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, pregnant women are generally excluded from clinical investigations used for product approval. Registries and other observational studies, by virtue of being sustainable over longer periods of time and more amenable to small site-to-patient ratios than registration trials, can facilitate the active surveillance of safety in these populations. In addition, using computerized claims or billing data for pregnancy safety monitoring is hampered by the fact that patients often do not present early in pregnancy, by a lack of relevant data on other exposures (since these are often unrelated to reimbursement), and by difficulty linking maternal and infant records. Therefore, direct prospective data collection remains the best source of meaningful safety data related to pregnancy. A challenge for pregnancy registries is to identify and recruit women early enough in pregnancy to obtain reliable information on treatments used during the first trimester, which is a critical time for organogenesis, and to obtain information about early pregnancy loss, since this information is not always volunteered by women. It is also important to obtain information on treatments and other putative exposures before the outcome of the pregnancy is known, to avoid selective recall of exposures by women experiencing bad pregnancy outcomes. For more information, see Chapter 21.

2.1.6 Special Conditions: Orphan Drugs

A product may be designated an orphan drug (or biologic, or medicine in the E.U.) if it fulfills 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 followup of patients treated with the products after authorization is likely to be a requirement.

With some orphan drugs, the disease may have been usually fatal before therapy was available. Determining the safety profile of these products is especially difficult, 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. In this situation, with a fatal disease and a first product with proven efficacy, it would not be ethical to randomize patients in a trial versus placebo for an extended

period of time, and so a registry may be the only effective means of obtaining long-term safety data. Registries in these situations may make meaningful contributions to understanding the natural history of the disease and the long-term effects of treatment, sometimes largely by virtue of the fact that most patients can be included and long-term followup obtained for orphan products. For more information, see Chapter 20.

2.1.7 Special Conditions: Controlled Distribution/ Performance-Linked Access Systems

Registries in the United States may also be part of risk evaluation and mitigation strategies , such as restricted distribution systems, referred to as performance-linked access systems (PLAS), which may be used to monitor the safety of marketed products as one of the Elements to Assure Safe Use.[20] One of the earliest PLAS was a blood-monitoring program for clozapine implemented in 1990 to prevent agranulocytosis; the program allowed clozapine to be dispensed only if an acceptable blood test had been submitted.[21] Other examples include the STEPS program for thalidomide (System for Thalidomide Education and Prescribing Safety), implemented in 1998 to prevent fetal exposure;[22] the TOUCH controlled distribution for natalizumab (Tysabri) for patients with multiple sclerosis, to detect the occurrence of progressive multifocal leukoencephalopathy (PML);[23] and the iPLEDGE system implemented for isotretinoin in 2006, which tightly links the dispensing of isotretinoin for female patients of childbearing potential to documentation of a negative pregnancy test, to prescriber confirmation that contraceptive counseling has occurred, and to prescriber and patient identification of contraceptive methods chosen.[24]

In many of these programs, access to the product is linked directly to participation in the related registry. Therefore, all patients treated with the product should be in the related registry because they cannot otherwise obtain access to it. The related registry is looking for a known AE (for example, PML) and collects data specifically related to that AE. The registry also collects information on other factors that may raise a patient's individual risk for this AE, information that helps provide important clinical context that would not otherwise be available in a systematic fashion on a large population of treated patients.[25]

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 use 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 the enactment of the European Union data protection directive. In some countries it is possible to mandate registration of patients in relation to particular products (e.g., clozapine in the United Kingdom 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 AEs, while risk minimization is achieved by controlled distribution with compulsory distribution of educational material, prescribing algorithms, and treatment initiation forms to anyone likely to prescribe the product. Despite the fact that patient registration is voluntary, high enrollment rates can be achieved, particularly when clinicians recognize that information on the safety profile of the product is limited.[26] 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 reasonably representative, since off-label use may be severely limited by difficulties obtaining the product.

2.1.8 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 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 therefore rarely used. Additionally, the lack of unique device identifiers has posed a challenge for safety surveillance of devices. Recently, the FDA proposed a new system that will establish a unique identifier for most medical devices, with the goals of supporting more accurate reporting and analyzing of medical device AE reports (see Chapter 23).

Despite these challenges, the safety of medical devices is very important due to their widespread use; of particular concern are long-term indwelling 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 Björk-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 decisionmaking about which devices should be explanted.[27, 28] Identification of the characteristics of valves at high risk of failure was very important due to the perioperative 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. Some of the challenges relating to studying medical devices have to do with being able to characterize and evaluate the skill of the "operator," or the medical professional who inserts or implants the device. These operator characteristics may be as, or more, important in terms of understanding risk than the characteristics of the medical devices themselves.[29] For more information, see Chapter 23.

3. Registries Designed for Purposes Other Than Safety

Registries may be designed to fulfill any number of other purposes, including examining comparative effectiveness, studying the natural history of a disease, providing evidence in support or national coverage decisions, or documenting quality improvement efforts. Although these registries may gather data on AEs and report those data (to regulatory authorities, manufacturers or others), not all data may necessarily be reported through the registry. Thus, the registry may not record all events, which would result in an imprecise, and possibly inaccurate, estimation 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 may 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 rehospitalizations for a condition or quality of life, but may not be specifically of sufficient sample size to reliably assess overall safety in this population.

It is more challenging to accurately and precisely detect AEs 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 them. Also, much the same as for registries designed specifically to detect AEs, 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 followup 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, but, when the data are combined with safety data from other sources, trends or signals may become apparent within the data set.

4. Ad Hoc Data Pooling

One way to capitalize on data that, because they were collected for another purpose, may be insufficient for meaningful standalone analysis and interpretation due to study size or lack of comparators, is to pool the data with other similar data. As with any pooling of disparate data, the use of appropriate statistical techniques and the creation of a core data set for analysis are critically important, and are highly dependent on consistency in coding of treatments and events and in case identification.

It is essential to have an understanding of how every data set that will be used in a pooled analysis was created. For example, what is recorded in administrative health insurance claims depends largely on what benefits are covered and how medications are dispensed. Noncovered 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 traditional 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. Also, AE data coded using the same coding dictionary (e.g., Medical Dictionary for Regulatory Activities, or MedDRA) may still be plagued by inconsistency in the application of coding guidelines and standards. Recoding of verbatim event reports may be required, if feasible, prior to analysis. Depending upon the purpose for which the data were collected, data on the treatments of interest are not always recorded, or are not recorded with the specificity needed to understand risk (e.g., branded vs. generic, dosage, route of administration, batch).

Another consideration is differential followup, including the duration and vigor of followup in the registries to be pooled. Particular care is needed when combining data sets 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 population. Similar caution is also advisable when combining information from disparate health systems within a single country, as some treatments of interest may be noncovered benefits in some systems and consequently not recorded in that health system's records. An alternative to pooling data is to conduct meta-analyses of various studies using appropriate statistical and epidemiologic methods.

While the types of registries described above may not be individually of sufficient sample size 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 data sets for AEs 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 orthopedic joint implants. Currently, there are several prominent registries in the United States with varying numbers of 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 AEs. However, only by aggregating common data sets across many of these registries can a broadly representative population be evaluated and enough data accrued to understand the safety profile of specific types of devices in particular populations.

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 health care products or services. Yet many registries, especially disease registries, are conducted by nonregulated entities such as provider associations, academic institutions, and nonprofit research groups, whose role in AE 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 safety analyses can require a high degree of statistical sophistication. Enrolling additional patients or committing additional resources for specialized analyses in order to achieve a general societal benefit through safety reporting is not feasible for most registries when the 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.[30] As facilitated reporting methodologies become more common and easier for registries to implement, there will be fewer reasons for nonparticipation. 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.

5. Signal Detection in Registries and Observational Studies

Although subject to debate, according to the World Health Organization definition, a safety signal is defined as "reported information on a possible causal relationship between an AE and a drug, the relationship being unknown or incompletely documented previously."[31] 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."[32] The authors further posit that signals, following assessment, could subsequently be categorized as indeterminate, verified, or 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 the Council for International Organizations of Medical Sciences (CIOMS), the FDA, and the United Kingdom's Medical and Healthcare products Regulatory Agency. Nelson and colleagues recently provided FDA with a comprehensive evaluation of signal detection methods for use in postmarketing surveillance, and included a discussion of "conventional Phase IV observational safety studies," which would encompass registries, as part of a multipronged approach to surveillance.[33] They noted 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 FDA's Sentinel Network, the need for more detailed data regarding exposure and outcome measurement, as well as collection of relevant confounder data, will require that prospective observation studies be conducted to address prespecified 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 payer coverage, remains an important question and is unlikely to be uniformly applicable to all products and situations. A report was issued in 2010 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 and to provide practical advice.[34]

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.[35] 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 the ascription of 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," or, in other words, 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 methods currently used 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.[36, 37] 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 and quantitative assessment of extrinsic factors (e.g., an artificial spike in reporting due to media attention) and potential confounders; in some cases, even with quantitative and qualitative assessments, the data may be insufficient to establish causality. Depending on the original data source, it may be impossible to address these issues within the database itself and either abstracted medical record data or prospective data collection may be required to gather reliable data. The long-term followup 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 whether that threshold changes over time.

While some registries can serve as sources of initial safety signaling or hypothesis generation, they may also be used 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 postmarket setting that off-label use was very common and that the risk of restenosis and other long-term outcomes in the real-world patient population was 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.[38] This use of procedure and national registries provides an example of how a registry that included a well-defined population allowed for safety assessments coincident with comparative effectiveness.

6. 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: (1) What is the role of registries not designed for safety purposes with respect to the search for AEs? and (2) What are the obligations, especially for those registries not sponsored by regulated manufacturers, to further investigate and report these events when found? 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 these distinctions, several factors 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, not only for detecting the signal of interest, but for handling unanticipated events and reporting them to appropriate authorities. Only in the case of registries supported by the regulated industries are rules for reporting drug or device AEs explicit. Therefore, it would be helpful if other registries would also formulate plans that ensure that 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. 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. In the United Kingdom, the General Medical Council includes in its advice on "Good Medical Practice" the requirement to "report suspected adverse drug reactions in accordance with the relevant reporting scheme."[39] It is therefore clear that in the United Kingdom contributing to the safety profile of a medicine is regarded as part of the duties of a medical practitioner. During its review of research registries, an institutional review board (IRB) in the United States or ethics committee (EC) in Canada or the European Union may specify the creation of an explicit incidental findings plan prior to approval. Such a plan is often part of studies producing or compiling nonclinical imaging and genetic data. In addition, some investigators will have an obligation to report to an IRB or EC any unanticipated problems involving risks to subjects or others under the regulations on human research protections. In turn, IRBs and ECs have an obligation to report such incidents to relevant authorities.

At a minimum, all registries should ensure that standard reporting mechanisms for AE information are described in the registry's procedural documents. These mechanisms should also be explained to investigators and, where feasible, their reporting efforts should be facilitated. For example, all registries in the United States can make available to registry participants access to the MedWatch forms[40] and train them in the appropriate use of these forms to report spontaneous events. As described in Section 4 above, in the near future it should be possible for registries that collect data electronically to actually facilitate the reporting of AEs by linking with facilitated safety reporting mechanisms. This mechanism is attractive because it reduces the work of the investigator in generating the report

and ensures that the report will go to a surveillance program 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 that inaccurate and potentially injurious information will be generated. For example, publicizing product safety issues can result in some patients discontinuing use of potentially life-saving products regardless of the strength of the scientific evidence. As described earlier, registries designed for safety assessment should ideally have both adequate sample size and signal evaluation expertise in order 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 may not have the financial resources to devote to unplanned analyses and investigations. It would seem that, at a minimum, registries not designed for safety purposes should use facilitated reporting (via training, providing forms, etc.) 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, obligations arise.

While registries that are approved by IRBs report safety issues to those IRBs, incidental analytic findings, which may represent true or false signals, may need more definition and 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. To avoid doubt, registry developers should consider these issues carefully during the planning phase of a registry, and should explicitly define their practices and procedures for AE detection and reporting, their planned analyses of AEs, and how incidental analytic findings will be managed. Such a plan should lay out the extent to which registry owners will analyze their data for AEs, 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.

7. Summary

The ongoing challenge, in the use both of existing data and of prospective data collection efforts such as registries, is to cast a wide enough net to capture not only rare events, but also more common events and events that are not anticipated (i.e., not part of a preapproval or postapproval potential risk assessment). In some cases, existing registries may add additional data collection to address questions regarding possible AEs 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 medical product safety and, specifically, to signal detection and verification.

In contributing to the evidence hierarchy surrounding the generation of signals for detection and confirmation of potential AEs, registries are likely to make their strongest contributions through: detection of novel AEs associated with product use as reported by treating physicians, which, in turn, constitutes a signal necessitating further study; gathering information about pregnant women and other hard-to-study subpopulations of product users; linking 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 confirming or validating 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 whether 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 to collect, analyze, and report safety information if doing so is not a planned objective of the registry, and if the registry sponsor is not directly required by regulation to conduct such reporting.

Thoughtfully designed registries can play important roles in these newly emerging strategies to use multiple available data sources to generate and strengthen hypotheses in product safety.

However, as with all data sources, it is important to assess the effects of registry design, the type of data, reason for the data collection, how the data were collected, and the generalizability to the target population, in order to assess the strengths, weaknesses, and validity of the results provided and their contribution to the knowledge of the safety profile of the medicine or device under study.

Case Examples for Chapter 19

Case Example 44. Using a registry to assess long-term product safety

Description	The British Society for Rheumatology Biologics Register is a prospective observational study conducted to monitor the routine clinical use and long-term safety of biologics in patients with severe rheumatoid arthritis and other rheumatic conditions. The United Kingdom-wide national project was launched after the introduction of the first tumor necrosis factors (TNF) alpha inhibitors.
Sponsor	The British Society for Rheumatology (BSR) commissioned the registry, which receives restricted funding from Abbott Laboratories, Biovitrum, Schering Plough, Roche, and Wyeth Pharmaceuticals. The registry is managed by the BSR and the University of Manchester.
Year Started	2001
Year Ended	Ongoing
No. of Sites	All consultant rheumatologists in the United Kingdom who have prescribed anti-TNF therapy participate.
No. of Patients	More than 17,000

Challenge

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by joint damage, pain, and disability. Among the pharmacologic treatments, nonbiologic disease-modifying antirheumatic drugs (DMARDs) are considered the first-line treatment. Novel biologic therapies represent a new class of agents that prevent inflammation and have demonstrated efficacy in RA patients. The most commonly used biologics are tumor necrosis factors (TNF) inhibitors (etanercept, infliximab, and adalimumab). However, results from clinical trials and pharmacovigilance studies have raised potential safety concerns, and limited long-term data on these therapies are available. Of particular concern has been an increase of tuberculosis observed in patients treated with anti-TNF therapy.

Proposed Solution

A prospective observational registry was launched in 2001 to monitor the safety of new biologic treatments. The registry collects data on response to treatment and potential AEs every six months, and patients are followed for the life of the registry. Over 4,000 patients are enrolled for each of the anti-TNF agents (etanercept, infliximab, and adalimumab), and the registry represents approximately 80 percent of RA patients treated with these biologics in the United Kingdom. In addition to patients receiving anti-TNF therapy, the registry has enrolled a control cohort of patients receiving nonbiologic DMARDs.

Case Example 44. Using a registry to assess long-term product safety (continued)

Results

Data from the registry were analyzed to determine whether an increased risk of tuberculosis existed in RA patients treated with anti-TNF therapy (Dixon et al., 2010). In more than 13,000 RA patients included up to April 2008, 40 cases of tuberculosis were observed in the anti-TNF cohort and no cases in the DMARD group. A differential risk was reported among the three anti-TNF agents, with the lowest risk observed in the etanercept group. The incidence rates were 144, 136, and 39 cases per 100,000 person-years for adalimumab, infliximab, and etanercept, respectively. In addition, the incidence rate ratio, median time to events, and influence of ethnicity were evaluated.

Key Point

As novel drugs and treatments are developed and licensed, registries may be useful tools for collecting long-term data to assess known and emerging safety concerns.

For More Information

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Zink A, Askling J, Dixon WG. et al. European biological registers: methodology, selected results and perspectives. Annal Rheum Dis. 2009;68:1240–6.

Case Example 45. Using a registry to monitor long-term product safety

Description	SINCERE™ (Safety in Idiopathic arthritis: NSAIDs and Celebrex Evaluation Registry) was a multi-center registry designed to monitor the long-term safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with juvenile idiopathic arthritis (JIA). The registry included patients ages 2 to 17 and collected demographic, developmental, clinical, and safety data. The followup period was at least 2 years, and as long as 4 years for some patients.
Sponsor	Pfizer, Inc.
Year Started	2009
Year Ended	2012 (terminated early)
No. of Sites	16 sites in the United States
No. of Patients	Planned enrollment of 200 patients on celecoxib and 200 patients on other NSAIDs. Actual enrollment of 219 patients on other NSAIDs, 55 on celecoxib, for a total of 274.

Challenge

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been used for more than 30 years to relieve pain and inflammation in juvenile idiopathic arthritis (JIA), and it is estimated that 80 to 90 percent of JIA patients will use an NSAID at some point. However, little is known about the long-term safety of chronic use of NSAIDs in children with JIA. This question is particularly important, as many children with JIA will continue to use NSAIDs well into adulthood. Due to the rarity of JIA and the special ethical issues surrounding children's participation in experimental studies, randomized controlled trials of NSAIDs in JIA are considerably smaller and of shorter duration than adult arthritis trials; the pivotal trial for celecoxib in JIA, one of the largest NSAID JIA studies, had 100 patient-years of exposure. In addition, randomized trials may not be generalizable to typical JIA populations. Lastly, it is unclear if the emerging safety concerns in adult NSAID and celecoxib users translate to children, who are much less likely to develop serious cardiovascular thromboembolic events or gastrointestinal bleeding events.

The development of a long-term observational study was necessary to address these knowledge gaps, fulfill a postmarketing safety commitment, and respond to concerns of regulators, patients, physicians, and the sponsor.

Proposed Solution

This multicenter registry was designed to gather long-term safety data on NSAIDs use in children with JIA, and was intended to enroll a quasi-inception cohort of patients aged 2 to 17 years and >10 kg who were prescribed (not more than 6 months prior) either celecoxib (n=200) or other NSAIDs (n=200). Pediatric rheumatologists from 16 sites in the United States entered data quarterly for the first 12 months and twice annually thereafter. The registry intended to follow all patients for at least 2 years and as long as 4 years, as all patients were encouraged to remain in the registry until the last patient completed the minimum followup. Concomitant medications and treatment switches were permitted, and patients were followed for residual effects even if NSAID treatment was discontinued.

Targeted events of interest (i.e., cardiovascular, gastrointestinal, and hypertension) and general safety serious and nonserious AEs were collected in a systematic manner. The Common Terminology Criteria for Adverse Events (CTCAE ver 3.0) criteria were used to both code and grade all AEs to minimize variability across physicians. In designing the registry, particular attention was paid to collecting potential covariates relevant to confounding by indication, given the expected differential prescribing between celecoxib and other NSAIDs. The analyses summarized the incidence of the targeted events and AEs in general, and exploratory analyses may further characterize AE rates by other clinical and demographic factors.

Case Example 45. Using a registry to monitor long-term product safety (continued)

Results

The registry was terminated early due to low patient recruitment, despite multiple attempts to improve site and patient enrollment. The primary issue identified as a barrier to enrollment was that the treatment paradigm had changed since celecoxib was first approved: with the advent and increasing use of biologic therapies, NSAIDs were no longer being used long-term in JIA very often. As a result, the objective of the study, to assess the long-term safety of celecoxib as used for JIA, could not be met. This change in treatment paradigm, coupled with safety information from the registry and other sources that indicated no new signals nor change to the benefit-risk profile of celecoxib as used in children with JIA, allowed the FDA to release the sponsor from the commitment and terminate the study early due to futility. The registry nevertheless provided over 410 patient-years of observation in this cohort of NSAID and celecoxib users, providing additional safety data on these drugs as used for JIA in routine clinical practice; no new safety issues were identified. This information may facilitate appropriate therapeutic decisionmaking for doctors and patients.

Key Point

Registries may be useful tools for examining long-term product safety, particularly in populations such as children that are difficult to study in randomized controlled trials. Changes in the treatment paradigm of a disease may affect the utility and feasibility of a long-term product safety registry.

For More Information

Beukelman T, Patkar NM, Saag KG, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011 Apr;63(4):465-82.

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Chapter 20. Rare Disease Registries

1. Introduction

There is no single, unifying definition of a rare disease. Rare diseases are defined, from a regulatory and policy perspective, as any condition or disease affecting fewer than 200,000 individuals in the United States, or alternatively, determined to be of low prevalence (fewer than 5 individuals per 10,000) in the European Union.[1, 2] In the United States, the Orphan Drug Act (P.L. 97-414) was adopted in 1983 in an effort to encourage activities by industry (and to a lesser extent other funding and research bodies) through tax incentives, market exclusivity, user fee exemptions and other incentives to target development of therapies for rare diseases. This legislation, as well as other regulations and similar international initiatives, resulted in a marked increase in rare disease research funding and development efforts for related drugs and biologics. Success of these compounds in coming to market, however, has been hampered by an incomplete understanding of the underlying disease mechanisms and relevant clinical endpoints, as well as limitations associated with identifying a large enough sample of comparable patients for clinical trials.

The scarcity of relevant knowledge and experience with most rare diseases creates a unique need for cooperation and infrastructure. Support is needed for research initiatives that aim to better understand the distribution and determinants of these diseases and to develop new therapies and other interventions. Innovations in genetics, molecular and computational biology, and other technological advances in basic research are rapidly evolving; however, translating this progress into clinic research and securing governmental or private funding in early stages remains challenging. Some of these challenges can be addressed efficiently through a systematic collection of clinical, genetic, and biologic data in the form of longitudinal patient registries and other coordinated data sources.

The use of observational data methods, including prospective long-term patient registries, is a critical tool in building a broad and comprehensive knowledge base for these often heterogeneous diseases. Important data include the prevalence and distribution of these diseases and key patient, familial, and disease characteristics, including the natural history of the disease. Although many of the basic concepts around registry planning, design, and implementation are directly applicable these disease registries, rare diseases pose some unique challenges. The range of stakeholders for rare diseases is inherently different, which has a direct effect on implementation, governance, funding, communication and as well as their level of interest and willingness to participate in the study of rare diseases. Clinicians with relevant expertise and direct exposure to managing these patients are limited, necessitating a broad outreach to identify and recruit enough patients to understand the epidemiology and natural history of the disease. In addition, because of knowledge gaps, the scope and objectives of rare disease registries are often broader than in a typical disease registry. The absence of standards of care or treatment guidelines in many cases, the common use of experimental and adjunctive therapies, and the incomplete understanding of how these conditions should be monitored in the absence of established or widely accessible biomarkers provide opportunities for rare disease registries to set the agenda for disease research. Since amassing a sizable population from which any patterns of rare diseases can be discerned is more difficult, novel approaches are often required to both define rare diseases and their relevant outcomes (in other words, scientifically validated and accepted criteria may not exist). Lastly, patient advocacy and support groups are smaller for these often less well-known diseases and may play different roles than in a more traditional disease registry.

This chapter provides an overview of the development of patient registries for rare diseases and the key stakeholders and challenges that are specific to these registries. Case Examples 46, 47, and 48 offer some descriptions of rare disease registries. The reader is directed to other chapters regarding relevant good registry practices.

2. Genesis of a Rare Disease Registry

2.1 Rare Disease Registry Objectives and Scope

Rare disease registries are initiated by many organizations, such as patients and their families, patient advocacy groups, clinicians, national health systems, and biopharmaceutical product manufacturers, for many reasons. Often, rare disease patient registries have grown organically. In rare diseases where patients are few, research agendas do not exist, standard case guidelines are absent, and patient communities have not yet formed, patient registries are an intuitive first step for stakeholders trying to understand the number of people affected, their geographical distribution, and the basic demographic and clinical characteristics of the disease. The scope of these registries may evolve over time, maturing from an outreach/community-building effort or a means for a basic understanding of patient and disease characteristics, to a supportive mechanism for research funding and attracting health care providers. As with all registries, a single rare disease registry need not fulfill all goals for all potential stakeholders. Ideally, however, a well-designed registry provides an infrastructure that can support different needs in an efficient way and eliminate barriers to scientific progress.

It should be noted that rare disease registries include not only diseases that are inherently rare, but also common diseases that are rare in specific populations, especially those defined by demographics. Thus, plaque psoriasis—common among adults—is rare in children, and breast cancer—common among women—is rare among men. While some of the objectives specific to rare disease registries will apply (e.g., patient identification and recruitment), others may not (e.g., disease classification, measuring disease-specific outcomes).

Registries can be developed to serve multiple purposes. The design of the registry depends upon the maturity of the research plan around the disease, the availability and duration of funding, and, to some extent, the number of patients affected. For rare diseases, the perception of relative importance of research often correlates with the number of patients affected or the number of empowered disease advocates.

The specific objectives of rare disease registries typically cluster into the following categories:

1. *To connect affected patients, families, and clinicians*. Patients and families of affected individuals are often interested in knowing about others who share their disease. Many rare diseases have a genetic basis. However, even if multiple family members are affected with the condition, the motivation to be connected to others may be quite strong, driven by their personal desire to know more about the condition, its natural history, alternative coping mechanisms and treatment options, and the diversity of clinical courses and outcomes. The need to connect is enhanced if the patient or family has difficulty in finding an expert to provide advice or the doctor or genetic counselor points out how little is known about the rare condition.

   Registry meetings provide an opportunity to talk and to share personal experiences. These meetings may include lectures and discussion among patients and families and with experts in medicine, dentistry, nursing, sociology, and many other fields. The advent of social media has increased patient involvement in these types of activities by encouraging patient-to-patient dialogue and assisting with recruitment for research and support. Patients and families often want to connect to advocate support of patients' services and financial support for patient care and research.

   Similarly, physicians and other clinicians may want to connect with other clinicians to learn more about the disease and possible treatment

options. Most clinicians have not seen a wide spectrum of rare diseases, and little information on some diseases may be available in the literature. Registries may offer a connection to essential information and to experts in the disease area to assist health care providers with advising and counseling patients.

2. *To learn the natural history, evolution, risk, and outcomes of specific diseases*. Stakeholders often initiate registries to learn the natural history of a rare disease. Typically, rare diseases are described in a general way based on their symptoms at the time of diagnosis. With refinement in diagnostic techniques, including genetic, biochemical, and physiological testing, classical disease descriptions are broadened, and diseases are better described in terms of the range and likelihood of specific outcomes. Unlike more common diseases, for which criteria for classification will often evolve, such evolution may not be possible for rare diseases, but the acceptance of some general criteria that derive from these studies will inform and help subsequent research. As general and specific therapies emerge, the natural history often changes and the "classical description" may no longer apply. With better therapies for treatment and supportive care, new complications may also be recognized. For treatments that extend life expectancy, what is known about the trajectory of disease can change drastically. A disease registry incorporating patients with rare diseases from many centers allows for gathering stronger and more generalizable safety, diagnostic, and prognostic information.

   For industry, natural history of disease registries are often developed to better understand the burden of disease, elements of disease progression, disease genotypic and phenotypic heterogeneity, and potential endpoints (or surrogate endpoints) that may be used in therapeutic clinical development. Increasingly, these types of disease registries are also used to understand patient and caregiver quality of life and the economic consequences of these diseases, as well as to understand the background risk of specific outcomes (i.e., to provide a reference population) that usually cannot be found or inferred from other sources of data when the disease is rare.

3. *To support research on genetic, molecular, and physiological basis of rare diseases*. Research on features of disease, both clinical and basic, is a common objective of a registry. Clinical research depends on having a representative population for determining the timing and frequency of natural events and complications, such as development of autoimmune complications, unusual infections, and related or unrelated malignancies. For this reason, rare disease registries benefit from a comprehensive database that is sufficient to address critical clinical questions, while at the same time not being so all-inclusive that the data cannot be acquired and maintained with reasonable effort on the part of the registry team.

   Patients, researchers, and clinicians share interests in understanding diseases at the genetic, molecular, and cellular level. Such studies usually require a biorepository of materials for research, including tissue (fresh and frozen), DNA, RNA, cellular proteins, and bodily fluids. Creating a meaningful repository for the study of rare diseases requires collection of materials from a sufficient population to permit generalization about the fundamental features and diversity of the disease at the genetic, molecular, and cellular level. A registry is an important complement to any biorepository; similarly, biorepositories are far stronger if they are closely linked to a registry that contains relevant longitudinal clinical or phenotype data. In cases where multiple small or regional registries exist for a specific condition, a centralized biorepository can serve as a common link and research resource. Valid interpretation of biosample research depends on understanding the clinical features of the patients and the heterogeneity of the disease in the study population. In addition, the existence of parallel relevant longitudinal clinical data allows for assessment of genetic and environmental disease modifiers.

4. *To establish a patient base for evaluating drugs, medical devices, and orphan products*. Stakeholders are vitally interested in developing drugs, devices and other therapies for rare diseases, and many rare disease registries have been developed to support the drug development process. Patient registries for rare diseases may emerge from suggestion, pressure, or advocacy of affected patients and/or families. Direct influence can be seen when patients and their caregivers decide they want a registry, raise the funds, and push for its creation. Indirect influence can be seen when patients or special interest groups drive government to make research on that disease a priority. Researchers and industry recognize that a population of patients is essential for clinical testing, and industry may provide rare disease groups with support to begin or expand a fledgling registry so that ultimately a potentially useful drug or device can be tested in the disease population.

   Often, developing a treatment for a rare disease will provide information about pathophysiology that informs treatment development of a related disease. If the rare disease is serious with few or no treatment options, regulators may relax some of the requirements for drug registration (as is indicated by the requirements for orphan drug development).

2.2 Rare Disease Registry Stakeholders

Any registry endeavor has a number of stakeholders, often with both convergent and divergent agendas. Stakeholders may include patient advocacy groups (often multiple), regulatory agencies (especially if the registry is being developed to support future drug development and approval or to fulfill postmarketing commitments or requirements), clinicians, scientists, industry, payers, and the individuals and families affected by the disease. Collaboration between stakeholder groups has been critical to the progress made in research and product development, the adoption of important public policy changes in the United States and worldwide, and the promotion of patient access to treatments as they become available.[3] Table 20–1 describes potential registry stakeholders and the roles they may play in registries.

The importance of patient registries in rare diseases and the need to support many organizations has also brought umbrella patient organizations (e.g., NORD, the Genetic Alliance, EURORDIS) in as stakeholders, as these groups are charged with advising and supporting the development of registries. As the number of registries increases along with the number of commercial companies to develop and host them, these umbrella organizations are becoming brokers for services and are motivated to identify standards and shared efficiencies to support patient registries for the thousands of rare disorders that need them. In addition, the proliferation of patient registries for rare diseases brings standards development organizations and standards interests into the fold, as the need for standards that can facilitate data sharing (i.e., common data elements) between patient registries and other aspects of health care and clinical research has become evident. More broadly, the vision of patient registries that can share data between electronic health records and personal health records, as well as with clinical research or national public health efforts, has engaged a variety of commercial application providers in the field.

Representatives from any of the groups mentioned as stakeholders can function as registry sponsors or developers. A distinction is made between registry *sponsors*, as the entities who fund, plan, and often select data collection content for a registry, and *developers*, as the technology and computing professionals who build the registry.

Table 20–1. Role of stakeholders in rare disease registries

Stakeholder	Role in Registry	Motivations for Registry Involvement
Patients and their families/ caregivers	Participants	Increase knowledge about the disease; create community; facilitate development of new treatments.
Patient advocacy groups	Advocates, sponsors	Increase knowledge about the disease; increase access to care; support training and research in disease area; raise profile of the disease to encourage funding for more research.
Clinicians/Investigators	Data contributors	Increase knowledge about the disease; learn from the registry community; gather data to refine complex or undefined diagnoses; develop and inform treatment guidelines.
Academia	Principal investigators, scientific advisors	Improve understanding of disease; create data source for research in disease area.
Biopharmaceutical industry	Sponsors, developers	Understand the natural history of the disease to design better clinical trials and evaluate potential relevant clinical endpoints; fulfill postmarketing commitment; provide patient pool for interventional studies; determine potential market share and access patients; generate publications.
Government/regulatory agencies/payers	Sponsors, recipients of information	Increase knowledge about the disease; monitor the safety of approved products; evaluate cost-effectiveness and budget impact; evaluate evidence for reimbursement.

Although data from registries are not a substitute for controlled trials, rare disease registry data may be the only source of information (especially about a specific product's use) available to stakeholders. This information may serve to inform industry such that a controlled trial can be determined to be feasible, designed appropriately, and well informed upon inception. Disease registry data complement trials, especially those conducted in rare diseases, for which other sources of data are rare or nonexistent. Industry supports many rare disease patient registries, both disease-based and product-based, as sponsors and developers. This is particularly common in rare disorders for which the clinical development program is often abbreviated and inclusive of only a small, relatively heterogeneous subpopulation of the disease population. These registries are often well received by patient groups who do not have funds to operate a registry independently, but stakeholder objectives are not always aligned. For example, industry-sponsored registries are in some cases treatment- or product-based registries, where patients are included for study based upon treatment exposure. However, some product exposure registries create a fragmented system that does not allow researchers or policymakers to see the entire spectrum of disease.[4] These different product registries have different sponsors and collect different data (often at the behest of regulators who seek answers to different questions), rendering them difficult to combine during research. When more than one treatment exists for a given condition, the different postmarketing treatment registries are often not comparable, nor are the full spectrum data (from multiple registries hosted by multiple companies) easily accessible for academic researchers. Additionally, if patients are exposed to multiple treatments, their data might be in multiple registries, but their full experience across treatments is not appreciated.

Disease registries (rather than exposure or treatment registries) create the possibility of assessing the long-term safety and benefit of different treatments, perhaps leading to treatment algorithms that allow more choices for patients

and clinicians. Regulators have increasingly recognized the value of disease registries for historical comparator data and long-term evaluation (especially for drug safety) and as a complement to randomized clinical trials to "fill in the blanks" about outcomes that were not addressed in the limited controlled studies. These registries become even more important to regulators (and others involved) when the disease is rare and registries may be the only means by which data can be obtained. The marriage of stakeholder interests may create conflicts of interest for these registries that require careful scrutiny of available resources. If an effective partnership can be established and maintained, the creation of clinician and patient/caregiver communities can be a powerful agent in the success of a product in development or evaluation.

Even more effective in rare disease research is a collaborative approach in which multinational and multi-institutional stakeholders combine resources. As resources are combined, standardization becomes more important to allow data to be compared across registries. Regulatory organizations such as the U.S. Food and Drug Administration and the European Medicines Agency can guide standardization across multiple postmarket registries within specific disease areas and promote the creation of multisponsor registries where appropriate. Other organizations like PARENT (PAtient REgistries iNiTiative) are facilitating cross-border collaborations to develop comparable and transferrable patient registries. Resources and tools for identifying and sharing patient registry questions, such as the PRISM (Patient Registry Item Specifications and Metadata for Rare Diseases) library of patient registry questions,[5] will support these standardization efforts.

Although the creation of a single global registry for each disease (or group of diseases) is theoretically a sound idea, in practice it may not always be feasible or in the best interest of researchers. A viable alternative can be a network of registries and resources, such as TREAT-NMD (Translational Research in Europe—Assessment & Treatment of Neuromuscular Diseases), a network of neuromuscular disease researchers that was launched in early 2007. TREAT-NMD aims to create an infrastructure to promote the development of tools (e.g., core outcome sets) that industry, clinicians, and scientists need to bring novel therapeutic approaches through preclinical development and into the clinic and to establish best-practice care for neuromuscular patients worldwide.[6] Similarly, multiple registries could be connected via a centralized biorepository or biobank to provide larger sample sizes to understand disease processes and how they correlate with patient outcomes. As with any collaborative research, the challenges lie in who manages the collaboration, who funds it, and what governance infrastructure is required to bring together researchers who may be reluctant to share their data. The availability of indices of registries [e.g., OrphaNet[7] in Europe and the new Registry of Patient Registries (RoPR) in the United States[8]] is helpful for identification of potential data sources and collaborators.

3. Implementation of a Rare Disease Registry

3.1 Patient Population

Because patient registries can collect clinical information from larger, more heterogeneous populations than those included in a clinical trial, they are becoming increasingly valuable, particularly for diseases affecting very small patient populations, such as lysosomal storage disorders and for specific populations such as children.[9] Whereas selection of patients may be highly restrictive in general disease registries, rare disease registries often have more liberal criteria for inclusion. In many cases, a physician diagnosis, rather than the more common strict classification schema, may be sufficient for inclusion in a rare disease registry. Reasons may include: (1) no classification criteria exist; (2) knowledge of the rare disease is so limited that being more inclusive is desirable; and (3) the population is so small that being more inclusive is desirable. With some exceptions, rare disease registries typically do have broad inclusion criteria and attempt to enroll most, if not all, eligible patients within a targeted geographical area.

Although they may not be sufficient for population-based estimates of disease, these data sources can be used to estimate the numbers of affected patients and the number of patients potentially available for research, and can enable the mobilization of disease-specific communities for advocacy. Since a large proportion of recognized rare diseases are genetic in origin, enrolling family members greatly improves understanding of the disease, but may create additional complexities around confidentiality, logistical issues (e.g., different last names and other tracking issues), and considerations for enrollment of minors. The issue of "study fatigue" should also be considered when developing patient enrollment plans. Because of the limited numbers of available patients, some patients may be asked to participate in multiple studies over time. Patients may become overtaxed by frequent participation in studies and reluctant to join new studies.

For registries examining treatment-related outcomes, the challenges in creating an inclusive patient cohort include differences in health care delivery systems, local regulations, and budgetary considerations that create barriers to care and/or specific treatments. For example, if a disease is rare, a drug or device manufacturer may choose not to go through the rigorous process required to have the product approved or priced locally—for example, in a small country—as the number of patients who might ultimately use the product does not support the cost of time and effort. This may create difficulties in enrolling a representative patient cohort from such regions.

3.2 Data Collection

Most registries are tempted to (and often do) include as many data elements as possible in order to glean as much information as possible from their study population. This often leads to increasing respondent and investigator burden, high rates of discontinuation, and substantial challenges in data management. In some registries, these drawbacks may be offset by the ability to continue to recruit additional patients and/or the availability of sufficient numbers of patients already enrolled despite dropout. This is rarely the case, however, with rare disease registries. Thus, balancing the need for a broad dataset with the burden of data collection is highly important for rare disease registries.

In many respects, data collection for rare disease registries is similar to data collection for other types of registries. Like other registries, rare disease registries aim to collect a uniform set of data on each patient. Data elements should be clearly defined to ensure consistency in interpretation across participating sites, and data collection and management procedures should be designed to support the collection of high quality data. Other chapters in this document discuss these concepts in more detail as they apply to registries generally. However, while many of the best practices described elsewhere in this document are applicable to rare disease registries, rare disease registries face unique data collection challenges not addressed by those best practices. In particular, rare disease registries may encounter additional hurdles when attempting to use common data elements, selecting quality of life or patient-reported outcome measures, collecting biomarkers, obtaining long-term followup data, and assuring data quality.

3.3 Creating Efficiencies in Registry Development

A major step in the development of any registry is the selection of the data elements. This task can be time consuming and resource intensive, particularly when multiple stakeholders are involved in defining the data set. As noted in Chapter 4, the primary goals in selecting data elements are to ensure that the necessary data are collected to achieve the objectives of the study and that the data set is not so overly burdensome as to limit participation in the registry. A critical component of developing the data set is defining the data elements and determining how each piece of data will be collected. Many registries develop and define their own data elements. This approach can be costly, and it limits the ability of data from the registry to be linked or compared with data from other registries or data sources. It is more challenging to standardize the data collection for rare diseases, as the understanding of the disease is

likely to be limited and, until recently, established standardization efforts were limited.

Common data elements (CDEs) may offer a potential solution to some of these issues. A CDE can be defined as "a data element that can be consistently collected across all clinical studies."[10] CDEs include standard definitions, code lists, and instructions so that the data are collected and stored in the same manner by each participating site, in each study. CDEs may be general, meaning they can be used across disease or therapeutic areas (e.g., demographics, vital signs)[11] or disease-specific, meaning they are designed for research in a particular disease area (e.g., congenital muscular dystrophy).[12] By using CDEs, registries may be able to reduce the time and effort involved in developing a dataset and to enable the registry data to be linked or compared with data from other studies using the same CDEs.

CDEs are particularly important for rare disease research. CDEs may lower the cost of developing a new registry, making registries more accessible for diseases where funding is limited. CDEs may also enable data from multiple small registry projects to be linked or compared to increase knowledge about the disease. The Institute of Medicine noted the potential importance of CDEs for rare disease research. In the 2010 report, *Rare Diseases and Orphan Products: Accelerating Research and Development*, the IOM stated, "The NIH [National Institutes of Health] should support a collaborative public-private partnership to develop and manage a freely available platform for creating or restructuring patient registries and biorepositories for rare diseases and for sharing de-identified data. The platform should include mechanisms to create standards for data collection, specimen storage, and informed consent by patients or research participants."[1] Recognizing the potential value of CDEs, NIH recently funded the PRISM project. The objective of the PRISM project, which is administered through the National Library of Medicine and supported by the Office of Rare Disease Research (ORDR), is to develop a library of standardized questions that will be relevant to a broad mix of rare diseases and that can be used to develop new registries or to update existing registries. Ultimately, the project aims to develop tools that will support the rapid implementation of new rare disease registries, the revision of existing registries, and interoperability between rare disease registries and other data sources.[5, 13]

In January 2010, NIH and ORDR hosted a workshop titled "Advancing Rare Disease Research: the Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data,"[14, 15] which launched the development of the Global Rare Disease Registry and Data Repository, a Web-based data registry that will link existing registries, future registries, and biorepositories.[16] Two significant work results are expected out of this initiative. The first is a 2-year pilot program in collaboration with Patient Crossroads, Children's Hospital of Philadelphia, and WebMD that will develop a Web-based template to allow any patient group to establish its own patient registry. The second work result is a preliminary set of recommended CDEs[17] that has been drafted and has undergone revision based on feedback received from public comment. The CDEs are generally applicable to any rare disease registry. This CDE list mixes required and optional elements in the following categories: current contact information; sociodemographic information; diagnosis; family history; birth and reproductive history; anthropometric information; patient-reported outcome; medications, devices, and health services; clinical research participation and biospecimen donation; communication and preferences. ORDR is working closely with the Clinical Data Interchange Standards Consortium (CDISC), which has reviewed the ORDR CDEs[18] and is in the process of a similar initiative focused on CDEs for clinical trials. Planned next steps include working with the rare disease community (including clinicians, patients, and advocacy groups) to develop CDEs for specific rare diseases.

While CDEs have significant potential for rare disease registries, they do have some limitations. First, while general CDEs may be relevant for rare disease registries, these CDEs can typically only cover a small portion of a data set necessary for studying a rare disease. The currently available disease-specific CDEs tend to focus on prevalent diseases, such as cancer, cardiovascular disease, and neurological disorders. (Refer to Chapter 4 for

a table of currently available CDEs.) Some of these CDEs may be relevant for some rare disease registries, but many may not be useful. Second, CDEs may change over time to reflect changes in practice or new trends in clinical research. Registries with shorter durations (1 to 2 years) may not be affected by changes in CDEs, but rare disease registries are often designed to follow patients for long periods (e.g., several years or until death). To retain the benefits of linkage and comparison, registries that use CDEs would need to update their data collection tools to reflect the changes in CDEs.

In selecting data elements for a rare disease registry, it is useful to consider using CDEs as a first step, before developing new data elements independently. Available CDEs may be relevant for basic information, such as demographics, and for some disease-specific information, and the use of these CDEs is encouraged, when possible. When CDEs are not available, a review of the literature and searches of ClinicalTrials.gov and other similar databases may identify other registries or clinical studies in the disease area. Those studies may be willing to share information on their data sets, so that the new registry can either align with those data elements to support future linkages or comparisons or perhaps learn from issues that have come up in the other studies and apply that knowledge to the development of a new data set. As noted in Chapter 4, other considerations in selecting data elements include feasibility (Are the data elements routinely collected in clinical practice?), burden (What scope of data collection is desirable; what burden on participants is tolerable?), and geographic variations in terminology and practice (Do disease definitions differ? Are data collected the same way in all registry locations? Do terminologies vary by country?).

3.4 Including Quality of Life or Patient-Reported Outcome Measures

Quality of life measures and patient-reported outcome measures (PROs) are increasingly being used in registries to understand patient experiences and preferences. In rare disease research, quality of life data and PROs may be particularly important when well-defined, widely accepted clinical outcomes are not available. The progression and mechanisms of rare diseases are often not well understood, a situation that inhibits the identification of meaningful clinical outcomes, the development of new therapies, and the assessment of the effectiveness of existing therapies or disease management strategies. Quality of life measures and PROs may provide useful data to show that disease management strategies or treatments are effective at improving patient (and caregiver) outcomes or quality of life.

The selection of quality of life measures or PROs for a rare disease registry can be challenging. Disease-specific measures are often not available, and generic measures that were developed with consideration to more common diseases (e.g., the SF-36) are not detailed enough to capture relevant changes in the patient's (or caregiver's) quality of life. New measures may be difficult and expensive to develop, given the small number of patients, validation requirements, and the need to have measures that can be used in multiple languages. As with the selection of data elements, registries may seek to identify other existing studies in the disease area and use similar measures to allow for future comparisons. When selecting measures, burden on the participant is a major consideration. The inclusion of multiple quality of life measures and PROs can be tempting, but they may deter patient participation if the burden is excessive. Considerations for selecting measures, collecting the data, and analyzing and interpreting the data are further discussed in Chapter 5.

In addition to utilizing a PRO tool, a registry may be used to validate one or more PRO instruments across a large number of centers and in some cases countries. Nonvalidated tools, such as patient diaries and other electronic or paper-based data collection methods (e.g., treatment logs to track compliance, symptom checklists), may also be integrated across the registry or within a subpopulation of interest.

Health economic data may also play an important role in a rare disease registry. While the major goals of the registry may be to improve understanding of the disease or to monitor treatments, an underlying objective may be to

build the case for new research in the disease area and the development of new therapies. Health economic data may be useful for more broadly demonstrating the global burden of disease. Because of the rarity of the disease, the burden may not be well understood, and global burden of disease data may be used to gain support for funding new research in the disease area. In addition, if therapies are developed for rare diseases that were once only treated with supportive care, some aspects of disease burden may improve, while other considerations, such as long-term disease management, may be introduced.

3.5 Biomarkers

Biomarkers, which may describe risk, exposures, intermediate effects of treatment, and biologic mechanisms, are an important component of rare disease research and may serve as important surrogate endpoints for health outcomes.[19] In their report on accelerating rare disease research, the IOM identified biomarkers as an important avenue. When biomarkers have been identified for a rare disease, registries in that disease area should consider collecting biomarker data as part of the registry. Registries in disease areas for which biomarkers have not been identified may also consider collecting biological specimens, physiological tests, or radiographic studies, in the hope of furthering efforts to develop and validate biomarkers.[1]

When determining whether to collect biomarkers or other biological specimens, registries must consider several factors, addressing the following questions:

- Does the biosample need to be collected once or on an ongoing basis? If ongoing, how often?
- Does the biosample need to be examined by a central laboratory? Will multiple laboratories be needed because of geographic constraints (e.g., the fact that samples collected in the European Union cannot be sent to a laboratory in the United States) or time constraints (e.g., that sample processing is required within 24 hours)?
- What privacy and ethical issues will the collection and storage of biosamples introduce?
- How will the informed consent document discuss the collection and storage of biosamples? How broad can the language be? Can it address unanticipated use of these samples?
- How long will the biosample data be stored? For what research purposes may it be used?

As more is learned about a rare disease and its origins, the ability to perform exploratory analyses on existing samples is critical and should be considered when a biorepository is established.

3.6 Collection of Followup Data

Collection of long-term followup data is often an important component of debilitating but not fatal rare disease registries. Many rare diseases are chronic and lifelong, meaning that registries may wish to track patients for several years or even until the patient's death. The collection of long-term followup data for rare diseases raises some unique challenges, including what type of providers should participate (specialist vs. general clinician), how to encourage retention, and minimizing lost-to-followup patients.

Many patients with rare diseases see a specialist in the disease area on a regular but infrequent basis (e.g., annually) and see other clinicians on a more regular basis. The specialist may see several patients with the same disease and may have specialized knowledge of the disease; in that sense, the specialist may be an ideal candidate for registry participation. However, participation by the specialist may result in infrequent data collection on the individual patients or missing data collected by other clinicians. The registry may miss events that occur between specialist visits and may not obtain an accurate picture of the day-to-day impact of the disease. Participation by the clinician (or clinicians) that treats the patient on a regular basis is another option. These clinicians may only see one or two patients with the disease and they may not have specialized knowledge of the condition; however, they may be able to provide more frequent updates on the patient's condition. Both of these approaches have

strengths and limitations. The most comprehensive approach is to collect data from both the clinician and the specialist. This allows the registry to gather both the specialist's overall perspective on the patient's condition and the more granular details of the patient's care. However, this approach raises privacy issues, as the registry may need to share the data collected from the specialist with the clinician and vice versa. It may also present recruitment issues, as both providers must participate in order to avoid significant missing data. The registry will also need to plan for both physicians to participate in order to avoid having duplicate patients entered into the registry.

Because the collection of long-term data is often critical to the registry's objectives, the registry must devote sufficient effort to patient and physician retention. Over time, patients and physicians may lose interest in the registry and stop participating. Patients who enrolled in the registry as minors may change physicians and locations on multiple occasions and upon reaching adulthood. Patients may move and begin seeing a new physician, or physicians may retire and stop participating. Direct input and access to registry data by affected individuals is technically possible and would allow for ongoing registry involvement and foster retention of patients. It has been observed that patient/family-entered data is reliable information, but that it may not be as in-depth or conveyed in medical language as is the information provided by a physician. Depending on the objectives of the registry, one approach would be to facilitate patient/family entry of data to the patient registry with better design of data entry forms/screens, appropriate contact and followup with participants, and sharing of study results and summary data from the patient registry with participants.

Chapter 10, Section 3 describes many factors that can encourage retention, as well as some potential pitfalls that may impede it. Rare disease registries with long-term followup components should have plans in place to monitor retention rates and should have consistent procedures for when to consider patients lost to followup. Registries that collect sufficient identifiers may also consider linking to other data sources, such as the National Death Index in the United States, to determine if patients have died. Procedures used to locate missing registry participants should be articulated in policies and procedures documents and communicated to participants. In addition, processes to retain patients as their status changes (e.g., from treating clinician to clinician; from minor to adult) should be clearly stated, and multiple contact points should be available for both the individual and their next of kin/designated secondary contact.

3.7 Data Analysis

Patient registries are critical for accruing a sufficient sample size for epidemiological and/or clinical research for rare diseases. In most cases, the registries are not statistically powered for hypothesis testing, and the analytic goals should focus on the descriptive techniques relevant to observational research. The uptake of common data elements could facilitate the formation of analysis data sets from the combination of multiple data sources in situations in which two or more disease registries exist, thus increasing sample sizes.

Data collected in rare disease registries prior to the introduction of therapies that drastically alter standard of care and/or treatment guidelines can provide useful information regarding the natural history of disease. If these data do not exist, removing the effects of widespread treatment(s) from registry analysis on disease progression, particularly in highly heterogeneous disease, is challenging. An additional challenge in rare disease registries is the fragmentation of the data. Patients may contribute data sporadically, but not be completely lost to followup. If data are combined across registries (or other databases), care should be taken to identify potential duplicate patients prior to analysis, as this is more likely to occur in a limited population. Many of the other considerations for analysis (e.g., controlling for confounding, handling of missing data, loss to followup) are not unique to rare disease registry data and are addressed in other chapters, such as Chapters 2, 3, and 13.

3.8 Data Access and Communication

Because populations with rare diseases are often considered vulnerable and under-resourced, and because such populations are smaller, it is important to plan for registry data access and communications. Data ownership, data access, and communication are important issues for all registries, but rare disease registries often must pay special attention to these issues because of the broad range of stakeholders involved and the potential interest to others in the disease. Ownership of the data should be clearly specified during the planning phase of the registry and should be communicated to stakeholders and participants in the registry. In many cases, the data owner is the sponsor of the registry. Some registries, though, may have multiple sponsors, or the sponsor may designate that another group will own the data. In addition to ownership of the actual data, ownership of the intellectual property resulting from the registry (e.g., case report forms, patient-reported outcomes tools, reports, analyses, and associated biosamples) should be clearly specified.

Rare disease registries should also develop and adhere to a data access plan. Many data access scenarios are possible. For example, the registry data may only be accessible to the data owner or the sponsor. Alternately, the registry may develop data sharing policies that allow other researchers to access the data. The registry may limit data sharing to investigators participating in the registry, or may allow outside investigators to access the data. For example, an outside researcher may use data from the registry to assess incidence of a particular complication for the purposes of informing protocol development for a new study. As discussed in Chapter 2, data sharing policies should address who can access the data, for what purposes, and under what circumstances (timeframes, access fees, etc.). For example, will manufacturers be able to access data to inform the design of new clinical trials? Will researchers be able to link the data to other data sources for new studies? These types of questions should be carefully considered and addressed in data sharing policies so that all participants (including patients) are aware of the policies and plans for the registry data. Written registry policies and procedures are encouraged and required by many regulatory entities (e.g., institutional review boards).

Publication rights and plans for disseminating information from the registry should also be considered during the planning phase. This is particularly important for rare disease registries with multiple stakeholders, who may have diverse and conflicting interests. There may also be considerations about academic and other interested parties not included in the registry who may wish to use these data at some later point in time. For example, a registry with strong patient advocacy group support and industry funding may need to balance the desire to publish early (in order to share information with the patient community) with the desire to publish later (in order to protect proprietary information related to treatment development). Clear publication plans that are shared with registry stakeholders can help to avoid disagreements once the registry has begun collecting data, and can promote registry transparency.

Like all registries, transparency is important for rare disease registries, and perhaps especially important.[1] Because rare diseases have a limited pool of patients, they need to maintain a highly motivated patient community engaged and actively participating in the registry. Transparency in registry operations, analyses, and publications can help to reassure participants that the registry is fulfilling its objectives and continues to be a worthwhile endeavor. This may take the form of regular updates on registry enrollment and data collection, newsletter updates from principal investigators, and information sharing about abstracts or publications based on registry data. Transparency also requires full disclosure to participants about the use of their data, the registry funding sources, and any underlying goals or motivations for the registry.

3.9 Governance

The governance of a rare disease registry can be extraordinarily simple or, more often, fairly complicated. Complexity stems from the variety of stakeholders involved and their different agendas, as well as the geographical and cultural

distances between the interested parties, particularly for international registries. Simplicity depends upon having clear goals and adept leadership. Registry leadership may be in the form of an Advisory Board or other leadership committee. Advisory boards and general governance principles are discussed in Chapter 2, Section 2.6.

Rare disease registries present unique governance challenges because they often represent collaborations with many stakeholders and may be international in scope. Some examples are included below.

- *Funding*: If not centrally funded, who takes responsibility for raising money, writing grants, and securing the necessary funds for the operation of the registry? If fully funded, what role in decisionmaking does the financial sponsor(s) have? What are the startup costs versus maintenance costs?
- *Privacy*: Patients with rare diseases are more vulnerable than most to being identified by their health information. How does the registry protect the privacy of the individuals and families while at the same time creating a database of information and resources for the benefit of all persons having the rare disease of interest?
- *Outreach*: How does the registry identify affected and interested persons for participation in the registry?
- *Information*: What database is needed for the registry? What demographic, clinical, and/or longitudinal databases are needed? How will the registry adapt as new data needs are identified?
- *Ownership*: Who owns the information collected by the registry? For a tissue repository, who owns the materials in it?
- *Agenda*: Who sets priorities and establishes the work plan for the registry? What are the respective roles of the stakeholders in setting the agenda?
- *Collaborations*: Does the registry governing body create collaborations or can individual participants make collaborative agreements? What approvals are required? How are conflicts avoided and handled?
- *Publications*: Who takes responsibility for determining the publication plan, submitting abstracts, writing journal articles, and otherwise publishing about the activities of the registry? Who does the work? Who gets the credit? Are all of the professional and nonprofessional participants treated equally?

4. The Future of Rare Disease Registries

Existing literature suggests that rare diseases occur infrequently and there is a scarcity of information; however, in reality, difficulty in correct diagnosis and appropriate identification of patients with rare diseases is a global issue that precludes knowledge of these patients. The lack of information reflects the uncertainties in diagnostic criteria and perhaps even inadequacies in data gathering procedures. As the patient community continues to grow throughout the world, fostered by electronic communication and social media, knowledge of the prevalence of rare diseases will increase and access to patients will be more readily available. Improved access to information on rare diseases continues to expand as rare diseases are addressed on a global basis and more people are aware of the informational needs of the rare diseases community.

The increasing interest in rare disease patient registries by a range of stakeholders will likely lead to the development of many more patient registries. In the absence of a central health care system with all demographic and clinical data in one place, individual registries for different diseases are likely, each with a smaller and smaller set of patients. Organizational collaboration and shared resources, plus engagement of the rare disease community, are needed to move research and knowledge forward. These registries may be used to identify new pathways for treatment, develop clinical research tools such as endpoints, scales, or outcome measures, and recruit potential participants for clinical trials. However, the development of each individual registry requires significant effort and resources. For some diseases,

well-organized private foundations or manufacturers with an interest in product development or monitoring are capable of developing effective registries. For many other diseases, there are few resources to support an independent registry. Some efforts are underway to develop linked networks of registries for rare diseases. For example, the NIH has put forth the idea of creating a federation of Internet-based registries for rare diseases. The goal of this effort is to reduce the costs of developing and running a registry. The idea was part of the discussion at a January 2010 conference on patient registries and rare diseases sponsored by the NIH's ORDR.[20]

The proliferation of registries and the need for global multidisciplinary cooperation for rare disease research creates an urgent need for standards and best practices for these types of patient registry projects. The large number of registries and the various purposes and stakeholders for each complicate any attempts to inventory, standardize, or prescribe good design features for patient registries in general. As previously described, ORDR, in collaboration with the rare diseases community, is working to establish the Global Rare Diseases (Patient) Registry and Data Repository to enable analyses of data across many rare diseases. ORDR has developed and posted for public use a set of general CDEs to be used for rare diseases; these have gained support at NIH, CDISC, and in the international community. At a recent meeting of the International Rare Diseases Research Consortium (IRDiRC) in Bethesda, the CDEs were accepted as a starting point for rare diseases. The ORDR also will make available to all patients/patient advocacy groups a Web-based template to establish a patient registry with the ability to link patients' data and medical information to their biospecimens. In addition, ORDR will encourage all individuals and organizations that elect to develop a patient registry to participate in the Registry of Patient Registries to increase public exposure to these vital research tools. The next stage is to develop organ/system–specific and disease-specific CDEs developed as collaborative efforts of patients, research investigators, industry clinicians, and other partners in the rare diseases community. ORDR continues to collaborate with NIH research institutes to identify existing rare disease patient registries and use the common data elements.

Because of the increase in the number of registries, more efficient ways to implement and maintain rare disease registries and maximize utility for all stakeholders will be required. Technological advances, such as means for integrating data sources, should result in processes that are more streamlined for the data provider as well as the analyst. The growth of Web-based patient communities and social media may also be increasingly integrated into registry data collection and conduct, as community building across geographical boundaries continues to become simpler.

Case Examples for Chapter 20

Case Example 46. Using registries to understand rare diseases

Description	The International Collaborative Gaucher Group (ICGG) Gaucher Registry aims to enhance the understanding of the variability, progression, and natural history of Gaucher disease, with the ultimate goals of better guiding and assessing therapeutic intervention, and providing recommendations on patient care to the medical community that will improve the outcomes for patients affected by this disease around the world.
Sponsor	Genzyme, a Sanofi company, Cambridge, MA
Year Started	1991
Year Ended	Ongoing
No. of Sites	700+ sites have enrolled patients
No. of Patients	More than 6,500 with open-ended followup

Challenge

Rare diseases pose special and unique research challenges. The small number of affected patients often results in limited clinical experience within individual health care centers. Therefore, the clinical description of rare diseases may be incomplete or skewed. The medical literature often consists of individual case reports or small case series, limiting understanding of the natural history of rare diseases. Furthermore, randomized controlled trials with adequate sample size and length of followup to assess treatment outcomes may be extremely difficult or not feasible. The challenge is even greater for rare diseases that are chronic in nature, where long-term followup is especially important. As a result, rare diseases are often incompletely characterized and lack published data on symptomatology, disease manifestations, and long-term treatment outcomes.

Gaucher disease, a rare enzyme deficiency that affects fewer than 10,000 known patients worldwide, illustrates many of the challenges facing researchers involved in rare diseases. Gaucher disease has three clinical presentations: Type 1, non-neuronopathic; Type 2, acute neuronopathic; and Type 3, subacute neuronopathic. Physicians who encounter patients with Gaucher disease typically have just one or two affected patients in their practices; only a few physicians around the world have more than 10 to 20 patients with Gaucher disease in their care. Understanding Gaucher disease is further complicated by the fact that it is a highly heterogeneous and rare disorder with variable progression among patients; a patient cohort from a single center may represent a subset of the entire spectrum of disease phenotypes.

The rarity and chronic nature of Gaucher disease also pose challenges in conducting clinical research. The clinical trial that led to U.S. Food and Drug Administration approval of enzyme replacement therapy (ERT) for Gaucher disease (Ceredase®, alglucerase for injection) in 1991 was a single-arm, open-label study involving only 12 patients followed for from 9 to 12 months. In 1994, a recombinant form of ERT was approved (Cerezyme®, imiglucerase for injection) based on a randomized two-arm clinical trial comparing Ceredase and Cerezyme in 30 patients (15 in each arm) followed for 9 months.

Proposed Solution

Established in 1991, the registry is an ongoing, international, longitudinal disease registry, open to voluntary participation by physicians who care for patients with all subtypes of Gaucher disease, regardless of their treatment status or treatment type. Data on patient demographics; clinical characteristics; treatment regimen; and laboratory, radiologic, and quality-of-life outcome measures are entered and analyzed to address the research challenges of this rare disease. Because of the rarity of Gaucher disease, it is important to create and maintain a reliable, comprehensive registry that serves as an

Case Example 46. Using registries to understand rare diseases (continued)

Proposed Solution (continued)

educational resource not only for physicians but also for patients and their families and caregivers. Responsibility for the use, integrity, and objectivity of the data and analyses is invested in the ICGG Board of Advisors, which consists of physician-investigators worldwide who are not employees of the sponsor and who advise on the medical and scientific agendas of the registry.

Results

The registry has longitudinal data on more than 6,500 patients from more than 700 health care centers in more than 60 countries. The followup period is open-ended, and the registry currently has up to 20 years of followup data from individual patients. The registry has collected more than 50,000 patient-years of followup during the past 21 years. Physician participation and patient enrollment have increased consistently from year to year since 1991.

Analyses of the extensive body of longitudinal data have increased knowledge of the disease in a broad range of topics, including the natural history of Gaucher disease; phenotypic and genotypic variation among patients; diagnosis, treatment, and management of the disease; disease manifestations in children; long-term treatment outcomes for ERT; bone disease and complications associated with the disease; and neuronopathic Gaucher disease. Data generated from the registry have been published in nearly 30 key articles and have provided much needed and important insight into this rare genetic disease.

In 2002, the registry published the clinical outcomes of 1,028 patients treated with ERT with up to 5 years of followup. As more data have been gathered through the registry over the past decade, long-term outcomes in patients with Type 1 Gaucher disease after 10 years of ERT have become available, thus providing new reference benchmarks for assessing clinical responses to ERT for various disease parameters. Other more recent publications based on analyses of data from the registry have focused on important specific aspects of Gaucher disease, such as the effects of early intervention with ERT on the incidence of bone pathology, demographic and clinical characteristics of patients with neuronopathic Gaucher disease, ERT dose-response relationships for disease parameters in patients with Gaucher disease type 1, and phenotypic heterogenicity and genetic variation among patients.

Along with the growth of the registry and the availability of data on Gaucher disease, interest in special patient populations and specific aspects of Gaucher disease continually emerge. As a result, research initiatives into disease subpopulations have been launched recently: the Neurological Outcomes Subregistry, which will begin to evaluate the neurologic manifestations of Gaucher disease and the effects of treatment on these complications; and the Pregnancy Subregistry, which will track the management of Gaucher disease during pregnancy as well as pregnancy outcomes.

The collective clinical experience of the registry led to the development of recommendations for evaluation and monitoring of patients with Gaucher disease. The analysis of registry data on treatment outcomes has facilitated the establishment of therapeutic goals for patients with Type 1 Gaucher disease. Together, these publications have formed the foundation for a consensus- and evidence-based disease management approach, something usually only possible for much more common diseases. In 2008, a benchmark analysis was published that documented the achievement of therapeutic goals after 4 years of ERT among registry patients.

As disease awareness has increased over time, health care providers have sought more direct access to general and patient-specific disease information. Therefore, when the registry changed its technology platform in 2011, it established two key objectives: to simplify data entry to help keep data complete and accurate, and to support the community's increased interest in access to data, aggregate reports, and collaborative expertise. To help meet these goals,

Case Example 46. Using registries to understand rare diseases (continued)

Results (continued)

the registry ensured that the new platform included functionality that allows physicians direct access to aggregate and patient-specific reporting as well as the ability to download their own data to support their own research. This important application of technology enables the registry to "give back" supportive and research tools to those who contribute to the overall registry data set. This includes the availability of data to address clinical and scientific questions; useful disease management tools, such as interactive patient case reports that a physician can share with other health care providers and with patients themselves; and a larger, better-connected, worldwide community of physicians and allied health providers who can share information, identify trends, improve best practices, and build awareness of Gaucher disease that will optimize patient outcomes.

Key Point

For rare or ultra-rare conditions, an international, longitudinal disease registry may be the best or only feasible way to comprehensively increase knowledge about the clinical characteristics and natural history of the disease and assess the long-term outcomes of treatment.

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Case Example 47. Studying rare diseases in an existing registry population

Description	The National Cooperative Growth Study (NCGS) collected data on children with growth disorders who were treated with a specific growth hormone (GH). The purpose of the multicenter, observational, post-marketing surveillance registry was to collect long-term safety and effectiveness information on the GH preparations, with the goals of better understanding the growth response to GH therapy and establishing a safety profile in large populations of different patient diagnostic groups.
Sponsor	Genentech, Inc.
Year Started	1985
Year Ended	2010
No. of Sites	More than 550
No. of Patients	65,205

Challenge

The registry was launched following U.S. Food and Drug Administration approval in 1985 of recombinant human growth hormone (rhGH). While the primary purpose of the registry was to monitor the safety and effectiveness of rhGH in all pediatric patients undergoing this treatment, there were insufficient numbers of patients in the clinical trials in each subgroup of patients for whom the drug was indicated to establish a true picture of their medical risks and the interaction or impact of GH on their medical safety. There was particular interest in studying girls with Turner syndrome (TS), a rare chromosomal abnormality known to be commonly associated with multiple medical conditions.

Proposed Solution

Pediatric patients with growth disorders were voluntarily enrolled in the registry when therapy with rhGH was initiated, and were followed until discontinuation of therapy. The median length of followup for patients in the registry is 3.3 years, allowing for longitudinal analyses of the natural history of growth disorders and their treatment, and addressing physician queries on the long-term safety and effectiveness of rhGH therapy for their patients. The broad enrollment criteria of the registry enabled capture of a meaningful sample of patients with rare syndromes or diseases. For example, the registry population included over 5,000 patients with TS.

Results

For 25 years, the registry monitored the safety and efficacy of rhGH therapy in 65,205 children with growth disorders treated in more than 550 sites in the United States and Canada, with more than 800 investigators, and accrued over 220,000 patient-years of observation. During this time, analyses resulted in more than 100 publications on safety, dosing, height prediction, outcomes, subgroups of patients, and regulatory safety assessments, with more than 1,200 citations in the research literature. The registry remains the largest North American repository for auxological and clinical outcome data for rhGH-treated children with growth-related disorders.

Analyses were conducted on 5,220 registry patients with TS, resulting in a seminal paper that described the safety profile of GH in this condition and highlighted the natural history of many of the known medical conditions these patients have. The safety profile included assessment of cardiac risks, development of autoimmune disorders, and detected occurrence of a disproportionate number of cases of pancreatitis, compared with the other patient groups in the NCGS. This later finding contributed to a recent label change warning of the risk of pancreatitis for all GH products, including a reference to the published data that suggest higher risk in patients with TS. In addition, a substudy in the registry assessed the degree to which pediatric endocrinologists were following recent guidelines for screening of concurrent medical conditions in TS. This guideline substudy revealed that, in a cohort of 955 girls, screening for cardiac, renal, and hearing abnormalities was not occurring at the

Case Example 47. Studying rare diseases in an existing registry population (continued)

Results (continued)

expected rate. The clinical implications of these studies were a broader picture of the natural health history of girls with TS as well as specific issues of safety with respect to GH.

The registry closed enrollment in 2010, but the database continues to be a resource for practicing physicians facing patient treatment decisions, averaging 1–2 queries per week from former investigators on the safety and effectiveness of GH treatment. Recent examples of query topics include patients with TS, safety in patients with intractable seizures, medulloblastoma and secondary malignancies associated with GH, primary pulmonary hypertension, and other conditions. One query, on rhGH use in GH-deficient or idiopathic short stature patients treated with stimulants for ADHD, led to a publication that found no significant differences in safety or effectiveness of rhGH treatment for these patients in comparison to non-ADHD treated patients.

Key Point

A large registry can provide a resource of study subjects for focused investigations on specific rare diseases. Even after study closure, registry data can be a useful resource for continued investigations, and for informing treatment in clinical practice.

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Case Example 48. Site motivation and retention in rare disease registries

Description	The Digital Ulcers Outcome (DUO) Registry collects data on patients with systemic sclerosis in an effort to describe digital ulcers disease history, clinical and patient-reported functional assessment status and treatment pattern at the time of enrollment, disease course, and patient management during followup. For patients treated with bosentan, data are collected on physician adherence to labeling guidelines and safety events.
Sponsor	Actelion Pharmaceuticals
Year Started	2008
Year Ended	Ongoing
No. of Sites	More than 350
No. of Patients	3,609

Challenge

Systemic sclerosis (scleroderma) is a rare disease affecting less than 2 in 10,000 persons worldwide. Digital ulcers affect nearly 30 percent of patients with this disease, resulting in substantial morbidity such as gangrene and amputation. Despite the severity of digital ulcers, very little is known about this complication, due to the rarity of the underlying condition. To improve understanding of this condition, data are needed from specialized participating scleroderma centers (sites).

The DUO Registry was mandated by the European Medicines Agency (EMA) as a post-approval licensing requirement for the expanded indication of bosentan to treat digital ulcers. The registry, which operates in 18 European countries, is observational and voluntary in nature, and participating sites are reimbursed solely for data entry time. After 4 years of operation, motivation of the participating physicians started to stagnate, and the sponsor observed a decrease in followup data entry. Because the registry was mandated by the EMA and because of the paucity of outcomes data available about digital ulcers, the sponsor sought to increase participation and, in particular, increase the collection of followup data.

Proposed Solution

The sponsor identified academic and professional interest in the registry's findings around digital ulcer management as one of the primary motivators for investigators to participate in the study. To respond to this interest, the sponsor implemented new efforts to engage investigators and regularly inform them of the study's progress. Efforts included the use of newsletters to provide enrollment updates and tips on using the electronic data capture system, presentation of abstracts in scientific congresses, and distribution of letters from the registry steering committee to the investigators encouraging them to enter followup data. An in-person investigator meeting was held, where the registry's scientific committee discussed registry findings with the investigators. The sponsor also established a process for investigators to suggest publication ideas and determined that all publications of registry data would include the phrase "and DUO Registry investigators" in the author byline.

Results

From 2011 to 2012, the proportion of patients having at least one followup visit increased from 63 percent to 73 percent, and the mean number of visits per patient increased from 1.7 to 2.6. The registry has now enrolled more than 3,600 patients.

The steering committee and registry investigators published the first original article on registry data in January 2012, reporting on data from 2,439 patients and confirming the disease burden of digital ulcers in systemic sclerosis patients. The sponsor had received feedback that the shared authorship is valuable to some investigators and a major motivating factor for their participation in the registry.

A poster highlighting the current variation in treatment of digital ulcers across Europe and stressing the need for a concentrated approach to establish disease management practices was presented at the European League Against Rheumatism 2012 Annual Congress.

Case Example 48. Site motivation and retention in rare disease registries (continued)

Key Point

Site engagement is particularly important in rare disease registries, because of the limited number of patients. Consistent communication highlighting study objectives and achievements, visibility at scientific meetings, and sharing authorship or acknowledgement on publications can bolster investigators' motivation.

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Chapter 21. Pregnancy Registries

1. Introduction

A pregnancy exposure registry is an observational prospective cohort of women receiving a biopharmaceutical product(s) of interest as part of their routine clinical care who are enrolled voluntarily during gestation, before outcomes can be known. Participants are followed until the end of pregnancy or longer to systematically collect information on specific pregnancy outcomes and evaluate their frequency relative to a scientifically valid reference population(s).[1-3] Specific examples of pregnancy registries can be found on the Food and Drug Administration (FDA) Web site.[4]

This chapter reviews the "why, how, and who" of conducting pregnancy registries. In it we first discuss why pregnancy registries are needed to assess risks and benefits of medications during pregnancy. Second, we describe the distinctive methodological aspects of these registries, including design, study population, enrollment and followup of pregnant women, ascertainment and definition of exposures and outcomes, reference groups, statistical power, and validity issues. Third, we take a more pragmatic approach and present key operational aspects such as protocol structure, recruitment and retention of participants, methods of data collection, timing of the release of findings, role of advisory boards, and challenges of global designs. Finally, we describe characteristics to consider when evaluating pregnancy registries. Case Examples 49, 50, 51, and 52 offer some descriptions of pregnancy registries.

2. Justification

All patients in need of treatment should have access to medications that have been adequately studied, and they should be given information to assess risks versus benefits of using the medication. Collecting postmarketing data on the safety of medications during pregnancy is commonly done through the use of pregnancy exposure registries or pregnancy disease registries that collect treatment information. Pregnancy registries are prospective observational studies specifically designed to collect clinically relevant data and provide information for treating or counseling not only women who are pregnant but also women of childbearing potential. In 2002, FDA published its guidance for pregnancy registries[2] with a goal of encouraging the regular use of more formal, prospective study designs to obtain clinically relevant human data that can be used in product labeling. Similar guidelines were published by the European Medicines Agency in 2005.[5] In 2007, the Food and Drug Amendments Act provided the authority under Title IX[6] to require pregnancy registries as a postmarketing requirement. Pregnancy registries are now required at the time of a new drug approval when there is a safety concern or when there is a need to gather data on the use of the product in pregnancy based on the following circumstances: (1) prior knowledge of the product suggests a safety concern based on the pharmacologic or chemical class, or on data from animal studies or clinical trials; (2) the product will be indicated for use during pregnancy (e.g., vaccines and medications for chronic illness); or (3) there is a high likelihood of use in females of reproductive age such that inadvertent exposure during pregnancy may be expected.

For nonpregnant individuals, safety and efficacy data that yield such information are derived from well-controlled clinical trials conducted prior to a drug's approval. When it comes to pregnant women, however, the situation is different. Clinical trials rarely include pregnant women because there is a lack of safety information on the drug's use in pregnancy.[7, 8] As a consequence, most information regarding the safety/risk profile of drugs during pregnancy is collected after the drug has been approved and used by pregnant women intentionally or unintentionally: intentionally because some conditions require treatment during

pregnancy, or unintentionally because approximately half of all pregnancies in the United States are unplanned,[9] so embryo/fetal exposure to medications can occur before pregnancy is detected.

Tests in animal models are a regulatory requirement for new drugs and biologics prior to approval. In some cases, these animal toxicology studies can provide a means to detect teratogenic effects. Often, however, results are not easily translated into human risk because of variations in teratogenic response among species.[10] In addition, animal toxicology studies are designed so that at least one dose tested will provoke an adverse toxic response. The results at those dose levels may not predict those that might be observed at the intended therapeutic doses used in humans.[11]

In humans, passive data collection such as FDA's Adverse Event Reporting System (AERS) can suggest potential drug safety issues for further study. The system includes any patient population that may have been exposed to the drug. Reporting to the database is voluntary (although required for manufacturers) and underreporting is a significant issue, with extent of reporting thought to vary substantially depending on the drug, the indication for use, and the nature of the adverse event.[12, 13] There is no reference group and no information is available on the number of individuals taking the drug who did not have an adverse event. It is often not clear whether the adverse event reported to AERS is a medication-related event, an event resulting from the underlying illness, or a coincidence. Since adverse pregnancy outcomes such as pregnancy losses and congenital malformations are relatively common, they will inevitably occur among exposed individuals; selected reporting of exposed cases can lead to false alarms. Consequently, although data from AERS can be useful for identifying initial signals of adverse events, it cannot be used to quantify risks for a particular product or to compare risks between drugs.[14] Similarly, case series published in scientific journals cannot distinguish chance from causation or be used to quantify and assign teratogenic risks.

Information on human teratogens must come from adequately controlled epidemiological studies, which include case-control and cohort designs. Case-control studies identify births with the outcome of interest (e.g., a specific birth defect) and compare their frequency of exposures to that in a control group without this outcome. This design offers advantages in detection and confirmation of associations between prenatal exposure to the medication and the risk for rare events.[15] However, case-control studies have some limitations. They collect information on exposure retrospectively, rarely have enough sample size to evaluate infrequently used medications, and can estimate the relative risks but not the absolute risks associated with the drug.

Followup studies of pregnant women have the advantage of identifying drug exposure before the adverse outcomes are recognized. In nonpregnant populations, health care utilization databases such as Medicaid claims files or records in large health maintenance organizations have become a standard source of information for drug safety studies.[16] These databases are a resource for large-scale observational postmarketing studies because they offer the ability to study rare consequences of drug use. Some of these databases have limitations for the study of pregnancy outcomes because they do not routinely record evidence of pregnancy (e.g., estimated date of conception) or provide child-mother linkages. Important reproductive information, such as gestational age at birth, birth weight, and maternal reproductive history, is rarely available.[17] Moreover, when exposure to the specific drug of interest involves a small fraction of the pregnant population, even these large cohorts are constrained in their statistical power. In this scenario, concentrating on women exposed to selected drugs through a pregnancy registry can increase efficiency. However, the FDA-funded Medication Exposure in Pregnancy Risk Evaluation Program has established collaboration among a selected group of large administrative databases with the ability to link mothers and babies and with linkage to birth certificates, which contain additional information.[18] This resource will serve as an important tool to study outpatient

dispensing of medications during pregnancy and a number of validated pregnancy outcomes.

3. Pregnancy Registry Objectives

The overall purpose of pregnancy exposure registries is to provide human data on the safety of biopharmaceutical products during pregnancy.[1, 19] Pregnancy registries should have specific primary and secondary objectives defined a priori in a scientifically sound study protocol.[2] Many exposure registries have as their primary objective to "assess the risk of major congenital malformations" in the offspring of women exposed to a given drug just before or during pregnancy. Implicit in this objective is to determine whether that risk is higher or lower than expected. Registries can evaluate multiple maternal, obstetrical, fetal, and infant outcomes, from pregnancy complications to developmental delays. Moreover, they may provide an opportunity to evaluate not only the safety, but also the effectiveness of drugs, as well as the risks associated with untreated diseases during pregnancy. They can also evaluate the effects of dose and gestational timing of exposure, as well as effect modification by maternal characteristics.[1]

Since the ultimate goal is to inform the decisions of medical care providers and patients, it is in the common interest of all the parties to initiate the registry as soon as possible after marketing authorization, use proactive enrollment strategies (i.e., if possible, broaden the source population to obtain, for example, 1,000 exposed women in 1 year rather than 100 per year for 10 years), and analyze the data and report findings on a regular basis.[2] As more data accumulate over time, the registry can provide narrower boundaries of uncertainty around the point estimates, which leads to increasing assurance of relative safety or more precise quantification of relative risks. These issues are discussed more extensively in Sections 17 and 17.9 below, respectively.

4. Design

Whether stated or not, one scientific question in the evaluation of drugs during pregnancy is often "What would have been the outcome of this pregnancy had the woman not been exposed?" Since the counterfactual outcome of a given pregnancy is unknown, the closest strategy to respond to this question would be to randomize a group of women periconceptionally either to the drug of interest or to a reference group and follow them in a blinded manner until the outcome of interest is fully assessed. This design would ensure that the groups differ only in their drug exposure and that the same methodology and clinical judgment are used to assess the outcomes. The reference group could be randomized to placebo, if not treating is clinically acceptable, or to an alternative therapy, and the comparative efficacy and safety of two or more therapeutic options could be evaluated. However, since for ethical reasons pregnant women are rarely included in sufficient numbers in randomized controlled trials (RCTs) during the process of drug development, the safety and effectiveness of drugs during pregnancy needs to be studied in postmarketing nonrandomized studies.[3, 19]

The specific design of a pregnancy registry is determined by its purpose.[1] To rule out strong teratogenic effects (e.g., more than a 20 percent risk of malformations after prenatal exposure to thalidomide), enrollment of 100 exposed pregnancies in a simple uncontrolled cohort might suffice. The effect of major teratogens is so large as to overwhelm the potential impact of common methodological biases on relative risks. However, most known teratogens are associated with a more moderate increase in the risk of relatively rare malformations.[20] To detect moderate teratogens, registries need to enroll a larger number of gestations and be carefully designed.[19]

Although the same rigor and most principles of RCTs can be applied to any observational study, the lack of randomization calls for additional epidemiological methods.[21] The following sections discuss how pregnancy registries differ from RCTs; how deviation from the standards of

RCTs can compromise the validity of results; and how biases can be minimized through collection of detailed data on exposure and other maternal characteristics, close followup, accurate assessment of outcomes, and inclusion of comparable reference groups.

5. Study Population: Who and When

Through clear inclusion and exclusion criteria, registries target a well-defined study population that, ideally, should be closer to real clinical practice than the selected populations of a RCT. However, to the extent that pregnancy registries rely on patients' or their health care providers' hearing about the registry, contacting the registry, and agreeing to participate, there is the potential for selective enrollment. Women who do participate may differ systematically from the population of exposed pregnant women who are not part of the registry, with respect to factors related to the pregnancy outcome. Therefore, baseline risks in the registry population may differ from those in the general population of women using the drug of interest.

In assessing the relative risks associated with the drug, there is often a tradeoff between generalizability and validity. For example, generalizability would be enhanced by use of a population-based sampling strategy in situations where the underlying population can be enumerated. However, inclusion of non-motivated individuals might increase losses to followup, misclassification of information, and the variability and impact of confounders, thus reducing validity. In addition, population-based sampling strategies can be logistically complicated and would arguably estimate a similar relative risk, since a teratogenic effect found in participants would probably apply to "non-volunteers" as well.

A peculiarity of pregnancy registries is that the population can be defined based on women, pregnancies, or fetuses. A woman might have more than one pregnancy, and she might enroll in the same registry more than once. Clustered analyses are often used in this situation. In addition, multifetal gestations result in more than one fetus "enrolled" within the same pregnancy. Although there may be several ways of dealing with multiple gestations, it is prudent to collect information about all the fetuses. When reporting risks, whether using fetuses or pregnancies as the unit of analysis, both the numerator and denominator should be consistent with the choice.[22]

6. Enrollment and Followup

An ideal pregnancy cohort would enroll women at conception and follow them for months beyond delivery. However, this sequence rarely happens for logistical reasons, and consequently pregnancy cohorts have some degree of unintended truncation on both sides of the ideal followup. Left truncation occurs because followup can only start after women realize they are pregnant (in patient-initiated enrollment in registries) or health care providers identify the pregnancy in a patient (in clinician-initiated enrollment in registries), and the process of enrollment itself can further delay the inclusion. Right truncation occurs because followup would end with unknown outcomes when there are losses to followup or pregnancy terminations without fetal autopsy.

As a result, time from enrollment to end of followup can range from 1 month to over 1 year. In any study, longer followup periods naturally lead to higher opportunities for diagnosis and therefore both larger cumulative risk estimates and greater statistical power. We will examine later how inclusion of either prenatal diagnoses or outcomes identified during infancy would result in higher risks than restriction to delivery hospital discharge diagnoses. More worrisome in pregnancy registries is that selection bias can be introduced if the outcome explicitly or implicitly affects enrollment (e.g., a known outcome affects eligibility or influences self-selection) or retention in the cohort (e.g., through exclusion of study subjects after an abortion or neonatal death).

6.1 Enrollment

Registries should include women as soon as possible after conception, or even earlier at pregnancy planning stages, to allow the evaluation of early pregnancy events. For instance,

pregnancies enrolled earlier in gestation would result in higher risk estimates for spontaneous abortions and terminations than those enrolled later. Still, unless periodic pregnancy tests are conducted, studies will never pick up fetal losses that occur before pregnancy is known.

Women should be enrolled before the pregnancy outcome is known to avoid a selection into the study affected by the outcome. Retrospective enrollment of women after prenatal screening (i.e., nuchal translucency, chorionic villous sampling, amniocentesis, alpha fetoprotein measurements, and second-trimester ultrasound—first-trimester dating ultrasounds do not assess malformations), can introduce bias towards a lower or higher risk of malformations. Bias may be introduced regardless of whether the prenatal screening test is normal or abnormal.[1]

Underestimation of the risk may occur if enrollment after informative screening tests are conducted selects a survivor cohort of women with uneventful pregnancies. For example, women might be less willing to contact a "pregnancy registry" after a major malformation diagnosis, clinicians enrolling patients might miss women who had a therapeutic abortion, and some registries do not allow enrollment of women with abnormal prenatal tests or pregnancy losses when an abnormality has been identified. On the other hand, overestimation of the risk might occur if participation is allowed after an abnormal test and there is a preferential enrollment of women with a diagnosis; for example, if the diagnosis prompts the exposed woman to look for information, find the registry, and enroll. These two scenarios can coexist and even occur differentially in unexposed and exposed women, leading to spurious associations. For example, unexposed women might be more willing to volunteer to be in a reference group if they are enjoying an uneventful gestation, while women with chronic conditions (e.g., rheumatoid arthritis) might contact a pregnancy registry after receiving an adverse pregnancy diagnosis, seeking both personal support and contact with peers with the same medical condition. Because this bias is difficult to identify and correct in the analytic phase, it needs to be prevented in the design by enrolling subjects prospectively before the outcome is known.

6.2 Followup

Another peculiarity of pregnancy studies is that followup needs to go beyond the onset of the outcome under study. For most major structural congenital anomalies, the theoretical followup would be from conception to the end of fetal organogenesis (i.e., on average 3 gestational months). However, one often learns about the fetal outcomes only after birth. Longer followups will identify more congenital problems, since some structural and many functional malformations might become clinically apparent only months or years later.[19, 23] In pregnancy registries, followup typically stops at 3 to 12 months after the end of pregnancy. Some registries restrict the cohort to infants with a minimal standard followup time, such as at least 3 months after birth. (Of note, fetal deaths and infant deaths before the minimal followup should also be included in the assessment to avoid excluding lethal malformations). Efforts should be made to minimize losses to followup and to obtain outcome information for all participants. Information needs to be collected on the number of losses and, if possible, on their reasons, in order to assess whether they are similarly distributed among the exposed and unexposed populations.

7. Exposure Ascertainment

How registries collect information can affect the accuracy of the data. Some registries obtain information from the women themselves. Women generally know more about their habits, occupations, medical and obstetrical history, and compliance with the drug than individual health care providers. Other registries rely on reporting by the clinicians and have no contact with the patients. Clinicians can provide more complete and accurate information regarding diagnoses and indications.[24] However, there is a risk of exposure misclassification if women stop or incompletely comply with the prescription drug regimen during pregnancy. A woman might be more willing to tell an interviewer not related to her care than to tell

her doctor that she decided to reduce her dose or quit taking a medication. Including unexposed subjects in the exposed group (i.e., false positives) can dilute any potential association.

In order to maximize the quality of data, the combination of several sources of information is an optimal strategy. With adequate help, women can recall exposure during pregnancy. As noted previously, they should be enrolled before the pregnancy outcome is known to reduce selection bias, as well as to obtain reliable prospective information on exposure and other characteristics not affected by the outcome. One interview should take place at enrollment (i.e., during the first trimester), and at least one interview should take place postpartum (e.g., 2 months after end of pregnancy). Additional interviews (e.g., midpregnancy in order to update exposure information; 12 months after delivery in order to evaluate development) might be useful depending on the objectives of the pregnancy registry. Data from treating physicians can document the medical condition and confirm the prescription. Confirmation of exposure should be blinded to the outcome.

8. Exposure Definition

If one is concerned about structural malformations, the etiologically relevant period of exposure is the first trimester of pregnancy. To identify this period, one needs to establish gestational timing. Obstetricians typically time pregnancies from the first day of the last menstrual period (LMP), determined by maternal recall or, preferentially, by a more accurate early pregnancy ultrasound. Depending on the pharmacological characteristics of the drug, the specific defect, and the accuracy of timing information, the window of interest might be the second and/or third month, any time during the first 4 months after the LMP, or even weeks before LMP for drugs with long half-lives or unspecified period of effect (e.g., vaccines). Exposures later in pregnancy can adversely affect other outcomes.[25-27]

Treatment strategies change during pregnancy, and doses are commonly adjusted. Therefore, it is recommended that detailed information be collected on start and stop dates, dose, frequency, duration, and indication.[28] Some medications (e.g., anticonvulsants) are prescribed in combination with other drugs. The effect of polytherapy resulting from concomitant treatments, or from switching drugs, within the first trimester should be explored in the analyses. Not only the number of drugs, but which drugs are combined, might affect the outcome of interest. Although the power is usually limited, analyses of dose response can inform recommendations, analyses of specific timing within the first trimester can assess biological plausibility, and analyses of indications might help explore confounding. If possible, maternal body mass index should be considered when evaluating dose effects.

9. Covariates: What Else To Collect?

There is always a tension between simplicity and a desire to be comprehensive. Although there is no general rule, one widely accepted principle is that quality is more important than quantity—if the information is not trustworthy, do not collect it. Minimizing the effort and time from participants can increase both the willingness and the quality of participation. Necessary information on exposure, outcome, and key confounders (e.g., history, status, severity, and management of the indication) should take preference over desirable but less useful information. Most registries collect information on demographics, concomitant illnesses and medications, and reproductive history. A list of variables commonly collected in pregnancy studies is provided in Table 21–1.

Table 21–1. Variables commonly collected in exposure pregnancy registries

Identification	Exposure	Outcome	Covariates
Study ID Date of enrollment LMP date or EDD Gestational age at enrollment Date of first data collection Date(s) of followup data collection(s) Date of end of followup Followup status (e.g., complete, loss to followup, withdrawal) Contact information: Woman Alternative contact(s) Obstetrician/prenatal health care provider: Specialist Pediatrician	Drug For each drug, each episode of use, and each dose if changed: Start date Stop date Indication and measure of disease severity (e.g., CD4 count for HIV patients, type of epilepsy and convulsions during pregnancy for anticonvulsants) Dose Route Frequency Duration	Sex Status: Live birth Elective termination Spontaneous abortion Late fetal death Number of fetuses (singleton or multiples) For fetal loss: Date end of pregnancy Reason for termination For live birth: Date of birth Birth weight Birth length Head circumference Gestational age at birth Conditions at birth (e.g. admission to intensive care unit, drug withdrawal syndrome) Congenital anomalies: Specific defects Date of diagnosis Methods of diagnosis Date and results of any prenatal testing Obstetric outcomes: Delivery (vaginal, C-section type) Preeclampsia Premature labor Preterm delivery Gestational diabetes	Demographics: Maternal age Race Occupation Education level Pre-pregnancy weight and height Reproductive history: Number of previous completed pregnancies and miscarriages Fertility interventions for past and current pregnancy Family history of defects (specific defect and degree of relationship) Habits: Cigarette smoking Alcohol intake Use of illicit drugs Chronic medical conditions: Diabetes Pregravid obesity Hypertension Epilepsy Depression Other psychiatric disorders Hepatitis Thyroid disease Autoimmune disease Asthma Sexually transmitted disorders AIDS Concomitant medications, including folic acid supplementation and potential teratogens.

10. Outcome Ascertainment

The source of information for outcomes in pregnancy registries is critical. Although registry designs that incorporate interviews with pregnant women can provide an initial source of data regarding the results of prenatal diagnosis, postnatal events, and malformations that are recognized during longer term followup periods, in most registries, validation by the health care provider of any maternally reported diagnosis is an important criterion for inclusion of specific outcomes such as major congenital anomalies (see Outcomes Definitions below). In registries in which the outcome is routinely collected from the woman and validated by health care providers, the mother's report can correct potential false negative reports from one clinician; in comparison, registries in which the outcomes are reported only by the provider rarely include maternal validation. In some circumstances, a more stringent level of validation might be required to confirm an outcome (e.g., an echocardiogram to validate the presence of specific heart defects). Requiring commitment from registrants at enrollment to provide consent and medical release of information from obstetrician and specialists can select a motivated patient population and minimize loss to followup and maximize access to medical data.[2]

Whether the exposure is ascertained from the patient or from the clinician, it is important to obtain delivery data from the obstetrician or hospitalization records to ascertain the outcome accurately. It is also important to follow up with subsequent providers, such as the infant's pediatrician and other specialists, because those treating a woman for a non–pregnancy-related condition often know little about obstetric or pediatric outcomes (e.g., a woman's neurologist might not know about the patient's preeclampsia), and obstetricians often know little about the infant after delivery.[1, 19] Obtaining this information may require the woman's consent and therefore contact with her. In addition, treating physicians might have a legal or ethical conflict of interest if they are asked to report on a pregnancy outcome when they were responsible for the exposure.

It is important to recognize that maternal report alone can result in misclassification of the presence or absence of any defect and/or the presence or absence of a specific defect. Although specificity is most relevant for the evaluation of infrequent outcomes, to maximize sensitivity medical validation may be required for all births and not just those in which the mother reports an abnormality.

Other primary or supplemental methods of ascertainment of birth defect outcomes can be employed. These include linkage to claims data, public birth registries, or birth defects surveillance systems. In any case, comparable methods for ascertainment of outcomes must be used in the exposed and reference groups.

11. Outcome(s) Definition

As part of the study design, pregnancy registries must set a priori criteria for defining outcomes. Outcomes are typically ranked in order of importance to the registry's objectives. For example, most pregnancy registries identify major structural birth defects as the "primary" outcome of interest. This outcome is frequently defined as primary because identification of an increase in major malformations, particularly specific major malformations, in association with a given gestational exposure may indicate a teratogenic effect. In addition, some pregnancy registries incorporate a measure of "minor" structural defects as an outcome representing a broader spectrum of potential structural differences that may be attributable to an exposure.

Other "secondary" endpoints frequently include measures of fetal growth deficiency, preterm delivery, spontaneous abortion or stillbirth, and elective terminations. Some pregnancy registries incorporate longer term measures of outcomes that can include, for example, postnatal growth deficiency, cognitive and behavioral development, or measures of immune function, depending on the characteristics of the exposure under study in the registry. However, the cost and logistics of following children over time usually are prohibitive.

Using the primary outcome of major structural defects as an example, but relevant to all outcomes in any pregnancy registry, the following definitions must be determined a priori.

11.1 Inclusion/Exclusion Criteria for a Defect To Be Defined as "Major"

Criteria for defining defects as "major" must be established for a pregnancy registry. For example, major structural defects might be defined as abnormalities in structural development that are medically or cosmetically significant, are present at birth, and persist in postnatal life unless or until repaired. Similarly, criteria must be established for defects that will be excluded. For example, those that are transient and maturational and do not represent an abnormality in embryonic or fetal development, such as a patent ductus arteriosus or an inguinal hernia that might occur in a preterm infant simply as an artifact of shortened gestational age, might be excluded. Another example of an excluded defect might be a small muscular ventricular septal defect that may spontaneously close with no consequences for the infant. Attention must be paid to the comparability of definitions for inclusion and exclusion between the exposed and the reference groups.

Frequently, pregnancy registries employ an existing standard coding system for inclusion and exclusion of structural defects, such as that developed by the U.S. Centers for Disease Control and Prevention's (CDC) Metropolitan Atlanta Congenital Defects program.[29] This system was created and is maintained for use in an ongoing population-based surveillance program for birth defects that are identifiable up to 1 year of age. For some pregnancy registries, additional definitions or modified inclusionary/exclusionary criteria may need to be employed, depending on the length of followup or the specific outcomes of interest. Even with standard coding criteria, the information available for some reported defects may be insufficient or ambiguous for classification, such that an additional level of review is required to classify the defect appropriately. A method for expert adjudication of defect classification, blinded to exposure status, is an important component of a pregnancy registry.

Minor malformations are defined as those uncommon structural differences in the infant that have no serious medical or cosmetic consequences (e.g., an extra hair whorl on the head). Although these minor structural defects are of potential interest as more subtle measures of outcome, they may not be reliably assessed and therefore are frequently excluded unless they are uniformly evaluated in all patients. Similarly, positional deformities are often excluded (e.g., abnormal head shape or plagiocephaly that spontaneously resolves shortly after birth).

The source of information regarding a major structural defect must also be defined as meeting the criteria for inclusion. For example, maternal report of a malformation with no validation by a physician or postnatal diagnostic test may be defined as insufficient for inclusion of a major defect. Another example of a situation that might be defined as exclusionary is a defect that is suggested through prenatal diagnostic tests but for which no postnatal validation is available.

11.2 Timeframe of Diagnosis

A specified period for followup, during which standardized efforts will be made to collect outcome information on major birth defects, should be determined as part of the pregnancy registry design. As length of followup increases, the baseline risk of major structural defects is expected to increase because not all structural defects are reliably recognized at birth. Ideally, the longer the followup, the more complete an assessment of major birth defects could be. Specific outcomes of interest for the exposure under study may require longer followup to be appropriately assessed. However, the length of followup selected for the registry may be influenced by the availability of resources and the registry's ability to maintain contact with registry participants and/or health care providers over a longer term. For comparability reasons, it is essential that the timeframe for diagnosis be identical in the exposed and the reference population or group.

In addition, the case of major birth defects occurring in pregnancies that end in embryonic or fetal demise must be considered in the registry design. Major defects might be identified in spontaneous pregnancy losses by postnatal pathology, and criteria for inclusion of those defects must be established, as not all spontaneously aborted pregnancies or stillbirths will be uniformly evaluated for the presence or absence of defects. In the special case of elective terminations, criteria for ascertainment of malformations are critical because terminations for defects that are identified on prenatal diagnosis may represent an important subset of outcomes within the registry. Elective terminations for social reasons may not be uniformly evaluated by prenatal diagnosis for major structural defects. For these reasons, many pregnancy registries treat malformations identified in pregnancies ending in live birth separately from malformations included in the overall sample of registry pregnancies including terminations, spontaneous abortions, and stillbirths. Failure to include defects detected among terminations can decrease power and introduce bias, particularly for defects for which termination is often chosen after prenatal diagnosis (e.g., neural tube defects).

11.3 Analytical Approach

No known teratogen increases the risk of all major birth defects. Typically, a specific defect or pattern of defects occurs with increasing frequency following a teratogenic exposure in the critical gestational window for susceptibility. However, specific major defects are rare events in the general population—the most common occur no more frequently than approximately 1 in 1,000 live births. Pregnancy registries usually do not have sufficient sample size/power to evaluate increased risks for specific defects unless the relative risks are quite large. Therefore, most registries compare the overall proportion of all major defects combined in the exposed group to the overall proportion in the reference group. The rationale for this approach is that if specific defects are increased following exposure, these specific defects will incrementally inflate the overall proportion of malformations in the exposed sample and therefore reflect the excess risk associated with that exposure. For example, if the baseline risk of major malformations is 3 percent and the risk of neural tube defects is 0.1 percent, a fivefold increased risk of neural tube defects would inflate the overall risk to about 3.4 percent. Although the analytic approach for a registry may be based on a comparison of all malformations combined, it is important for pregnancy registries to evaluate any potential excess of specific defects in the exposed group, even if this evaluation is descriptive.

In some registry designs, it is argued that malformations of known etiology should be excluded from the overall proportion of major structural defects, as they do not have the potential to have been "caused" by the exposure. Examples might be chromosomal anomalies, those defects that have a known single gene cause, or defects that occur in families with a positive history for that defect. The rationale for these exclusions is that inclusion of defects not thought to be caused by teratogens can decrease power to detect an overall difference in risk between exposed and unexposed fetuses. Arguments against exclusion of such defects in the analysis are that the true cause of the defect may not be known and that it is possible that exposure to a medication modifies other risks for that defect in a multifactorial manner. Therefore, by excluding such defects one could miss the effect.[30] Inclusion or exclusion of chromosomal defects or those of other known etiology may also be driven by the inclusion or exclusion of those defects in the reference population that is selected for comparison.

12. Reference Group(s): Internal or External, Exposed or Unexposed?

A critical element for pregnancy exposure registries is the choice of comparator groups. The most valid reference group will have comparable (1) outcome definition (e.g., exclusion of minor anomalies); (2) outcome assessment (e.g., intensity of screening, frequency of terminations, inclusion of prenatal diagnoses, availability of diagnostic tests, start and stop of followup);[23] (3) selection of subjects into the study (e.g., gestational age at

enrollment); and (4) baseline risk (e.g., distribution of risk factors, including indication). Ideally, each registry is constructed to include one or more internal reference groups. When this is not possible, an external reference group must be selected with care. Each comparison group has its advantages and disadvantages. For example, an external population-based reference group is generally larger and can provide more stable estimates for specific malformations, while an internal comparison group, which may be too small to support assessment of specific malformations, may be able to provide more comparable estimates for malformations overall. More than one comparison group can be used to increase the study generalizability. In anticipation of potential conflicting results, however, a primary comparison group or groups should be identified and justified a priori.

External comparators are usually considered less valid than internal comparators; for example, an RCT or observational study on the relative risk of stroke in an elderly population exposed to a drug would never use an external reference. However, pregnancy registries often compare their estimates with the background risk in "standard populations" such as the CDC's Metropolitan Atlanta Congenital Defects Program, where the frequency of malformations among pregnancies of 20 weeks or greater is 2.1 percent when diagnosed prenatally or within the first week of life, and 2.6 percent if infants are followed until the first birthday;[19, 23] or European Congenital Anomalies and Twins Registers (EUROCAT) data in Europe, where the prevalence of malformations at birth is 2.0 percent.[31] Two advantages of the use of available data from large external reference populations are that it avoids the costs in time and money of enrolling unexposed subjects, and that it provides stable risk estimates for common specific malformations in the general population.

External reference groups must be used with caution, since the estimated risk of "major malformations" can vary widely depending on the population, the definition, and the ascertainment methodology. When external references are the only alternative, they must be appropriate to the population being studied. Analyses should at least take into account the characteristics of the surveillance program and use the same methodology in their exposed group. For example, characteristics to be considered are whether prenatal diagnoses and terminations were counted, whether malformations were identified during the delivery hospitalization or also through followup over a number of months, and whether chromosomal malformations and minor malformations were included. Many registries use external references as a necessity. Information from these sources can be helpful, particularly when there are no other data available, as long as findings are interpreted with caution. For example, external references can identify major teratogens (like thalidomide), generate hypotheses when unusual patterns of malformations are identified, and inform the need for additional, targeted, epidemiological studies.[24]

Some registries enroll an internal reference group of unexposed women who undergo the same processes as the exposed; these registries subsequently adjust for potential confounding by matching or adjusting for key covariates. There is still some risk of differential gestational time at enrollment (exposed women may tend to enroll earlier) and lack of comparability (unexposed women rarely have the underlying condition for which the drug was indicated). To make groups more comparable, some registries use women exposed to other non-teratogenic drugs as the reference (e.g., OTIS registries)[32] or enroll pregnant women with a common condition or indication treated with various drugs or untreated (e.g., the multi-sponsor North American Antiepileptic Drug [NAAED] Pregnancy Registry,[33] and the HIV Antiretroviral Pregnancy Registry[34]). More recently, the scientific community has moved toward the evaluation of the comparative safety and efficacy of different treatments for similar indications, in similar populations whenever possible. This approach enhances the comparability of groups, although sometimes more severe conditions are channeled to specific treatment while milder ones can remain untreated; thus, confounding by severity or type of disease is still possible. In addition to improving

validity, using alternative treatments as a reference would answer the clinically relevant question of "how to treat" rather than whether to treat. Moreover, safety data is often needed for multiple drugs with the same indication, evaluation of a variety of drugs used to treat the same condition could be most efficient. The feasibility of multiple-drug registries depends in part on the sponsorship.

Taking advantage of the etiologically relevant periods of exposure during pregnancy, some studies compare first-trimester use of the drug with second- or third-trimester use. These comparisons are only possible for nonchronic treatments, and researchers should consider that the outcome can affect the opportunity for exposure after the first trimester. For example, if the pregnancy is terminated because of a malformation, there would not be second- or third-trimester exposures; therefore, later exposures might be artificially associated with lower risks.

13. Analysis of Registry Data

Pregnancy registries frequently include multiple outcomes as endpoints and may have more than one comparison group; in addition, as stated above, major birth defects among live births may be evaluated separately from major birth defects among all pregnancies. To address the problem of multiple comparisons in analysis and interpretation of registry data, it is essential to establish an analysis plan that identifies the primary hypothesis being tested—typically the proportion of pregnancies involving a major birth defect—and to specify which are the primary groups being compared.

Similarly, the analysis plan should attend to the design of the registry and the expected sample size. For example, registries that involve multiple centers/multiple countries should use appropriate conditional methods of analysis that account for center. For outcomes with low frequencies (e.g., major structural defects), sample size projections should indicate when exact methods must be used for analysis. To evaluate the robustness of findings in the registry, the analysis plan can incorporate a plan for post hoc sensitivity analyses under various scenarios.

14. Statistical Power, Registry Size, and Duration

The projected sample size for a specific pregnancy registry is affected by the frequency with which the medication is used by women of reproductive age, the proportion of exposed pregnancies it is estimated are possible to identify and recruit into the registry, and the scope of the registry (local, national, international). The power of the study to detect an effect at or above a certain level is affected by the sample size and the baseline risk for the outcome in the population.[19] The estimated losses to followup will affect the useful sample size. The duration of followup for outcome assessment will affect the cumulative risk estimate. Missing therapeutic abortions will affect both.

If the medication under study typically is taken only for a few days or intermittently, this fact should be considered in calculations of power and sample size. The effective sample size of pregnancies exposed only in specific gestational windows of time (any one of which may be a risk period while others are not) may be much smaller than the registry's overall projected sample size of pregnancies exposed. These factors must be balanced against the amount of time needed to accumulate a sample size that is sufficient to produce a clinically relevant result.

For example, in a pregnancy registry that compares the overall proportion of pregnancies resulting in an infant with a major birth defect among exposed women with the proportion in an external reference population with a baseline prevalence of major defects of 3 percent, a sample size of 200 exposed live born infants would be sufficient to detect a 2.2-fold relative risk with 80 percent power at an alpha of 0.05. However, the same sample size of exposed live births would be sufficient to detect only a 10.4 or greater relative risk for cleft lip with or without cleft palate.[34]

Because of the limits of power associated with typical sample sizes for pregnancy registries, especially in detecting risks for specific birth defects, an approach that has been used in some registries is the "rule of three": An alert is triggered when three or more occurrences of

specific defects are reported for a specific exposure. This rule is based on the less than 5 percent likelihood of a chance finding of three or more occurrences of the same specific, relatively rare, defect in a cohort of 600 or fewer subjects. Although some defects or defect groups occur frequently enough that the "rule of three" would not apply, this method can be used to flag an unusual finding for further review.[34]

15. Biases

15.1 Selection Biases

Because pregnancy registries typically enroll women only after recognition of pregnancy and in some cases much later in pregnancy, the group of enrollees is a selective group of pregnancies that have survived to that point in gestation and may have a shortened remaining period at risk of incurring the outcome of interest. There is "left truncation" of the registry cohort such that it is devoid of women who have already had a spontaneous abortion, an elective termination, or a stillbirth, depending on the gestational age of enrollment. Although statistical methods can be used to address left-truncation, survivor bias threatens ability to evaluate risk for pregnancy outcomes including birth defects, and calls for a registry design that encourages recruitment of participants as early in gestation as possible. In the extreme, one cannot study infertility in a cohort of pregnancies because, by definition, the women have conceived. Nor would one estimate the incidence of spontaneous abortions in women enrolled after 20 weeks of pregnancy. Spontaneous abortions can still be evaluated when women are enrolled during the first trimester, by assessing the rate of miscarriages per gestational month, thus taking into account both the decreasing trend as gestation progresses and the gestational time at enrollment.

Early enrollment is also of benefit with respect to biases potentially introduced by prenatal diagnosis. Prospective registry enrollment before any prenatal diagnostic test for major birth defect avoids bias in the direction of an increased risk for defects so identified, or in the other direction if women enroll preferentially after prenatal diagnosis that has shown no defect. Pregnancy registry guidelines recommend that only participants enrolled prior to prenatal screening be included.[2] However, as prenatal diagnosis becomes feasible earlier in gestation, this becomes more difficult to achieve.

Many registries also collect data retrospectively, but these data should be analyzed separately. Women enrolled after an abnormal pregnancy test can be analyzed as case series in passive surveillance systems of spontaneous adverse event reports.[2] Malformations can be evaluated for biological plausibility, and specific patterns of malformations or distinct congenital abnormalities can generate hypotheses. On the other hand, retrospectively enrolled subjects without malformations would offer limited information, therefore, the benefit (and ethics) of including these women is questionable.

Registries should report the gestational age at enrollment for their exposed and reference groups. If enrollment time differs, methods should be applied that adjust for left censoring, such as restriction to prospective pretests enrollees.

Another bias might be associated with right truncation of the registry cohort. This occurs when pregnancies with unknown outcomes are considered ineligible for analyses. By excluding terminations, spontaneous abortions, and losses to followup, one assumes that the exposure had the same effect in these pregnancies as in those that remain under observation. Such an assumption is less plausible if the exposed group has a higher frequency of these outcomes than the reference group. The frequency of spontaneous and therapeutic abortions, losses to followup, and withdrawals should be reported for the exposed and reference groups. Of note, a higher frequency of terminations among exposed women might reflect a higher risk of malformations, as well as more fear of malformations with consequent abortion if the drug is suspected of being teratogenic.

Bias may also occur with events that shorten the followup (e.g., preterm delivery that cuts the

possible number of weeks of exposure to the drug of interest). The assessment of transient exposures (e.g., vaccines) during pregnancy in relation to outcomes associated with shorter gestations (e.g., preeclampsia, prematurity, pregnancy weight gain) needs to take into account the smaller opportunity for exposure in shorter pregnancies.

Biases can also be introduced into the analysis by stratification or adjustment for covariates that are themselves affected by the exposure of interest and that are affected by the outcome or share common causes with the outcome (e.g., adjusting for gestational age at birth when studying the effect of a pharmaceutical on structural malformations).[35-37]

15.2 Information Bias

As noted above, pregnancy registries are preferentially "prospective" in design. With prospective design, the outcome cannot directly affect the accuracy of exposure information, and any misclassification of drug exposure tends to be nondifferential with respect to the outcome. However, nondifferential misclassification of exposure is still problematic for safety evaluation, since it tends to bias any potential effect toward the null. It is therefore crucial to maximize the quality of drug exposure information.

When the women provide information on exposure, the accuracy of the recall can be maximized by using structured questionnaires, detailed questions, and calendars to help establish gestational timing and enhance recall of dates. Maternal reports on drug utilization are sometimes cross-validated with medical records. When the health care provider is the only source of data, information on prescriptions may not reflect the real use of the drug during pregnancy if patient compliance is incomplete. Since pregnancy registries typically focus on uncommonly used medications, the impact of false positives among the exposed group is much greater than the occasional inclusion of false negatives among the unexposed reference group.

At the time of enrollment in the registry, women are reporting their medical history retrospectively, knowing that they are enrolled in the registry because there is lack of information on the safety of the drug under study. This situation can potentially influence the accuracy of recall for baseline covariates (i.e., recall may be more accurate for exposed than for unexposed groups because there is a different motivation to recall a medical history) and affect the ability to control for confounding. For this reason, methods for validation of key covariates are of benefit.

Diagnostic bias, or outcome misclassification, also can occur in pregnancy registries. These biases can be either nondifferential or differential between the exposed and the reference group, and can bias the estimate of an effect toward or away from the null. For example, participation in the registry itself or concern that a drug exposure might pose a risk could lead to more access to or uptake of prenatal diagnostic measures such as ultrasound and to more careful examination of infants for defects postnatally, potentially leading to differential accuracy in detection and classification of defects among exposed and unexposed groups. The risk of differential outcome classification among the exposed and the reference group is greatest when external control reference groups are used.

As mentioned above, reported major malformations must be validated. Although neither treating physicians nor women are blinded to the treatment, registries can do blinded validation and adjudication of outcomes. To detect malformations not reported by the patients, records for all pregnancies would have to be reviewed. For example, women might be less likely to volunteer information regarding male genital malformations in their infants, which could result in under-ascertainment of these malformations. To detect malformations identified by screening and frequently terminated (e.g., anencephaly), therapeutic abortions need to be included. To detect an increase in abnormalities incompatible with life, it is important to collect information on autopsy results at stillbirth and, if possible, on examinations of the fetus after spontaneous or induced abortion. The study of spontaneous abortions and pregnancy terminations itself presents an additional methodological challenge, especially in countries where abortions are illegal

or when studies include pediatric populations, because induced fetal losses are sometimes categorized as spontaneous in medical records, and questions about terminations might be considered sensitive.

15.3 Confounding

Several sources of confounding may affect pregnancy registries, as in any other observational study. Socioeconomic status, maternal age, tobacco and alcohol use, illegal drug use, maternal body mass index, and vitamin use are examples of potential confounders that might be related to, or impact, the exposure under study and are also risk factors for some pregnancy outcomes.

With medications, there is the concern of confounding by indication (e.g., the association of a weight loss drug with birth defects might be confounded by the maternal obesity the drug is used to treat). Confounding by indication is difficult to address in nonrandomized studies for common chronic conditions such as depression, asthma, epilepsy, HIV, and autoimmune diseases, where separating the effect, if any, of the drug from the underlying disease can be challenging. A related form of confounding that may be of concern is channeling bias (i.e., women with more severe underlying disease may be most likely to be selected to receive the drug of interest).

Each of these potential confounding concerns provides a strong rationale for inclusion of actively recruited comparison groups that are matched to the exposed registry participants on the maternal underlying disease and, to the extent possible, similar in distribution of maternal disease severity.

16. External Validity or Generalizability

As mentioned above, pregnancy registries typically rely on volunteers to participate. With appropriate selection of comparison groups and control for sources of confounding, pregnancy registries can make assertions about internal validity. However, there is usually little known about the characteristics of the entire population of exposed pregnant women from whom the sample is drawn. For this reason, it is difficult to make conclusions about external validity or generalizability for any pregnancy registry. If the participants represent a select group, it may be difficult to generalize the findings from the registry. However, the registry volunteers would have to differ from nonparticipants with respect to some characteristic that modifies the effect of the drug on the pregnancy outcome (e.g., a teratogenic effect might vary by race or by baseline folate levels in the population).

17. Operations

17.1 Study Protocol

Pregnancy registries are scientifically rigorous studies designed to monitor safety of product use in pregnancy. As such, they have formal written protocols based on epidemiologic principles and on regulatory authority guidance documents for pregnancy registries.[2, 5] A pregnancy registry protocol should include a brief and cogent review of the literature, registry objectives, study design, detailed data collection procedures including sources of data, inclusion and exclusion criteria for patient enrollment, operational aspects of enrollment and retention, definitions of relevant endpoints, analytic considerations, statistical plan, regulatory and ethical considerations, reporting and publication plans, governance, and criteria for registry termination. While RCT protocols are registered (e.g., on ClinicalTrials.gov), it is still controversial whether those for observational studies should also be registered.[38]

Pregnancy registries have procedural differences distinct from RCTs and from other observational study designs. Thus, they often require specific standard operating procedures that clearly document their unique processes. Each pregnancy registry should also have its own registry management plan that serves as the registry team's roadmap. For more details see Chapter 2, Section 2.10.

17.2 Human Subjects, Informed Consent, and Medical Records Release Forms

Pregnancy registries involve human subjects research and thus institutional review board approval; informed consent of participants; and protection of confidentiality in data collection, data storage, and publication. Pregnant women are considered a "vulnerable" population in legal/ethical terms, but, importantly, unlike other populations considered in this section of regulations (mentally challenged patients, inmates in penal institutions, and children), they are able to give consent. Therefore, registries must adhere to guidelines for human research protection in pregnant women. Pregnancy registries are typically considered minimal risk protocols. As with participation in any research of this type, there is the potential for loss of the confidentiality of the information provided. Methods to manage this risk must be in place and communicated to the potential participant. There is also the psychological risk of participation in a pregnancy registry that may occur when a woman becomes more aware of the potential effects of exposure on the fetus. Resources for expert counseling on fetal risks are available in the United States and Canada through the Organization of Teratology Information Specialists (https://www.mothertobaby.org/).

Informed consent is typically required for participation in a pregnancy registry. Some registries collect data directly from health care providers without collecting patient identifiers. These types of registries may qualify for a waiver of informed consent. For pregnancy registries in which the patient is identified and data are collected from multiple sources, informed consent is required. However, under several conditions, signed informed consent may be waived and verbal consent allowed. Additionally, in order for pregnancy registries to collect data from a woman's health care provider(s) and/or her newborn's pediatric health care provider, the woman must complete medical release forms for each clinician who will report data or provide medical records to the registry. Chapter 7 thoroughly discusses the application of ethical principles for registries.

17.3 Recruitment and Enrollment

In some registries, pregnant women self-identify and self-enroll by calling a toll-free number that can be found in key Web sites, printed materials in specialists' offices, or drug inserts. In other registries, women are referred by general practitioners, specialists treating the condition of interest, or obstetricians. Direct enrollment of women may allow inclusion of participants earlier in gestation, since they are usually the first to know about their pregnancy. Enrolling women directly may also facilitate pregnancy and postnatal followup. However, for some drugs, it might be unrealistic to expect self-enrollment and, for some conditions, it might be more efficient to identify eligible women through specialists. Some countries do not allow self-enrollment. Who initiates enrollment has implications for data collection and informed consent processes.

Pregnancy registries can be conducted by regulatory or other government agencies, academic centers, contract research organizations (CROs), or drug manufacturers. Who sponsors and who conducts the registry can affect the participation of health care centers, some of which may have barriers for collaborations with industry. Biopharmaceutical companies sometimes identify exposed pregnancies as outcomes reported to their surveillance system for drugs not recommended for pregnant women. If identified and enrolled before prenatal tests, these pregnancies can be followed, yielding a pregnancy registry nested in a passive surveillance system.

To maximize enrollment and maintain efficiency, pregnancy registries typically do not use a traditional "site-based" approach. Rather they employ a single coordinating center that recruits and enrolls all eligible pregnant women as soon as possible after conception. The number of coordinating centers that would make the study feasible varies among countries and among

registries. Therefore, awareness campaigns must reach out to pregnant women and their health care providers in a broad variety of settings. A carefully constructed awareness plan should be designed specifically for each pregnancy registry, accounting for the aims of the registry, its target population, and its geographic scope. In general, the plan should incorporate a variety of persistent awareness strategies to ensure broad coverage, including announcements of the registry with contact information posted in the following:

- Product label
- Registry and/or product Internet sites
- Personal mailings to health care specialists, particularly high prescribers and high-risk obstetricians
- Professional journals
- Exhibits or scientific presentations at professional meetings
- Lay magazines
- Advocacy group newsletters and/or Internet sites
- Social media

For pregnancy registries sponsored by individual biopharmaceutical companies, promotional materials are subject to 21 CFR 314.81(b)(3) or 601.12(f)(4), and should be submitted to the FDA Division of Drug Marketing, Advertising, and Communications. In general, registry recruitment and awareness materials should not promote use of the product in pregnancy nor imply that the product is safe and effective in pregnancy unless sufficient scientific evidence exists to support these claims.

Enrollment may also be affected by the lag time between approval of the pharmaceutical and launching of the registry. Awareness and interest may peak right after approval, which is also the ideal time to collect safety data in the postmarketing setting. Streamlined procedures for informed consent and data privacy/HIPAA authorization have been demonstrated to increase enrollment in pregnancy registries.[39]

17.4 Retention of Participants During Followup

Participant retention is crucial to achieving the registry goals. Retention can be encouraged by engaging registry participants, including pregnant women and their health care providers, in the reporting process, and making it as easy as possible to report data to the registry. Registry staff should be trained to collect data for observational studies from both patients and health care providers who do not usually participate in research activities. They should develop a rapport with the reporters that facilitates data collection and promotes retention through relationship building.

Streamlined data collection processes and simple, concise data collection forms are essential for reducing the burden of reporting. For registries sponsored by pharmaceutical companies, duplication of work because of safety reporting should be avoided as much as possible. A small monetary stipend may also encourage retention but may not be universally accepted by registry reporters. For health care providers, especially obstetric care providers, registry data are often more valuable than a stipend. Giving interim data reports to health care providers who report data to the registry is a powerful recruitment and retention incentive.

17.5 Data Collection

Like any other epidemiological study, registries can benefit from the technologic advances in communications (e.g., ability to enroll subjects through social networks and collect data through confidential Web sites). Most registries enter the data directly into an electronic database, either from records or questionnaires or by means of computer-assisted telephone interviews. To ensure confidentiality, identifiers should not be included in the database containing clinical information. The goal is to make reporting data to the pregnancy registry as easy and unobtrusive as possible. Providing a variety of data-reporting mechanisms that are simple to use and fit the reporters' preferred communication practices facilitates recruitment and retention. If feasible, a

pregnancy registry should be designed to allow participants to report data through telephone interviews; paper data collection forms that can be mailed, scanned, or faxed to the registry; simple Internet-based electronic data capture systems; and mobile applications. For details on these data capture systems, see Chapter 11, Section 2.3.

Pregnant women are ideally enrolled into a pregnancy registry before or soon after the exposure of interest and then followed throughout pregnancy. If a live infant is born, the infant may be followed for a period typically ranging from 3 to 12 months. Data may be collected at several different time points:

- At enrollment, information may be collected on product exposure(s), maternal characteristics, prenatal testing, and other baseline data.
- During the second and/or third trimester of pregnancy, a brief update on the status of the pregnancy and exposures may be obtained.
- At the end of pregnancy, information may be collected on additional exposures during pregnancy, risk factors, and details regarding the pregnancy outcome, including any congenital anomalies, gestational age and birth weight, and perinatal complications.
- For live births, data may be collected at several points in time (typically 3, 6, and/or 12 months) on infant characteristics and health outcomes including congenital anomalies, functional or developmental deficits, and other outcomes pertinent for the drug of interest.
- Targeted followup may be needed to collect additional detailed data on specific outcomes of interest.

The source of baseline and followup data is an important consideration. It is best to evaluate all options for obtaining data to determine the most appropriate source for the specific data requested. The pregnant woman can provide detailed data on drug use including exposures to the drug of interest as well as other drugs, on relevant risk factors, and on the pregnancy outcome. Her health care providers, such as the prescriber, specialists, and/or obstetrician, should be able to provide or verify this information. The collection of data from a variety of sources throughout pregnancy and during infancy contributes to the accuracy and comprehensiveness of pregnancy registry data. Requiring information from multiple health care providers, as well as from the patient, is a distinct challenge of pregnancy registries.

Data quality is of the utmost importance in a pregnancy registry, and multiple levels of quality assurance should be employed, beginning with the design of data collection instruments. Instruments should be designed with care, thoroughly vetted, and pilot tested to ensure ease of reporting valid, reliable data. Instructions for self-reporting should be clear and succinct. Electronic data capture systems should include validity checks. If interviews are to be used, the interviewers should be thoroughly trained to conduct neutral, unbiased interviews using detailed interview scripts. Once captured, the data should go through a rigorous cleaning and quality assurance process to reduce errors, missing data, and misclassifications. When possible, patient-reported data should be verified by health care providers or medical records.

17.6 Adjudication of Outcomes

Many pregnancy registries enlist the services of a clinical geneticist or dysmorphologist to review and classify all congenital anomalies. A standardized classification system should be used, such as the CDC's Metropolitan Atlanta Congenital Defects program.[29] The assessor and method of assessment should be the same for both the exposed group and comparison group, and the assessor should be blinded to the exposure of interest. The assessor may also evaluate likely causes for the particular birth defect, such as family history, genetic factors, and/or exposure to known teratogens.[28] If the exposure of interest is made available, the assessor may examine the timing of the exposure relative to the origin of the birth defect (to attempt to determine if the timing of the exposure is relevant to the formation of the birth defect).[28] Registries can engage the scientific advisory board and/or a subgroup of the board to review each case and the assessor's classification and reach consensus on the classification.

17.7 Process of Releasing Findings

17.7.1 Reporting Findings to Regulatory Agencies

FDA considers individual case reports from a pregnancy registry as derived from active solicitation of patient information (FDA 1997), including reports from participants enrolled both prospectively, where the exposure is reported prior to knowledge of the pregnancy outcome, and retrospectively, where the pregnancy outcome is already known at the time the exposure is reported.[2] A company sponsor holding marketing authorization for an approved drug or licensed biological product must submit to FDA, within 15 calendar days, reports of pregnancy registry adverse events that are both serious and unexpected by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event. Current reporting requirements in the regulations consider any congenital anomaly a serious adverse event.

Pregnancy registries conducted independently of any sponsors holding marketing authorizations are not subject to postmarketing regulatory reporting requirements. However, investigators conducting such registries may forward reports of any serious adverse events including congenital anomalies to the sponsor of the medical product or report directly to FDA's MedWatch office (1-800-FDA-1088 or http://www.fda.gov/Safety/MedWatch/default.htm).

Any company conducting a pregnancy registry required by FDA must submit an annual status report to the agency. Companies conducting pregnancy registries not subject to annual reporting requirements are encouraged to include a status report in the periodic safety report. The status/interim report should describe the study design and summarize the status of the planned, initiated, in progress, or completed pregnancy registry conducted by or otherwise obtained by the sponsor during the reporting period. The status report should also provide a descriptive summary of progress to date, interpretation of findings, and appropriate analyses with comments on the clinical significance of the findings. Copies of full reports may be appended, if appropriate. Any publications based on data from the registry should be included.

The registry status report should include the following, presented separately for prospective and retrospective reports:

- Number of pregnant women enrolled to date
- Number of pregnancies with outcome known (stratified by live birth, spontaneous abortions, elective terminations, fetal deaths/stillbirths)
- Number of pregnancies with outcome pending, and number of pregnancies lost to followup (p 16, FDA guidance)[2]

For pregnancies with known outcomes, line listings (which are tables that organize key information about cases with each row representing one case and each column representing a variable of interest[40]) and summaries of the following:

- Demographics, obstetrical and medical history of mothers
- Weeks of gestational age at exposure
- Dose and duration of exposure
- Whether multiple gestation
- Weeks of gestational age at completion or termination of pregnancy
- For live births and deaths/stillbirths:
- Small for gestational age
- Preterm delivery
- Congenital anomalies or other fetal abnormalities

Finally, for spontaneous abortions and elective terminations, abnormalities in products of conception, if known.

17.7.2 Reporting to Sponsors

There are no specific rules for reporting events to the sponsor company. The sponsor company negotiates this with the academic center or CRO. Some pregnancy registries have regular (semiannual or annual) data cutoff points and issue corresponding periodic interim reports summarizing the aggregate data. The sponsor can then use this interim report for any regulatory reporting requirements.[1] Others, such as the

NAAED, have prespecified criteria for release of results for a positive association.[33]

Most pregnancy registries administered by CROs or academic institutions report all adverse pregnancy outcomes (birth defects, spontaneous fetal losses, induced abortions), and maternal and nondefect fetal events, regardless of attribution or seriousness, to the sponsor within a few business days. Some sponsors only request specific outcomes, or serious and attributable events, reported to them. The sponsor reports these events to regulatory agencies. Pregnancy is not considered an adverse event (AE). The registry might also report spontaneous AEs (not registry-related outcomes) to the sponsor, although these may be received infrequently. If the sponsor requires further information on a pregnancy-related AE, it can contact the registry, which would contact the health care provider. The sponsor follows up on any non-registry cases as needed.

17.7.3 Publication Policy

Some pregnancy registries have formal publication committees.[34] In others, such as NAAED, the investigators review plans to publish registry data and conclusions with the independent scientific advisory committee, and a consensus to publish is developed.[33] Others simply publish the findings when they have them. Registry results should be published as soon as the number of women in the registry permits, in order to allow dissemination of the results to the scientific and clinical communities.

17.8 Role of (Scientific) Advisory Board

An independent scientific advisory committee usually oversees the scientific conduct and analysis of the registry. This committee can advise and participate in the design and establishment of the registry, as well as assist in the review of data, the classification of any birth defects, and the dissemination of information to ensure that results are interpreted and reported accurately. The role and duties of the committee should be specified in the protocol. Members of the committee could include experts in obstetrics, embryology, teratology, pharmacology, epidemiology, pediatrics, clinical genetics, and any relevant therapeutic areas; and consumers representing the disease state being treated; and may include members from the CDC, the National Institutes of Health, academia, and the private sector. The advisory committee might review the registry data, develop consensus statements, provide recommendations on modifications or enhancements to the registry, and/or assist in the dissemination of information and the formulation of strategies to encourage enrollment. In addition to the scientific advisory committee, multicompany-sponsored pregnancy registries may also include a steering committee composed of representatives of the sponsoring pharmaceutical companies.

17.9 Stopping Rules

The criteria to determine when to end the study may be predetermined and specified in the protocol. If the registry is conducted by a drug company as a regulatory requirement, the decision as to when to actually end the study is made jointly by the company and the regulatory authority. In other pregnancy registries, it is the scientific advisory committee that decides or contributes to the decision about when to stop. Sometimes, findings from the registry might affect the decision as to whether it should continue.

Criteria for possible discontinuation of a pregnancy registry include the following:

1. Sufficient information has accumulated to meet the scientific objectives of the registry (i.e., numeric targets or predetermined effect size, such as the “no evidence of risk” or “evidence of relative safety” thresholds defined in the newly created Vaccines and Medications in Pregnancy Surveillance System:[20] “Estimates of safety cannot be absolute; rather, they reflect the degree of confidence that is consistent with an observation of no increased risk between a given exposure and outcome. As more data are collected over time, power increases; for a null observation, increasing power leads to increasingly narrower confidence bounds and increasing assurance of relative safety.”[20] For example, evidence of relative safety might be

reached when the upper bound of the 95 percent confidence interval excludes a twofold increased risk.

2. The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, and/or high rates of loss to followup.
3. Other methods of gathering appropriate information, such as case-control surveillance or large health care databases, become achievable or are deemed preferable.[2]

17.10 Multidrug Pregnancy Registries

A multidrug pregnancy registry actively collects information on exposure to various drug therapies for specific diseases, such as the Antiretroviral Pregnancy Registry[34] and NAAED.[33] In some cases, a general multidrug registry, such as that conducted by a teratogen information service, collects information on drugs for either unrelated or related indications. Multidrug registries have advantages over single-drug registries with respect to both efficiency and economy; they also allow the examination of polytherapy. They may also have the advantage of having readily available comparison groups of pregnant women unexposed to the specific medical product(s) of interest but with the same indication (e.g., disease registries) or exposed to other drugs for the same indication.

Disease pregnancy registries for common conditions in women of childbearing age (e.g., multiple sclerosis) treated with any available drug would make most sense from logistical (avoidance of duplicating efforts), methodological (validity and power), and clinical (comparative safety) points of view. However, their establishment would require collaboration among companies competing for the same therapeutic area, which may be difficult.

17.11 Multicenter and Global Registries

Like RCTs, registries can be multicenter, national, or international. Currently, registries are centralized by sponsors, CROs, government agencies, or academic centers; they typically focus on a single drug, multiple drugs within a class, multiple drugs for different indications, or are disease based and evaluate drugs used to treat a particular condition.[1] In the future, rather than conducting a new registry for each drug, a global centralized mega pregnancy-exposure registry may exist, guided and coordinated by collaborations among regulatory agencies, pharmaceutical companies, contractor organizations, and academic centers.[19] Although appealing, in practice it will be a challenge for this approach to accommodate the case-specific needs for each drug.

In terms of setup, management, and analysis, a locally run registry is very different in scope from a global registry. The latter's geographic scope includes many challenges (e.g., language, culture, time zone, regulatory differences) that must be taken into consideration in the planning process. A distinct feature of a country-specific registry is that the patient population tends to be more homogeneous with respect to demographic characteristics, exposures, length of followup, and diagnosis of outcomes than international registries.

18. Advantages of Pregnancy Registries

Pregnancy registries are often the initial proactive step in assessing the safety of use during pregnancy of new drugs after they are first marketed, because they provide a number of advantages over other approaches:[1] While many pregnant women use medications, their use of individual drugs can be quite rare.[41] By enrolling an exposure group made up only of women who took the medication(s) of interest, pregnancy registries are efficient for evaluating the effects of infrequently used drugs in the population. This is a distinct advantage over other study designs, such as case-control studies and small health care utilization databases, which usually do not have sufficient power to evaluate outcomes following rare exposures.

The longitudinal nature of pregnancy registries allows the estimation of absolute risks of pregnancy outcomes. For example, registries that enroll women before any prenatal testing has been performed can estimate the risk of malformations

among infants whose mothers used a drug of interest. This is in contrast to case-control studies that estimate risk relative to that for a reference group. Information about the absolute risk of outcomes is particularly helpful when counseling women who are planning a pregnancy or who have already become pregnant while taking a drug. Prospective enrollment facilitates ascertainment of drug exposures close to the time a medication is actually used and before information about the pregnancy outcome is known. When registries interview pregnant women directly, they can obtain accurate information about the timing in relation to gestational age, dose, frequency, and duration of medication use, as well as covariates, and can therefore reduce exposure misclassification, recall bias, and confounding.

Pregnancy registries can compare the risk of outcomes among women who have used a variety of treatments for a single condition, including different monotherapies, different polytherapy combinations, or no treatment at all. This information is useful both to women and health care providers in making decisions about whether to treat a condition during pregnancy and which of multiple alternate therapeutic strategies to use. An additional advantage is that a single registry can monitor a variety of pregnancy and infant outcomes after medication exposure, including postnatal outcomes.

19. Limitations of Pregnancy Registries

The pregnancy registry approach also has a number of limitations. While pregnancy registries are an efficient means to assess rare exposures, they lack the statistical power to evaluate rare outcomes. Most teratogenic exposures do not increase the prevalence of all malformations, but have a more selective effect on individual defects or distinct patterns of defects. Pregnancy registries are powered to detect common outcomes such as the total prevalence of all malformations, and can detect only very large increases in these rarer individual defects or patterns. However, many drugs associated with adverse effects in pregnancy result in only moderate increases in these rarer outcomes. Therefore, pregnancy registries are limited in their ability to detect teratogenic effects on specific malformations with statistical certainty. Nevertheless, registries can generate hypotheses that form the basis of further investigation using complementary approaches, study designs, and data sources.[20]

Another important limitation of some pregnancy registries is the lack of a comparable reference group. Ideally, a comparison group should be drawn from the same population as women with the exposure of interest, using the same methods for recruitment, enrollment, and ascertainment of outcomes so that both groups have the same baseline risk for adverse pregnancy outcomes. Comparison of registry findings with data from other studies, such as population-based surveillance programs or hospital deliveries, can lead to biased results if the subjects in the reference group have characteristics different from those of the registry participants, or it the methodology for case ascertainment is different. Identifying an appropriate reference group can be particularly difficult for global registries that recruit exposed women from multiple countries with potentially different populations and backgrounds. For registries such as these, a comparable unexposed group may not exist. Even when an internal reference group is recruited, differences between the exposed and unexposed groups with respect to factors such as the indication for the drug or the proportion of subjects lost to followup can affect the validity of the results.

An additional consideration is that findings from a pregnancy registry may not be generalizable to the broader population of all women who use a drug. Enrollment of women in pregnancy registries typically is voluntary and self-selected, and registry participants represent a small proportion of all women who have taken a drug. For these reasons, the characteristics and experience of women who participate in a registry may differ from those of nonparticipants, and these characteristics may modify the effect of the drug.

A final limitation of pregnancy registries is the length of time typically required to enroll sufficient numbers of exposed women to generate

stable estimates of pregnancy outcomes. This timeframe can be affected by the frequency of exposure in the general population, and by the methods and extent of recruitment efforts by the registry. Most registries continue for years before publishing final results. This extended period of evaluation before reaching conclusions regarding adverse pregnancy outcomes can be a disadvantage when there are pregnancy outcomes of concern that need to be evaluated quickly or when new therapeutic agents become available.

20. Evaluation of Reports From Pregnancy Registries

It is important to critically assess the results and conclusions of reports from pregnancy registries. Key issues to consider are summarized in Table 21–2.

Table 21–2. Issues to consider when evaluating reports from pregnancy registries

Area	Issues
Objectives	What question(s) is the registry attempting to answer? Are the design and methods appropriate to do so?
Background	What condition(s) is the drug used to treat (e.g., chronic vs. episodic)? In what settings is the drug likely to be used (e.g., as primary treatment or as adjuvant therapy with other drugs)? What is the recommended therapeutic dose and duration of use? Is the drug likely to be used off label for conditions other than the stated indication?
Study population	What is the target population from which pregnant women exposed to the drug are drawn? Does the report describe the characteristics of women enrolled in the registry? Could the study subjects differ from women in the target population in ways that would affect the generalizability of the results?
Exposure ascertainment	What are the sources of information about drug exposure (e.g., maternal interviews, physician reports, pharmacy records)? Are these sources likely to provide valid information about how women actually used the drug? Are the exposures ascertained in sufficient detail (e.g., dose, frequency, duration, timing during gestation) to accurately assess the drug's potential effects on the outcome(s) of interests?
Outcome ascertainment	What are the sources of information about pregnancy outcomes, infant and fetal health (e.g., maternal interviews, obstetricians' reports, pediatric records)? Are these sources likely to be knowledgeable about the occurrence of the outcomes being studied? Are outcomes among stillbirths, spontaneous abortions, and elective terminations included? Are the outcomes documented in sufficient detail?
Reference group(s)	What comparison group(s) does the registry use? Is an internal comparison group recruited? Are there potential differences between the exposed and comparison groups that could affect the validity of the findings?
Statistical power	Does the sample size provide sufficient statistical power to meet the objective(s)?

Table 21–2. Issues to consider when evaluating reports from pregnancy registries (continued)

Area	Issues
Biases	When did subjects enroll (i.e., gestational age at enrollment for exposed and reference groups)? What proportion of registry enrollees did not complete the study (i.e., were lost to followup)? Do their characteristics differ from those who completed the study in ways that could affect the validity of the results? Are exposed subjects comparable to the reference group? Were the same methods for data collection and outcome definition used in the exposed and reference groups? Are there other possible sources of bias in the results? Are these biases addressed sufficiently in the analyses or in sensitivity analyses?
Results	Does the report provide estimates of the absolute risk of the adverse pregnancy outcomes being studied? Are the results generalizable to the broader population of pregnant women who will use the drug?
Conclusions	Does the report explore possible alternative explanations for the findings? Does the report review and compare findings from other studies that assess the drug's effects during pregnancy, or findings for other drugs used to treat the same condition(s)? Do the registry findings provide information that will be useful to health care providers and women in making clinical decisions about use of the medication and pregnancy management?

21. Summary

Well-designed and -executed pregnancy registries are an efficient initial approach to assess the safety of biopharmaceuticals during pregnancy, and can provide data that health care providers can use in treating and counseling patients who are pregnant or wish to become pregnant. Although pregnancy registries are more appropriate to identify or rule out large increases in the risk for malformations than to identify more modest teratogenic risks, they are a valuable tool to establish safety boundaries around risk estimates as data accumulate. Pregnancy registries have some unique characteristics that distinguish them from other registries or types of surveillance. Critical methodological issues to consider in their design include the prospective enrollment of women before the pregnancy outcome is known, inclusion of a comparable reference group, thoughtful assessment of drug exposure, ascertainment of prenatal and postnatal diagnosis, and validation of outcomes. Chance and potential biases should be considered when interpreting results from any observational study. A surveillance program should consider a combination of different sources of data so that associations detected in one study can be replicated or refuted by others.[20]

Case Examples for Chapter 21

Case Example 49. Expanding an ongoing pregnancy registry

Description	The Antiretroviral Pregnancy Registry is the oldest ongoing pregnancy exposure registry. This multisponsor, international, voluntary, collaborative registry monitors prenatal exposures to all marketed antiretroviral drugs for potential risk of birth defects.
Sponsors	Abbott Laboratories, Apotex Inc, Aurobindo Pharma Ltd., Boehringer Ingelheim Pharmaceuticals Inc., Bristol-Myers Squibb Company, Cipla Ltd., Gilead Sciences Inc., HEC Pharm, Hetero USA, Janssen Infectious Diseases BVBA, Merck & Co. Inc., Mylan Laboratories, Novartis Pharmaceuticals, Pfizer Inc., Ranbaxy Inc., Roche, Teva Pharmaceuticals, and ViiV Healthcare (represented by GlaxoSmithKline).
Year Started	1989
Year Ended	Ongoing
No. of Sites	Not site-based; open to all health care providers. Nearly 2,000 health care providers have contributed data to the registry.
No. of Patients	16,732

Challenge

Antiretroviral treatments represent an area of particular concern for monitoring safety in pregnancy. Women may need to take the drugs during pregnancy to manage their own HIV infection and to reduce the risk of transmitting HIV to the infant, but these benefits must be weighed against the risk of teratogenic effects. Because of these factors, it is extremely important for clinicians and patients to understand the risks of using antiretroviral drugs during pregnancy in order to make an informed decision. However, ethical and practical concerns make a randomized trial to gather these data difficult, if not impossible.

In 1989, the first manufacturer of an antiretroviral drug voluntarily initiated a pregnancy exposure registry to track the outcomes of women who had used its product during pregnancy. The purpose of the registry is to collect information on any teratogenic effects of the product by prospectively enrolling women during the course of their pregnancy and following up with them to determine the outcome of the pregnancy. Physicians enroll a patient by providing information on the pregnancy dates, characteristics of the HIV infection, drug dosage, length of therapy, and trimester of exposure to the antiretroviral drug. Information on the pregnancy outcome is gathered through a followup form sent to the physician after the expected delivery date.

In 1993, the registry was expanded to include all antiretroviral drugs, as other manufacturers voluntarily joined the registry once their drugs were on the market. The registry is international in scope and allows any health care provider to enroll a patient who intentionally or unintentionally has used an antiretroviral drug during pregnancy. The U.S. Food and Drug Administration, which has used this registry as a model for new pregnancy registries, now requires participation in the registry for all new and generic antiretroviral drugs.

The year 2012 marks the 20th anniversary of the registry. Since 2006, the registry has more than doubled the enrollment of the first 15 years, increasing enrollment from 6,893 pregnancies in 2006 to 16,732 in 2012. This increase was partly due to the increased number of new antiretroviral medications on the market. In 2006, the registry monitored 28 medications from 8 companies; by 2012, it monitored 36 medications from 18 companies (including manufacturers of both branded and generic products). The registry has also increased enrollment as well as its geographic representation by incorporating the

Case Example 49. Expanding an ongoing pregnancy registry (continued)

Challenge (continued)

datasets of comparable, completed epidemiological studies. For example, the registry added data on nearly 1,000 women from a study conducted in Brazil and Argentina of antiretroviral-exposed pregnant women who delivered between the years 2002 and 2007.

In addition to this large increase in enrollment, electronic data capture (EDC) was introduced in 2010 as a data collection method for the registry.

In summary, early challenges for the registry included establishing standard processes for monitoring and assessing the safety of drugs during pregnancy. Key challenges in recent years have included managing the methodological and analytic implications of a rapid growth in size and the operational implications of adding EDC.

Proposed Solution

To ensure both rigor and consistency early on, the registry put in place predefined analytic methods and criteria for recognizing a potential teratogenic signal. Tools for coding and classifying birth defects were developed for the registry to maximize the likelihood of identifying a teratogenic signal. This unique system groups birth defects by etiology or embryology rather than by general location or category, as does the Medical Dictionary for Regulatory Activities (MedDRA). Grouping like defects together increases the likelihood of detecting a potential signal. The registry also codes the temporal association between timing of exposure and formation of the birth defect, aiding in signal detection.

Specific monitoring criteria were developed for evaluating signals at various levels, including the Rule of Three (the rule that three exposure-specific cases with the same birth defect require immediate evaluation). This rule is based on the statistical principle that the likelihood of finding at least three of any specific defect in a cohort of 600 or fewer by chance alone is less than 5 percent.

In the last few years of the registry's operation, large increases in enrollment required re-evaluation of the adequacy of existing signal detection rules. The Rule of Three continues to serve an important role; however, understanding weak signals is methodologically challenging. Incorporating enrollments from comparable epidemiological studies into the registry population has boosted enrollment, increased cultural diversity, and enhanced signal detection capabilities. Each merger of external data prompts the need to re-examine the potential for selection and ascertainment bias.

Operationally, each new participating manufacturer undergoes a series of trainings and is required to obtain institutional review board approval before participation in the registry. Registry trainings and standard operating procedures are reviewed at biannual steering committee meetings and revised as appropriate.

In expanding the options for data entry into the registry, a hybrid EDC-paper approach was deemed operationally feasible in lieu of an EDC-only approach. This allowed a subset of established reporters to use EDC, while limiting disruption for reporters who preferred to report data on paper CRFs.

Results

The registry now contains data on 16,732 prospective pregnancies with exposure to 36 medications from 18 companies. Approximately 40 percent of new enrollments in the registry are made using EDC technology.

Registry data have been used in 13 publications, 9 abstracts, and 25 presentations, and the registry design and operation have been the subject of many publications and presentations. The registry findings can help provide clinicians and patients with information to make informed decisions regarding use of antiretroviral drugs during pregnancy.

Key Point

A pregnancy exposure registry can employ continuous quality improvement practices to identify and define key quality processes and

Case Example 49. Expanding an ongoing pregnancy registry (continued)

Key Point (continued)

keep the registry current and innovative throughout its life cycle. The fact that the registry had established, standard policies and procedures for coding, monitoring, and analysis was critical in incorporating new partners and data sources quickly and easily. Regular review of these policies and procedures is essential to respond to the changing registry environment.

For More Information

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Scheuerle A, Covington D. Clinical review procedures for the Antiretroviral Pregnancy Registry. Pharmacoepidemiol Drug Saf. 2004;13:529–36.

Case Example 50. Using a pregnancy registry to detect major teratogenicity

Description	The International Lamotrigine Pregnancy Registry was established to monitor for the signal of major teratogenicity following in utero exposure to lamotrigine.
Sponsor	GlaxoSmithKline
Year Started	1992
Year Ended	2010
No. of Sites	Not applicable; health care providers reported lamotrigine exposure during pregnancy and subsequent pregnancy outcomes on a voluntary basis.
No. of Patients	1,558

Challenge

Lamotrigine is a second-generation anticonvulsant therapy, widely indicated for the treatment of epilepsy. Lamotrigine was approved in the United States for the treatment of epilepsy in 1994 and for the treatment of bipolar disorder in 2003. In 1992, following the approvals of lamotrigine in several different European countries, the International Lamotrigine Pregnancy Registry was established to monitor the frequency of major teratogenicity following in utero exposure to lamotrigine. Major congenital malformation (MCMs), identified after birth and before hospital discharge, was the primary outcome evaluated by the registry. The U.S. Centers for Disease Control and Prevention's Metropolitan Atlanta Congenital Defects Program case definition was used to classify MCMs. Due to the rarity of the outcome, the registry needed to enroll enough limotrigine-exposed patients in order to have adequate statistical power to detect changes in MCM frequencies.

Proposed Solution

The registry targeted an enrollment of 1,000 limotrigine-exposed pregnant women. Prospective reporting early in pregnancy was encouraged. The registry also received and reviewed retrospective reports, defined as those for which the pregnancy outcome was known at the time of reporting. Due to successful patient enrollment, the registry closed to new prospective enrollments in June 2009, and continued to follow up with existing enrollments through

Case Example 50. Using a pregnancy registry to detect major teratogenicity (continued)

Proposed Solution (continued)

March 2010. The results of the International Lamotrigine Pregnancy Registry were compared descriptively against the results of other ongoing anti-epileptic drug (AED) pregnancy registries. While major teratogenicity was evaluated, the registry was not powered to determine the frequency of specific malformation types; surveillance for specific types using the European Congenital Anomalies and Twins Registers (EUROCAT) network is planned.

Results

At registry closure, over 1,500 birth outcomes involving first-trimester monotherapy exposure had been evaluated during the 18-year registry period. The registry was thus adequately powered to meet its primary objective, to determine whether the overall rate of major malformations was increased among the offspring of exposed women. The registry did not detect an appreciable increase in the outcome of MCMs overall. Over an 18-year period, 35 infants with MCMs were observed among 1,558 first-trimester monotherapy exposures: 2.2% (95% CI, 1.6 to 3.1). This was similar to estimates from general population-based cohorts and no pattern of malformation frequency by dose was observed. However, the registry was not powered to exclude increases in the rates of specific defects.

First-trimester monotherapy results from the registry were consistent with several other ongoing AED pregnancy registries, such as the North American Antiepileptic Drug Pregnancy Registry (2.3%, 95% CI, 1.3 to3.8) and the EURAP international pregnancy registry (2.9%, 95% CI 2.1 to 4.1). Monitoring of specific malformations among lamotrigine-exposed pregnancies will continue through case-control surveillance in the EUROCAT network.

Key Point

A drug-specific pregnancy registry can provide valuable information about risks of major congenital malformations following in utero exposure; however, it may take several years to collect enough exposed patients to detect a signal of teratogenicity with sufficient statistical power. For such rare outcomes, accumulating data over long periods of time and from multiple registries is advantageous to monitoring the safety of medical treatments used in pregnancy.

For More Information

Cunnington MC, Weil JG, Messenheimer JA, et al. Final results from 18 years of the International Lamotrigine Pregnancy Registry. Neurology. 2011 May 24;76(21):1817-23.

Case Example 51. Implementing a non-mandated pregnancy registry

Description	The Global Gleevec®/Glivec® & Tasigna® Pregnancy Exposure Registry is an international, prospective, observational registry of women and their offspring exposed to Gleevec/Glivec (imatinib) and/or Tasigna (nilotinib) during pregnancy or within 6 months prior to pregnancy. The primary objective of the registry is to monitor pregnancies exposed to Gleevec/Glivec or Tasigna (tyrosine kinase inhibitors to treat some cancers) to assess the prevalence of birth defects. Secondary objectives include determining the impact of interrupted treatment on maternal disease status and assessing infant development around 12 months postdelivery.
Sponsor	Novartis
Year Started	2011
Year Ended	Ongoing
No. of Sites	4
No. of Patients	5 (expected enrollment of 150)

Challenge

Chronic myelogenous leukemia and gastrointestinal stromal tumor are rare oncologic diseases. Since the approval of Gleevec/Glivec in 2001, life expectancy for these diseases has substantially improved and treatment is now considered chronic. Tasigna, approved for chronic myelogenous leukemia treatment in 2007, is shown to have superior efficacy compared with Gleevec/Glivec. Patients of child-bearing age are now contemplating reproductive opportunities that would not have been possible previously, and are requesting information about the safety and effectiveness of these treatments during pregnancy. The sponsor sought to address this unmet medical need by collecting data on pregnancy outcomes and on the disease status of pregnant women who were exposed to Gleevec/Glivec or Tasigna during pregnancy.

Pharmaceutical companies typically establish pregnancy registries when they are mandated to do so by regulatory authorities. This registry is voluntary and was not mandated by regulatory authorities, and consequently the sponsor experienced challenges in study startup and in enrollment. Regulatory requirements in countries outside the United States evolved during startup, and these changes required revisions to study design. Additionally, both Gleevec/Glivec and Tasigna are classified by the U.S. Food and Drug Administration (FDA) as pregnancy category D, and the prescribing information carries a warning that these drugs should not be administered to pregnant women. Thus, the sponsor was careful to design an awareness campaign that did not promote exposure during pregnancy.

Most existing pregnancy registry models focus primarily on collecting birth outcomes and do not collect maternal disease status or postpartum data. Since this registry was not mandated, and information on maternal health as well as birth outcomes was desired, a novel model was needed.

Proposed Solution

The registry was launched in the United States in 2011 and in Russia, the Netherlands, and Denmark in 2012. The sponsor adopted a national coordinator (NC) model for the registry. The NC is a domestic entity responsible for submitting the protocol to the appropriate regulatory authority for approval and for facilitating the collection of registry data from multiple sources (e.g., oncologists, hematologists, obstetricians, pediatricians). In the United States, the NC is a contract research organization; outside the United States, the NC is a participating physician who has agreed to assume the above responsibilities. Data are collected on maternal disease status at 3 time points: enrollment, pregnancy outcome, and about 12 months postdelivery according to local standard of care. Data are also collected on the fetus/infant at pregnancy outcome and about 12 months of age.

Case Example 51. Implementing a non-mandated pregnancy registry (continued)

Proposed Solution (continued)

A Web site was constructed that provides information about the registry and instructs patients (only in the United States) and providers (globally) on how to enroll into the registry. The sponsor worked closely with regulatory authorities to ensure that the information presented on the Web site is educational and not promotional in nature. Patient recruitment is facilitated through the existing pregnancy reporting infrastructure in the sponsor's safety department; U.S. health care providers calling to report pregnancies are invited to enroll eligible patients into the registry. Additionally, collaborating with patient advocacy groups and preparing durable materials facilitates registry awareness.

Results

The sponsor encountered unanticipated delays and challenges from regulatory authorities, possibly because non-mandated pregnancy registries are unprecedented. Recent European Medicines Agency legislation expanding the safety reporting requirement for noninterventional studies has necessitated further revisions to the protocol and case report form. Work is continuing on expanding the registry to other countries.

Five patients have been enrolled to date, and this number is expected to increase when the registry's Web site and awareness materials are approved by FDA for use in the United States.

Key Point

Pregnancy registries not mandated by regulatory authorities present unique operational challenges. Beginning a study in locations with a favorable regulatory environment may help minimize delays in startup and allow sponsors to apply lessons learned before expanding the registry to other locations. Staying current with regulatory requirements in long-term pregnancy registries is critical to remaining compliant. When collecting data from several different sources (e.g., patients and multiple providers), consider an operational model that centralizes the responsibility for data collection and for health authority and ethics committee submission and approval.

For More Information

Juma M, Ericson S, Eng D, et al. Prospective, observational registry of branded imatinib and nilotinib exposure in pregnant women: voluntary post-authorization safety study. Poster presented at 2012 annual meeting of the American Society of Clinical Oncology (ASCO). Abstract # TPS6638.

Juma M, Ericson S, Eng DF, et al. Prospective, observational registry of branded imatinib and nilotinib exposure in pregnant women: Voluntary post-authorization safety study. Poster presented at the 2011 ASCO annual meeting. Abstract #82968.

Case Example 52. Using proactive awareness activities to recruit patients for a pregnancy exposure registry

Description	The Ribavirin Pregnancy Registry is a component of the Ribavirin Risk Management Program. It was designed to evaluate the association between ribavirin and birth defects occurring in the offspring of female patients exposed to ribavirin during pregnancy or the 6 months prior to conception, as well as female partners of male patients exposed to ribavirin during the same time period. The registry collects prospective, observational data on pregnancies and outcomes following pregnancy exposure to ribavirin.
Sponsor	Aurobindo Phama USA; Genentech, Inc.; Sandoz Pharmaceuticals Inc.; Schering Corporation, a subsidiary of Merck & Co. Inc.; Teva Pharmaceuticals USA, Inc.; Three Rivers Pharmaceuticals, LLC; Zydus Pharmaceuticals (USA) Inc.
Year Started	2003
Year Ended	Ongoing
No. of Sites	Not applicable (population-based)
No. of Patients	Approximately 230 evaluable pregnancies

Challenge

Ribavirin is used in combination with interferon alfa or pegylated interferon alfa for the treatment of hepatitis C. Chronic hepatitis C presents a serious health concern for approximately three million Americans, as the infection, if left untreated, can lead to end-stage liver disease, primary liver cancer, and death. When used as part of a combination therapy, ribavirin can significantly increase both viral clearance and liver biopsy improvement for hepatitis C patients.

However, ribavirin showed teratogenic properties in all animal models tested, making pregnancy exposure a concern. There are minimal data on ribavirin exposure in human pregnancies. Thus, the U.S. Food and Drug Administration (FDA) designated ribavirin as a Pregnancy Category X product based on the animal data, and ribavirin carries product label warnings against becoming pregnant.

Despite the product warnings, pregnancies continue to occur. Health care professionals have insufficient data on the teratogenic properties of ribavirin in humans to counsel pregnant women exposed to ribavirin either during pregnancy or in the 6 months prior to conception. The registry was established to gather prospective data on ribavirin exposure in pregnancy and pregnancy outcomes to better understand the actual risk.

The registry collects data on direct exposures through the pregnant female and indirect exposures through her male sexual partner. Health care providers, pregnant patients, or pregnant patients' male sexual partners may submit data to the registry. The registry collects minimal, targeted data at each trimester and at the outcome of the pregnancy through the obstetric health care providers. For live births, the registry collects data at 6 months and 12 months after the birth by contacting the pediatric health care provider.

To gather data on these patients, the registry needed to develop proactive awareness activities to make patients and providers aware of the program and encourage enrollment without promoting ribavirin use during pregnancy.

Proposed Solution

The registry team developed a multipronged approach to recruiting patients. First, the team developed a comprehensive Web site with information for patients and providers. The Web site contains fact sheets, data forms, information on how to participate, and contact information.

Case Example 52. Using proactive awareness activities to recruit patients for a pregnancy exposure registry (continued)

Proposed Solution (continued)

The site also contains a complete slide set that health care providers can use for teaching activities.

While the site contains detailed information on the scientific reasons for the registry, the tone and content of the Web site are patient friendly, making it a good resource for both potential patients and providers.

Next, the team began targeting professional service groups whose members might treat patients with ribavirin exposure during pregnancy. The groups included hepatologists, gastroenterologists, obstetricians, and pediatricians. By contacting the groups' leadership and sending individualized mailings to members, the team hoped to raise awareness across a broad spectrum of providers. The team communicated with nursing groups, including publishing an article in a nursing journal targeted to gastroenterology nurses, with the goal of utilizing the nurse's role as a patient educator. As a result of these efforts, the American Gastroenterological Association placed a link for the registry Web site on its Web site, and the American Association for the Study of Liver Diseases posted on its Web site an expert opinion piece written by the former registry advisory board chair.

The registry team also raised awareness among professional groups by attending conferences. In 2005, the team presented a poster about the registry, including some information on demographics and program objectives, at the Centers for Disease Control and Prevention National Viral Hepatitis Prevention Conference. In 2009, the team presented a poster at the International Society for Pharmacoepidemiology and in 2010 at the conference of the Teratology Society.

In 2010, to expand awareness efforts to health care providers, the registry published results after five years of enrollment, even though the targeted sample size had not been reached. In 2011, the registry developed an article for Peri-FACTS, a continuing education eJournal for OB/GYNs, nurses, and other health care providers, sponsored by the University of Rochester. Beginning in 2012, the registry began providing the executive summary of its annual interim report to health care providers upon request; this summary provides the most up-to-date snapshot of registry activity.

To raise awareness among patients, the team talked to hepatitis C patient advocacy groups. The registry gained exposure with patients when one patient group wrote an article about the registry for its newsletter and included the registry phone number on its fact sheet. This effort led to many patient-initiated enrollments, despite the lack of patient incentives. In working with patients, the registry has found that emphasizing the goal, which is to gather information to help future patients make better decisions, resonates with patients. Most patients submit data to the registry over the phone, and the rapport that the interviewers have developed with patients has helped to reduce the number of patients who are lost to followup.

In addition to targeting providers and patients directly, the team enlisted the help of public health agencies, since the registry has a strong public health purpose. Registry Web links are posted on the Web sites of the FDA's Office of Women's Health and the Department of Veterans Affairs. A description of the registry is posted on ClinicalTrials.gov.

The team also reviewed the registry process to identify potential barriers to enrollment. Under the initial rules for giving informed consent, the registry call center contacted patients and asked them if they were interested in participating. If patients agreed to participate over the phone, the call center sent a package of information through the mail, including an informed consent document, which the patients needed to sign and return before they could enroll. While many patients agreed to participate over the phone, a much smaller number actually returned the informed consent document. The team identified

Case Example 52. Using proactive awareness activities to recruit patients for a pregnancy exposure registry (continued)

Proposed Solution (continued)

the process of obtaining written informed consent as a key barrier to enrollment.

After discussions with FDA, the registry team and FDA approached the study institutional review board about receiving a waiver of written informed consent because of the public health importance of the registry. The board agreed that oral consent over the phone would be sufficient for this study. Now, the call center can complete the enrollment process in a single step, as they can obtain oral consent over the phone and then proceed with the interview. This change improved and streamlined the enrollment process and significantly increased the number of participants in the registry.

Throughout all of these recruitment activities, the registry team has emphasized that the purpose of the registry is to answer important safety questions for the benefit of future patients and providers. By focusing on the public health purpose of the registry, the team has been able to encourage participation from both patients and providers. The team has also found that a key element of their recruitment strategy is their detailed awareness plan, which calls for completing awareness activities monthly. Because the leadership and membership of professional groups change and new patients begin taking ribavirin, the team has found that continual awareness activities are important for keeping patients and providers aware of the registry.

Results

Through proactive awareness activities, the registry team has generated interest in the project and enrolled approximately 230 exposed pregnancies with outcome information to date. The streamlined oral consent process led to increased enrollment.

Key Point

Recruitment activities may include working with professional groups, contacting patient groups, targeting public health agencies, producing publications, and using a Web site to share information. Once recruitment and enrollment have begun, the registry team may need to re-evaluate the process to identify any potential barriers to enrollment if enrollment is not proceeding as planned. If a registry has an ongoing enrollment process, a plan to continually raise awareness about the registry is an important part of the recruitment plan.

For More Information

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Chapter 22. Quality Improvement Registries

1. Introduction

Quality assessment/improvement registries (QI registries) seek to use systematic data collection and other tools to improve quality of care. While much of the information contained in the other chapters of this document applies to QI registries, these types of registries face unique challenges in the planning, design, and operation phases. The purpose of this chapter is to describe the unique considerations related to QI registries. Case Examples 53, 54, 55, 56, and 57 offer some descriptions of quality improvement registries.

While QI registries may have many purposes, at least one purpose is quality improvement. These registries generally fall into two categories: registries of patients exposed to particular health services (e.g., procedure registry, hospitalization registry) around a relatively short period of time (i.e., an event); and those with a disease/condition tracked over time through multiple provider encounters and/or multiple health services. An important commonality is that one exposure of interest is to health care providers/health care systems. These registries exist at the local, regional, national, and international levels.

QI registries are further distinguished from other types of registries by the tools that are used in conjunction with the systematic collection of data to improve quality at the population and individual patient levels. QI registries leverage the data about the individual patient or population to improve care in a variety of ways. Examples of tools that facilitate data use for care improvement include patient lists, decision support tools (typically based on clinical practice guidelines), automated notifications, communication tools (e.g., patient educational materials), and patient- and population-level reporting systems. For example, a diabetes registry managed by a single institution might provide a listing of all patients in a provider's practice who have diabetes and who are due for a clinical examination or other assessments. Decision support tools exist that assess the structured patient data provided to the registry and display recommendations for care based on evidence-based guidelines. This is a well-reported feature of the American Heart Association's Get With The Guidelines® registries.[1] Certain registry tools will automatically notify a provider if the patient is due for a test, exam, or other milestone. Some tools will even send notifications directly to patients indicating that they are due for a treatment such as a flu vaccination. Reports are a key part of quality improvement. These range from reports on individual patients, such as a longitudinal report tracking a key patient outcome, to reports on the population under care by a provider or group of providers, either alone or in comparison to others (at the local, regional, or national level). Examples of the latter reports include those that measure processes of care (e.g., whether specific care was delivered to appropriate patients at the appropriate time) and those that measure outcomes of care (e.g., average Oswestry score results for patients undergoing particular spine procedures, compared with similar providers).

QI registries can further support improved quality of care by giving providers and their patients more detailed information based on the aggregate experience of other patients in the registry. This can include both general information on the natural history of the disease process from the accumulated experience of other patients in the registry and more individual-patient–level information on specific risk calculators that might help guide treatment decisions. Registries that produce patient-specific predictors of short- and long-term outcomes (which can inform patients about themselves) as well as provider-specific outcomes benchmarked against national data (which can inform patients about the experience and outcomes of their providers) can be the basis of both transparent and shared decisionmaking between patients and their providers.

In addition to these examples, there are tools that are neither electronic nor necessarily provided through the registry systems. Non-electronic examples range from internal rounds to review registry results and make action plans, to quality-focused national or regional meetings that review treatment gaps identified from the registry data and teach solutions, to printed posters and cards or other reminders that display the key evidence-based recommendations that are measured in the registry. Further, even electronic tools need not be delivered through the registry systems themselves. While in many cases the registries do provide the functionality described above, the same purpose is served when an electronic health record (EHR) provides access to decision support relevant to the goals of the patient registry. In other words, what characterizes QI registries is not the embedding of the tools in the registry but the use of the tools by the providers who participate in the registry to improve the care they provide, and the use of the registry to measure that improvement.

2. Planning

As described in Chapter 2, developing a registry starts with thoughtful planning and goal setting. Planning for a QI registry follows most of the steps outlined in Chapter 2, with some noteworthy differences and additions. A first step in planning is identifying key stakeholders. Similar to other types of registries, regional and national QI registries benefit from broad stakeholder representation, which is necessary but not sufficient for success. In QI registries, the provider needs to be engaged and active, as the program is not simply supporting a surveillance function or providing a descriptive or analytic function, but is often focused on patient and/or provider behavior change. In many QI registries, these active providers are termed "champions" and are vital for success, particularly early in development.[2] At the local level, the champions are typically the ones asking for the registry and almost by definition are engaged. Selecting stakeholders locally is generally focused on involving individuals with direct impact on care or those that can support the registry with information, systems, or labor. Yet, the common theme for both local and national QI registries is that the local champions must be successful in actively engaging their colleagues in order for the program to go beyond an "early adopter" stage and be sustainable within any local organization. Once a registry matures, other incentives may drive participation (e.g., recognition, competition, financial rewards, regulatory requirements), but the role of the champion in the early phases cannot be overstated.

A second major difference between planning a QI registry and planning other types of registries is the funding model. QI registries use a wide variety of funding models. For example, a regional or national registry may be funded entirely by fees paid by participating providers or hospitals. Alternately, the registry may supplement participation fees with funding from professional associations, specialty societies, industry, foundations, or government agencies. Some QI registries may not charge a participation fee and may receive all of their funding from other organizations. Local QI registries that operate within a single institution may receive all of their funding from the institution or from research grants. The funding model used by a QI registry largely depends on the goals of the registry and the stakeholders in the specific disease area.

Next, in order for a QI registry to meet its goal of improving care, it must provide actionable information for providers and/or participants to be able to modify their behaviors, processes, or systems of care. Actionable information can be provided in the form of patient outcomes measures (e.g., mortality, functional outcomes post discharge) or process of care or quality measures (e.g., compliance with clinical guidelines). While the ultimate goal of a QI registry is to improve patient outcomes by improving quality of care, it is not always possible for a QI registry to focus on patient outcome measures. In some cases, outcome measures may not exist in the disease area of interest, or the measures may require data collection over a longer period than is feasible in the registry. As a result, QI registries have often focused on process of care measures or quality measures. While this has been criticized as less important than focusing on measures of patient outcomes, it should be noted that quality measures

are generally developed from evidence-based guidelines and emphasize interventions that have been shown to improve long-term outcomes, increasingly recognized through standardized processes (e.g., National Quality Forum), and are inherently actionable. Patient outcome measures, on the other hand, do not yet have consensus across many conditions, may be influenced by systematic loss to followup, and may be expensive and difficult to collect. Furthermore, long-term outcomes are generally not readily available for rapid-cycle initiatives and may be too distant from the time when the care is delivered to support effective behavior change. Nonetheless, there has been an increasing focus in recent years on including outcome measures instead of or in addition to process of care measures in QI registries. This shift is driven in part by research documenting the lack of correlation between process measures and patient outcomes[3-5] and by arguments that health care value is best defined by patient outcomes, not processes of care.[6]

Selecting measures for QI registries typically requires balancing the intent to be relevant and actionable with the desire to meet other needs for providers, for example by reporting quality measures to different parties (e.g., accreditation organizations, payers). Frequently, this is further complicated by the lack of harmonization between those measure requirements even in the same patient populations.[7] Even when there is agreement on the type of intervention to be measured and how the intervention is defined, there still may be variability in how the cases that populate the denominator are selected (e.g., by clinical diagnosis, by ICD-9 classification, by CPT codes). In the planning stages of a QI registry, it is useful to consider key parameters for selecting measures. The National Quality Forum offers the following four criteria for measure endorsement, which also apply to measure selection:

1. Important to measure and report, to keep our focus on priority areas, where the evidence is highest that measurement can have a positive impact on health care quality.
2. Scientifically acceptable, so that the measure when implemented will produce consistent (reliable) and credible (valid) results about the quality of care.
3. Useable and relevant, to ensure that intended users—consumers, purchasers, providers, and policymakers—can understand the results of the measure and are likely to find them useful for quality improvement and decisionmaking.
4. Feasible to collect with data that can be readily available for measurement and retrievable without undue burden.[8]

The National Priorities Partnership[9] and the Measure Applications Partnership,[10] both of which grew out of the National Quality Forum and provide support to the U.S. Department of Health and Human Services on issues related to quality initiatives and performance measurement, also offer useful criteria to consider when selecting measures.

One approach to consider in selecting measures is to perform a cross-sectional assessment using the proposed panel of measures to identify the largest gaps between what is recommended in evidence-based guidelines or expected from the literature and what is actually done ("treatment gaps"). The early phase of the registry can then focus on those measures with the most significant gaps and for which there is a clear agreement among practicing physicians that the measure reflects appropriate care. The planning and development process should move from selecting measures to determining which data elements are needed to produce those measures (see Section 4 below). Measures should ideally be introduced with idealized populations of patients in the denominator for whom there is no debate about the appropriateness of the intervention. This may help reduce barriers to implementation that are due to physician resistance based on concerns about appropriateness for individual patients.

Once the measures and related data elements have been selected, pilot testing may be useful to assess the feasibility and burden of participation. Pilot testing may identify issues with the availability of some data elements, inconsistency in definition of data elements across sites, or barriers to

participation, such as burden of collecting the data or disagreement about how exclusion criteria are constructed when put into practice. In order for the registry to be successful, participants must find the information provided by the registry useful for measuring and then modifying their behaviors, processes, or systems of care. Pilot testing may enable the registry to improve the content or delivery of reports or other tools prior to the large-scale launch of the program. If pilot testing is included in the plans for a QI registry, the timeline should allow for subsequent revisions to the registry based on the results of the pilot testing.

Change management is also an important consideration in planning a QI registry. QI registries need to be nimble in order to adapt to two continual sources of change. First, new evidence comes forward that changes the way care should be managed, and it is incumbent on the registry owner to make changes so that the registry is both current and relevant. In many registries, such as American Heart Association's Get With The Guidelines Stroke program and the American Society of Clinical Oncologists' QOPI registry, this process occurs more than once a year. Second, providers participating in registries manage what they measure, and, over time, measures can be rotated in or out of the panel so that attention is focused where it is most critical to overcome a continuing treatment gap or performance deficiency. This requires that the registry have a standing governance body to make changes over time, a system of data collection and reporting flexible enough to rapidly incorporate changes with minimal or no disruption to participants, and sufficient resources to communicate with and train participants on the changes. The governance structure should include experts in the area of measurement science as well as in the scientific content. The registry system also needs to continuously respond to additional (not necessarily harmonized) demands for transmitting quality measures to other parties (e.g., Physician Quality Reporting System, Meaningful Use reporting, Bridges to Excellence, State department of public health requirements). From a planning standpoint, QI registries should expect ongoing changes to the registry and plan for the resources required to support the changes. While this complicates the use of registry data for research purposes, it is vital that the registry always be perceived first as a tool for improving outcomes. Therefore, whenever changes are made to definitions, elements, or measures, these need to be carefully tracked so that analyses or external reporting of adherence may take these into account if they span time periods in which changes occurred.

3. Legal and Institutional Review Board Issues

As discussed in Chapters 7, 8, and 9, registries navigate a complex sea of legal and regulatory requirements depending on the status of the developer, the purpose of the registry, whether or not identifiable information is collected, the geographic locations in which the data are collected, and the geographic locations in which the data are stored (State laws, international laws, etc.). QI registries face unique challenges in that many institutions' legal departments and institutional review boards (IRBs) may have less familiarity with registries for quality improvement, and, even for experts, the distinction between a quality improvement activity and research may be unclear.[11-14] Some research has shown that IRBs differ widely in how they differentiate research and quality improvement activities.[15] What is clear is that IRB review and, in particular, informed consent requirements, may not only add burden to the registry but may create biased enrollment that may in turn affect the veracity of the measures being reported.[16] Potential limitations of the IRB process have been identified in other reports, including potential problems for comparative effectiveness research. These issues will not be reviewed here.

For QI registries, which generally fit under the HIPAA (Health Insurance Portability and Accountability Act) definition of health care operations, the issues that lead to complexity include whether or not the registry includes research as a primary purpose or any purpose, whether the institutions or practices fall under the Common Rule, and whether informed consent is needed. The Common Rule is discussed in the Chapter 7, and informed consent and quality

improvement activities are discussed in Chapter 8. To assist in determining whether a quality improvement activity qualifies as research, the Office for Human Research Protections (OHRP) provides information in the form of a "Frequently Asked Questions" Web page.[17] OHRP notes that most quality improvement activities are not considered research and therefore are not subject to the regulations for the protection of human subjects. However, some quality improvement activities are considered research, and the regulations do apply in those cases. To help determine if a quality improvement activity constitutes research, OHRP suggests addressing the following four questions, in order:

1. Does the activity involve research? (45 CFR 46.102(d))
2. Does the research activity involve human subjects? (45 CFR 46.102(f))
3. Does the human subjects research qualify for an exemption? (45 CFR 46.101(b))

Is the nonexempt human subjects research conducted or supported by HHS or otherwise covered by an applicable FWA [Federalwide Assurance] approved by OHRP?[18]

In addressing these questions, it is important to note the definition of "research" under 45 CFR 46.102(d). "Research" is defined as "…a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge…." OHRP may not view quality improvement activities as "research" under this definition, and provides some examples of the types of activities that are not considered research.[19] It is also important to note the definition of "human subjects" under 45 CFR 46.101(b). "Human subject" is defined as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information." Again, OHRP may not view quality improvement activities as human subjects research if the data are not considered identifiable private information or were not collected through interaction or intervention with the individual patient (e.g., if the data were abstracted from a medical record).[20]

These questions provide some information helpful in determining whether a quality improvement registry is subject to the protection of human subjects regulations, but some researchers and IRBs have still reported difficulty in this area.[11, 12] Remaining questions include, for example, if the registry includes multiple sites, is separate IRB approval from every institution required? If the registry is considered human subjects research, in what circumstances is informed consent required?

There have been several recent calls to refine and streamline the IRB process for QI registries,[11] and some of this work is advancing. Recently, OHRP has proposed revisions to the Common Rule that would address some of these issues; the proposed changes were posted for a public comment period, which closed in October 2011.[21] Without some changes and greater clarity around existing regulations as they relate to QI registries, it will be difficult for some registries to be successful.

4. Design

Designing a QI registry presents several challenges, particularly when multiple stakeholders are involved. Staying focused on the registry's key purposes, limiting respondent burden, and being able to make use of all of the data collected are practical considerations in developing programs. First, the type of QI registry needs to be determined. Is the goal to improve the quality of patients with a disease or patients presenting for a singular event in the course of their disease? For example, a QI registry in cardiovascular disease will be different (i.e., with respect to sampling, endpoints, and measures) if it focuses on patients with coronary artery disease, versus patients with a hospitalization for acute coronary syndrome. In the first example, the registry may need to track patients over time and across different providers; reminder tools may be needed to prompt followup visits or laboratory tests. In the second example, the registry may need to collect detailed data at a single point in time on a large volume of patients.

Second, QI registries that collect data within a single institution differ from those that collect data at multiple institutions regionally or nationally. Single-institution registries, for example, may be designed to fit within specific workflows at the institution or to integrate with one EHR system. They may reflect the specific needs of that institution in terms of addressing treatment gaps, and they may be able to obtain participant buy-in for reporting plans (e.g., for unblinded reporting). Regional or national level registries, on the other hand, must be developed to fit seamlessly into multiple different workflows. These registries must address common treatment gaps that will be relevant to many institutions, and they must develop approaches to reporting that are acceptable to all participants.

The appropriate level of analysis and reporting is an important consideration for designers of QI registries. Reports may provide data at the individual patient, provider, or institution level, or they may provide aggregate data on groups of patients, providers, and institutions. The aggregate groups may be based on similar characteristics (e.g., disease state, hospitals of a similar size), geography, or other factors. The registry may also provide reports to the registry participants, to patients, or to the public. Reports may be unblinded (e.g., the provider is identifiable) or blinded, and they may be provided through the registry or through other means. In designing the registry, consideration should be given to what types of reports will be most relevant for achieving the registry's goals, what types of reports will be acceptable to participants, and how those reports should be presented and delivered. Reporting considerations are discussed further in Section 9.

As described above, there are many challenges in selecting existing measures or designing and testing new measures. Once measures have been selected, the "core data" can be determined. Since QI registries are part of health care operations, it is critical that they do not overly interfere with the efficiency of those operations, and therefore the data collection must be limited to those data elements that are essential for achieving the registry's purpose. One approach to establishing the core data set is to first identify the outcomes or measures of interest and then work backwards to the minimal data set, adding those elements required for risk adjustment or relevant subgroup analyses. For example, the inclusion and exclusion criteria for a measure, as well as information used to group patients into numerator and denominator groups, can be translated into data elements for the registry. Case Example 53 describes this process for the Get With The Guidelines Stroke program. Depending on the goals of the registry, the core data set may also need to align with data collection requirements for other quality reporting programs.

Many QI registries have gone further by establishing a core data set and an enhanced data set for participating groups that are ready to extend the range of their measurements. This tiered model can be very effective in appealing to a broad range of practices or institutions. Examples include the Get With The Guidelines program, which allows hospitals to select performance measures or both performance and quality measures, and the American College of Surgeons' National Surgical Quality Improvement Program, which has a core data set and the ability to add targeted procedure modules.

QI registries also may need to develop sampling strategies during the design phase. The goal of sampling in QI registries is to provide representativeness (i.e., to ensure that the registry is reflective of the patients treated by the physician or practice) and precision (i.e., to enroll a sufficient sample size to provide reasonable intervals around the metrics generated from each practitioner/practice to be useful in before/after or benchmarking comparisons). Sampling frames need to balance simplicity with sustainability. For example, an all-comers model is easy to implement but can be difficult to sustain, particularly if the registry uses longitudinal followup. For example, an orthopedic registry maintained by a major U.S. center sought to enroll all patients presenting for hip and knee procedures. Since the center performed several thousand procedures each year, within a few short years the numbers of followups being performed climbed to the tens of thousands. This was both expensive and likely unsustainable. On the other hand, a sampling frame can be difficult and confusing. While a

sampling frame can be readily administered in a retrospective chart review, it is much more difficult to do so in a prospective registry. Some approaches to this issue have included selecting specific days or weeks in a month for patient enrollment. But, if these frames are known to the practitioners, they can be "gamed," and auditing may be necessary to determine if there are sampling inconsistencies. Pilot testing can be useful for assessing the pace of patient enrollment and the feasibility of the sampling frame. Ongoing assessments may also be needed to ensure that the sampling frame is yielding a representative population.

An additional implication when considering how to implement a sampling strategy is that for QI registries in which concurrent case ascertainment and intervention is involved, only those patients who are sampled may benefit from real-time QI intervention and decision support. In these circumstances, patients who are not sampled are also less likely to receive the best care. This disparity may only increase as EHR-enabled decision support becomes increasingly sophisticated and commonplace.

5. Operational Considerations

As with most registries, the major cost for participants in a QI registry is data collection and entry rather than the cost of the data entry platform or participation fees. Because QI registries are designed to fit within existing health care operations, many of the data elements collected in these registries are already being collected for other purposes (e.g., claims, medical records, other quality reporting programs). QI registries are often managed by clinical staff who are less familiar with clinical research and who must fit registry data collection into their daily routines. Both of these factors make integration with existing health information technology systems or other data collection programs attractive options for some QI registries. Integration may take many forms. For example, data from billing systems may be extracted to assist with identifying patients or to pull in basic information about them. EHRs may contain a large amount of the data needed for the registry, and integration with the EHR system could substantially reduce the data collection burden on sites. However, integration with EHRs can be complex, particularly for registries at the regional or national level that need to extract data from multiple systems. A critical challenge is that the attribution of clinical diagnoses in the context of routine patient care is often not consistent with the strict coding criteria for registries, making integration with EHR systems more complex. Chapter 15 discusses integration of registries with EHR systems. Another alternative for some disease areas is to integrate data collection for the registry with data collection for other quality initiatives (e.g., Joint Commission, Centers for Medicare & Medicaid Services). Typically, these types of integration can only provide some of the necessary data; participants must collect and enter additional data to complete the CRFs.

The burden of data collection is an important factor in participant recruitment and retention. Much of the recruitment and retention discussion in Chapter 10 applies to QI registries. However, one area in which QI registries differ from other types of registries is in the motivations for participation. Sites may participate in other registries because of interest in the research question or as part of mandated participation for State or Federal payment or regulatory requirements. When participation is for research purposes, they may hope to connect with other providers treating similar patients or contribute to knowledge in this area. In contrast to registries designed for other purposes, participants in QI registries expect to use the registry data and tools to effect change within their organizations. Participation in a QI registry and related improvement activities can require significant time and resources, and incentives for participation must be tailored to the needs of the participants. For example, recognition programs, support for QI activities, QI tools, and benchmarking reports may all be attractive incentives for participants. In addition, tiered programs, as noted above, can be an effective approach to encouraging participation from a wide variety of practice or institution types. Understanding the clinical background of the stakeholders (e.g., nurses, physicians, allied health practitioners, and quality improvement

professionals) and their interest in the program is critical to designing appropriate incentives for participation.

6. Quality Improvement Tools

As described above, QI tools are a unique and central component of QI registries Generally, QI tools are designed to meet one of two goals: care delivery and coordination or population measurement. Care delivery and coordination tools aim to improve care at the individual patient level, while population measurement tools track activity at the population level, with the goal of assessing overall quality improvement and identifying areas for future improvement activities. For example, a report may be used to track an institution's performance on key measures over time and compared with other similar institutions. These types of reports can be used to demonstrate both initial and sustained improvements. Table 22–1 summarizes some common types of QI tools in these two categories and describes their uses.

QI registries may incorporate various tools, depending on the needs of their participants and the goals of the registry. Table 22–2 below describes the types of functionalities that have been implemented in three different registries—two at the national level and one at the regional level.

Table 22–1. Common quality improvement tools

Major Goal	QI Tool	Description
Care delivery and coordination	Patient lists	Lists of patients with a particular condition who may be due for an exam, procedure, etc.
	Patient-level reports	Summaries of data on an individual patient (e.g., longitudinal data on blood pressure readings).
	Automated notifications	To prompt provider or patient when an exam or other action is needed.
	Automated communications	Summaries of patient information in a format that can be shared with the patient or other providers.
	Decision support tools	Recommendations for care for an individual patient using evidence-based guidelines.
Population measurement	Population level standardized reports	Analysis of population-level compliance with quality improvement (QI) measures or other summaries (e.g., patient outcomes across the population).
	Benchmarking reports	Comparisons of population-level data for various types of providers.
	Ad hoc reports	Participants can analyze registry data to explore their own questions and to support continuous quality improvement activities.
	Population-level dashboards	Snapshot look at QI progress and areas for continued improvement.
	Third-party quality reporting	Registry data leveraged for reporting to third-party quality reporting initiatives.

Table 22–2. Quality improvement tools implemented in three registries

Registry	Disease/Condition	Functionalities Implemented
AHA Get With The Guidelines	Heart failure Stroke	• Decision support (guidelines) • Communication tools • Patient education materials • Real-time quality reports with benchmarks • Transmission to third parties
MaineHealth Clinical Improvement Registry	Diabetes	• Patient-care "gap" reports • Decision support • Transmission to third parties
National Comprehensive Cancer Network	Cancer	• Patient-care "gap" reports • Center-level reports • Educational materials

7. Quality Assurance

In addition to developing data elements and QI tools, QI registries must pay careful attention to quality assurance issues. Quality assurance, which is covered in Chapter 11, Section 3, is important for any registry to ensure that appropriate patients are being enrolled and that the data being collected are accurate. Data quality issues in registries may result from inadequate training, incomplete case identification or sampling, misunderstanding or misapplication of inclusion/exclusion criteria, or misinterpretation of data elements. Quality assurance activities can help to identify these types of issues and improve the overall quality of the registry data. QI registries can use quality assurance activities to address these common issues, but they must also be alert to data quality issues that are unique to QI registries. Unlike other registries, many QI registries are linked to economic incentives, such as licensure or access to patients, incentive payments, or recognition or certification. These are strong motivators for participation in the registry, but they may also lead to issues with data quality. In particular, "cherry picking," which refers to the nonrandom selection of patients so that those patients with the best outcomes are enrolled in the registry, is a concern for QI registries. In addition, whenever data are being abstracted from source documents by hand and then entered manually into electronic data entry systems, there is a risk of typographical errors, errors in unit conversions (e.g., 12-hour to military time, milligrams to grams). Automated systems for error checking can reduce the risk of errors being entered into the registry when range checks and valid data formats are built into the data capture platform.

Auditing is one approach to quality assurance for QI registries. Auditing may involve onsite audits, in which a trained individual reviews registry data against source documents, or remote audits, in which the source documents are sent to a central location for review against the registry data. Because auditing all sites and all patients is cost-prohibitive, registries may audit a percentage of sites and/or a percentage of patients. QI registries should determine if they will audit data, and, if so, how they will conduct the audits. A risk-based approach may be useful for developing an auditing plan. In a risk-based approach, the registry assesses the risk for intentional error in data entry or patient selection. Registries that may have an increased risk of intentional error include mandatory registries, registries with public reporting, or registries linked to economic incentives. Registries with an increased risk may decide to pursue more rigorous auditing programs than registries with a lower risk. For example, a voluntary registry with confidential reporting may

elect to do a remote audit of a small percentage of sites and patients each year. A registry with public reporting linked to patient access, on the other hand, may audit a larger number of sites and patients each year, with a particular focus on key outcomes included in the publicly reported measures.

Questions to consider when developing a quality assurance plan involving auditing include—

- What percentage of sites should be audited each year?
- What percentage of data should be audited (all data elements for a sample of patients or only key data elements for performance measures)?
- How should sites be selected for auditing (random, targeted, etc.)?
- Should audits be conducted on site or remotely?
- What constitutes passing an audit?

Depending on the purpose of the registry, quality assurance plans may also address issues with missing data, for example—

- What percentage of missing data is expected?
- Are data missing at random?
- What lost-to-followup rate is anticipated?
- Are certain subgroups of patients more likely to be lost to followup?

Lastly, quality assurance plans must consider how to address data quality issues. Audits and other quality assurance activities may identify problem areas in the registry data set. In some cases, such as when the problem is isolated to one or two sites, additional training may resolve the issue. In other cases, such as when the issue is occurring at multiple sites, data elements, documentation, or study procedures may need to be modified. In rare instances, quality assurance activities may identify significant performance issues at an individual site. The issues could be intentional (e.g., cherry picking) or unintentional (e.g., data entry errors). The registry should have a plan in place for addressing these types of issues.

8. Analytical Considerations

While registries are powerful tools for understanding and improving quality of care, several analytical issues need to be considered. In general, the observational design of registries requires careful consideration of potential sources of bias and confounding that exist due to the nonrandomization of treatments or other sources. These sources of bias and confounding can threaten the validity of findings. Fortunately, the problems associated with observational study designs are well known, and a number of analytical strategies are available for producing robust analyses. Despite the many tools to handle analytical problems, limitations due to observational design, structure of data, measured and unmeasured confounding, and missing data should be readily acknowledged. Below are brief descriptions of several problems to consider when analyzing QI registry data, along with indications of how investigators commonly address these problems.

Observational designs used in registries offer the ability to study large cohorts of patients, and allow for careful description of patterns of care or variations in practice compared with what is considered appropriate or best care. While not an explicit intention, registries are often used to evaluate an effect of a treatment or intervention. The lack of randomization in registries, which limits causal inferences, is an important consideration. For example, in a randomized trial, a treatment or intervention can be evaluated for efficacy because different treatment options have an equal chance of being assigned. Another important characteristic observational studies may lack is an even chance of a patient actually receiving a treatment. In a randomized trial, subjects meet a set of inclusion criteria and therefore have an equal chance of receiving a given treatment. However, a registry likely has some patients with no chance of receiving a treatment. As a result, some inferences cannot be generalized across all patients in the registry.

An inherent but commonly ignored issue is the structure of health or registry data. Namely, physicians manage patients with routine processes, and physicians practice within hospitals or other settings that also share directly or indirectly common approaches. These clusters or "hierarchical" relationships within the data may influence results if ignored. For example, for a given hospital, a type of procedure may be preferred due to similar training experiences from surgeons. Common processes or patient selections are also more likely within one hospital compared with another hospital. These observations form a cluster and cannot be assumed to be independent. Without accounting for the clustering of care, incorrect conclusions could be made. Models that deal with these types of clustered data, often referred to as hierarchical models, can address this problem. These models may also be described as multilevel, mixed, or random-effects models. The exact approach depends on the main goal of an analysis, but typically includes fixed effects, which have a limited number of possible values, and random effects, which represent a sample of elements drawn from a larger population of effects. Thus, a multilevel analysis allows incorporation of variables measured at different levels of the hierarchy, and accounts for the attribute that outcomes of different patients under the care of a single physician or within the same hospital are correlated.

Adequate sample size for research questions is also an important consideration. In general, registries allow large cohorts of patients to be enrolled, but, depending on the question, sample sizes may be highly restricted (e.g., in the case of extremely rare exposures or outcomes). For example, a comparative effectiveness research question may address anticoagulation in patients with atrial fibrillation. As the analysis population is defined based on eligibility criteria, including whether patients are naïve to the therapy of interest, sample sizes with the exposure may become extremely small. Likewise, an outcome of angioedema may be extremely rare, and, if being evaluated with a new therapeutic, both the exposure and outcome may be too small of sample to fully evaluate. Thus, careful attention to the likely exposure population after establishing eligibility criteria as well as the likely number of events or outcomes of interest is extremely important. In cases where sample sizes become small, it is important to determine whether adequate power exists to reject the null hypothesis.

Confounding is a frequent challenge for observational studies, and a variety of analytical techniques can be employed to account for this problem. When a characteristic correlates with both the exposure of interest and the outcome of interest, it is important to account for the relationship. For example, age is often related to mortality and may also be related to use of a given process. In a sufficiently large clinical trial, age generally is balanced between those with and without the exposure or intervention. However, in an observational study, the confounding factor of age needs to be addressed through risk adjustment. Most studies will use regression models to account for observed confounders and adjust for outcome comparisons. Others may use matching or stratification techniques to adjust for the imbalance in important characteristics associated with the outcome. Finally, another approach being used more frequently is the use of propensity scores that take a set of confounders and reduce them into a single balancing score that can be used to compare outcomes within different groups.

As QI registries have evolved, an important attribute is defining eligibility for a process measure. The denominator for patients eligible for a process measure should be carefully defined based on clinical criteria, with those with a contraindication for a process excluded. The definition of eligibility for a process measure is critical for accurate profiling of hospitals and health care providers. Without such careful, clear definitions, it would be challenging to benchmark sites by performance.

With any registry or research study, data completeness needs to be considered when assessing the quality of the study. Reasons for missing data vary depending on the study or data collection efforts. For many registries, data completeness depends on what is routinely available in the medical record. Missing data may be considered ignorable if the characteristics associated with the missingness are already

observable and therefore included in analysis. Other missing data may not ignorable, either because of their importance or because the missingness cannot be explained by other characteristics. In these cases, methods for addressing the missingness need to be considered. Various options for handling the degree of missing data including discarding data, using data conveniently available, or imputing data with either simple methods (i.e., mean) or through multiple imputation methods.

9. Reporting to Providers and the Public

An important component of quality improvement registries is the reporting of information to participants, and, in some cases, to the public. The relatively recent origin of clinical data registries was directly related to early public reporting initiatives by the Federal Government. Shortly after the 1986 publication of unadjusted mortality rates by the Health Care Financing Administration (HCFA), the predecessor of Centers for Medicare & Medicaid Services, a number of states (e.g., the New York Cardiac Surgery Reporting System),[22, 23] regions (e.g., Northern New England Cardiovascular Disease Study Group, or NNE),[24, 25] government agencies (e.g., the Veteran's Administration),[26-28] and professional organizations (e.g., Society of Thoracic Surgeons)[29-31] developed clinical data registries. Many of these focused on cardiac surgery. The surgery's index procedure, coronary artery bypass grafting (CABG), is the most frequently performed of all major operations; it is expensive; and it has well-defined adverse endpoints.

Registry developers recognized that the HCFA initiative had ushered in a new era of health care transparency and accountability. However, its methodology did not accurately characterize provider performance because it used claims data and failed to adjust for preoperative patient severity.[32] Clinical registries, and the risk-adjusted analyses derived from them, were designed to address these deficiencies. States such as New York, Pennsylvania, New Jersey, California, and Massachusetts developed public report cards for consumers, while professional organizations and regional collaborations used registry data to confidentially feed results back to providers and to develop evidence-based best practice initiatives.[33, 34]

The impact of public reporting on health care quality remains uncertain. One randomized trial demonstrated that heart attack survival improved with public reporting,[35] and there is evidence that low-performing hospitals are more likely to initiate quality improvement initiatives in a public reporting environment.[36] However, a comprehensive review[37] found generally weak evidence for the association between public reporting and quality improvement, with the possible exception of cardiac surgery, where results improved significantly after the initial publication of report cards in New York two decades ago.[23, 38, 39] Some studies have questioned whether this improvement was the direct result of public reporting, as contiguous areas without public reporting also experienced declining mortality rates.[40] Similar improvements have been achieved with completely confidential feedback or regional collaboration in northern New England[41] and in Ontario.[42] Thus, there appear to be many effective ways to improve health care quality—public reporting, confidential provider feedback, professional collaborations, state regulatory oversight—but the common denominator among them is a formal system for collecting and analyzing accurate, credible data,[43] such as registries provide.

Public reporting should theoretically affect consumer choice of providers and redirect market share to higher performers. However, empirical data failed to demonstrate this following the HCFA hospital mortality rate publications,[44] and CABG report cards had no substantial effect on referral patterns or market share of high and low performing hospitals in New York[45, 46] or Pennsylvania.[47, 48] Studies suggest numerous explanations for these findings, including lack of consumer awareness of and access to report cards; the multiplicity of report cards; difficulty in interpreting performance reports; credibility concerns; small differences among providers; lack

of "newsworthiness"; the difficulty of using report cards for urgent or emergent situations; and the finite ability of highly ranked providers to accept increased demand.[49-51] Professor Judith Hibbard and colleagues have suggested report card formats that enhance the ability of consumers to accurately interpret accurate report cards, including visual aids (e.g., star ratings) that synthesize complex information into easily understandable signals.[52, 53] A recent Kaiser Family Foundation survey[54] suggests that, particularly among more educated patients, the use of objective ratings to choose providers has steadily increased over the past decade, and health reform is likely to accelerate this trend.

The potential benefits of public reporting must be weighed against the unintended negative consequences, such as "gaming" of the reporting system.[55, 56] The most concerning negative consequence is risk aversion, the reluctance of physicians and surgeons to accept high-risk patients because of their anticipated negative effect on their report card ratings. Because these highest risk patients may derive the greatest benefit from aggressive intervention, risk aversion may produce a net decrement in public health and a net increase in long-term costs because the best treatments were not initially used.[57-59] Risk aversion unquestionably exists, but its extent and overall population impact are difficult to quantify. CABG risk aversion may have occurred in New York[60, 61] and Pennsylvania,[48] but studies in California[62] and England[63] have not demonstrated similar findings. Numerous studies document probable risk aversion in percutaneous coronary interventions.[64-66] Possible approaches to mitigate risk aversion include demonstrating to providers the adequacy of risk adjustment and modifying those models when appropriate; excluding highest risk patients from reporting; separate reporting of highest risk patients; and careful clinical review of patients turned down for interventions.

Irrespective of its end results, many believe that public reporting is a fundamental ethical obligation of physicians.[67, 68] It addresses the patient right of autonomy or self-determination in decisionmaking. Whether or not they choose to exercise this right, patients making a choice about treatments should be fully informed, which arguably includes their right to know the comparative performance of potential providers.

When a decision has been made to publicly report outcomes, such measures must meet strict criteria. Professional organizations have emphasized the need to use high quality, audited clinical data whenever possible, and to employ the most appropriate statistical methodologies.[69, 70] Professional society guidelines provide recommendations of varying strength and evidence strength, whereas performance measures should be a select subset of these guidelines that have the highest level of evidence and strongest class of recommendation (e.g., ACC/AHA [American College of Cardiology/American Heart Association] class 1[recommended] or 3 [not indicated, or harmful], level A evidence). National Quality Forum (NQF) requirements for performance measure endorsement have recently been updated. In addition to its four basic requirements of Importance, Scientific Acceptability, Usability, and Feasibility, NQF emphasizes the need for robust, systematic evaluation of the evidence base and comprehensive testing of reliability and validity.[8, 71, 72]

The unit of analysis in public reporting may be controversial. Many states report results for some procedures at the physician or surgeon level, but in many health care areas sample sizes and the small amount of variation attributable to the physician make it difficult to reliably discriminate performance.[73-75] Compiling data from a variety of process and outcome endpoints may help to mitigate sample size issues, as may aggregation of results over multiple years.

Report cards at the individual physician level may be more likely to cause risk aversion compared with group- or hospital-level reports. Changes in health care delivery models must also be considered. As patient care is increasingly provided by teams of providers that may even cross traditional specialty boundaries, individual physician reporting may become less relevant and feasible. Reimbursement will increasingly be based on the overall care provided to a patient or population, and leaders will have a direct financial incentive to assess the performance of individual

physicians in such care groups (e.g., Accountable Care Organizations or ACOs), whether or not such results are publicly reported.

10. Use of QI Registry Data for Research Studies

An emerging trend is the use of data from QI registries to support additional studies. QI registries may collect large volumes of clinical data that can be used to support research studies. Studies using data from QI registries generally are developed in one of two ways.

First, the registry may be modified to collect additional data for a substudy. For example, a registry may collect in-hospital data on patients admitted to the hospital for a specific procedure. To study long-term outcomes of the procedure, the registry protocol may be modified to collect followup data for a subset of patients. An example of this approach was the OPTIMIZE-HF registry, which collected in-hospital data on patients admitted with heart failure. A subset of patients provided consent to be contacted after 6 months to collect additional data.[3] QI registries can also be modified to support other types of studies, such as studies where a subset of participating sites are randomized (cluster randomization) or a subset of patients are randomized (experimental trial). When modifying the registry protocol to support a substudy, the impact on the primary purpose of the registry must be considered, as well as any additional ethical or regulatory requirements introduced by the new data collection effort.

A second approach to using QI registries to support additional studies is to use the registry data, either alone or linked to another data set. For example, a registry that collects in-hospital data may be linked to a claims database to obtain information on long-term outcomes or to examine other questions.[76] In these cases, the technical, legal, and ethical considerations related to linking registry data sets discussed in Chapter 16. Regardless of which approach is used, researchers using data from a QI registry for additional research studies must understand how the data are collected and how patients are enrolled in the primary registry in order to draw appropriate conclusions from the new study.

11. Limitations of Current QI Registries

To summarize some of the key points above, the ideal QI registry collects uniform data on risk factors, treatments, and outcomes at key points for a particular disease or treatment. It obtains the data from multiple sources and across care settings, and leverages existing health information technology systems through interoperability and other data sets (from registries, claims, national indices, etc.) through linkage. Such a registry uses standardized methods to ensure that the patients sampled are representative, that data are of high quality and that it is comparable across providers. Such registries provide feedback at the patient and population level, and, in addition to facilitating quality improvement, they perform quality reporting to third parties. Importantly, they maintain high levels of participation by providers and patients and have a long term, sustainable business model.

Clearly, most QI registries do not achieve this ideal. The term "QI registries" is currently used to refer to a broad spectrum of registries, from local or regional registries aimed at improving care for a specific patient population to large, national registries with sophisticated benchmarking data. Many current QI registries focus on isolated conditions or procedures (e.g., the ACC NCDR Cath/PCI Registry[77]; the STS Adult Cardiac Surgery Database[78]). Health reform will require the acquisition of data about the overall, comprehensive care of conditions such as coronary artery disease, or of populations.[6] This may be facilitated by linkages among related data registries, which might include outpatient preventive care, inpatient acute care and procedures, rehabilitation, and chronic disease management.

Current QI registries also have temporal limitations. They characteristically collect data only in-hospital or for 30 days after admission or a procedure. However, patients, payers, and regulators are also interested in longer term, longitudinal outcomes such as survival, readmission, reintervention, and cumulative resource use. Such information is useful for shared decisionmaking and for comparative effectiveness research. By linking together robust clinical data registries and administrative databases such as MEDPAR or the Social Security Death Master File[79, 80] that provide long-term data, many of these current limitations of clinical registries would be mitigated.

In order for such linkages to be implemented, a number of challenges would need to be overcome. These include a lack of standardized data sets; difficulties collecting data across care settings; inability to leverage existing health information technology systems to reduce duplication of clinician effort; inability to link to other data sources that might reduce data collection burden or enrich outcomes; significant variation in the quality of methods used to collect and report data; and quite different levels of participation and business models. Even registries in related conditions may not be fully compatible.

Potential solutions to such issues have been identified.[81] These include, for example, condition-specific and cross-condition efforts to standardize common or core data element specifications, data quality and audit standards, and methodological considerations such as risk adjustment. Collecting data across care settings will be improved by solving the patient identity management issues (discussed in Chapter 17), which will require clarification and perhaps revision of HIPAA and Common Rule regulations. Overcoming interoperability issues through the promulgation of open standards (e.g., Healthcare Information Technology Standards Panel TP-50) (as described in Chapter 15) could have dramatic impact if adopted widely by EHR systems and registries.

Significant hospital data collection costs are additional limitations of clinical registries. Some data elements such as laboratory values may be automatically extracted from EHRs, but detailed clinical data may still require manual extraction. Existing national registries must develop sustainable business models, and there must be incentives and assistance for the development of new registries where none currently exist.

12. Summary

QI registries have documented success at improving quality of care at the local, regional, and national levels. While QI registries differ in their area of focus, choice of measures, and level of reporting, their consistent features are the use of systematic data collection and other tools to improve quality of care. QI registries also differ from other types of registries in many ways, such as in their use of provider "champions," the inclusion of actionable measures, the frequency of major changes to the registry data collection, the motivations for participation, and the use of blinded or unblinded quality reports to providers, and, in some cases, the public. Because of these differences, QI registries must address unique challenges, particularly in the planning, design, and operations phases.

Case Examples for Chapter 22

Case Example 53. Using recognition measures to develop a data set

Description	Get With The Guidelines® is the flagship program for in-hospital quality improvement of the American Heart Association and American Stroke Association . The Get With The Guidelines—Stroke program supports point of care data collection and real-time reports aligned with the latest evidence-based guidelines. The reports include achievement, quality, reporting, and descriptive measures that allow hospitals to trend their performance related to clinical and process outcomes.
Sponsor	American Heart Association/ American Stroke Association
Year Started	2003
Year Ended	Ongoing
No. of Sites	1,664
No. of Patients	2,063,439

Challenge

The primary purpose of the Get With The Guidelines—Stroke program is to improve the quality of in-hospital care for stroke patients. The program uses the PDSA (plan, do, study, act) quality improvement cycle, in which hospitals plan quality improvement initiatives, implement them, study the results, and then make adjustments to the initiatives. To help hospitals implement this cycle, the program uses a registry to collect data on stroke patients and generate real-time reports showing compliance with a set of standardized stroke recognition and quality measures. The reports also include benchmarking capabilities, enabling hospitals to compare themselves with other hospitals at a national and regional level, as well as with similar hospitals based on size or type of institution.

In developing the registry, the team faced the challenge of creating a data set that would be comprehensive enough to satisfy evidence-based medicine but manageable by hospitals participating in the program. The program does not provide reimbursements to hospitals entering data, so it needed to keep the data set as small as possible while still maintaining the ability to measure quality improvement.

Proposed Solution

The team began developing the data set by working backward from the recognition measures. Recognition measures, based on the sponsor's guidelines for stroke care, contain detailed inclusion and exclusion criteria to determine the measure population, and they group patients into denominator and numerator groups. Using these criteria, the team developed a data set that framed the questions necessary to determine compliance with each of the guidelines. The team then added questions to gather information on the patient population characteristics. Since the inception of the program, data elements and measure reports have been added or updated to maintain alignment with the current stroke guidelines. Over time, certain measures have also been promoted to or demoted from the higher tiers of recognition measures, depending on current science and changes in quality improvement focus.

Results

By using this approach, the registry team was able to create the necessary data set for measuring compliance with stroke guidelines. The program was launched in 2003 and now has 1,664 hospitals and 2,063,439 stroke patient records. The data from the program have been used in several abstracts and have resulted in 38 manuscripts since 2007.

Key Point

Registry teams should focus on the outcomes or endpoints of interest when selecting data elements. In cases where compliance with

Case Example 53. Using recognition measures to develop a data set (continued)

Key Point (continued)

guidelines or quality measures is the outcome of interest, teams can work backward from the guidelines or measures to develop the minimum necessary data set for their registry.

For More Information

http://www.heart.org

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Schwamm LH, LaBresh KA, Albright D., et al. Does Get With The Guidelines improve secondary prevention in patients hospitalized with ischemic stroke or TIA? Stroke. 2005;36(2):416–P84.

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Case Example 54. Managing care and quality improvement for chronic diseases

Description	The Tri State Child Health Services Web-based asthma registry is part of an asthma improvement collaborative aimed at improving evidence-based care and outcomes while strengthening improvement capacity of primary care practices.
Sponsor	Tri State Child Health Services, Inc., a pediatric physician-hospital organization (PHO) affiliated with Cincinnati Children's Hospital Medical Center
Year Started	2003
Year Ended	Ongoing
No. of Sites	39 community-based pediatric practices
No. of Patients	12,365 children with asthma

Challenge

Asthma, a highly prevalent chronic disease managed in the primary care setting, has proven to be amenable to quality improvement initiatives. This collaborative effort between the PHO and Cincinnati Children's Hospital Medical Center was initiated in 2003 with goals of improving evidence-based care, reducing adverse outcomes such as asthma-related emergency room visits and missed schooldays, and strengthening the quality of knowledge and capacity within primary care practices. As the asthma initiative spans 39 primary care practices and encompasses approximately 35 percent of the region's pediatric asthma population, the PHO needed to implement strategies for improving network-level, population-based process and outcome measures.

Proposed Solution

To address the project's focus on improving process and outcome measures across a large network, the asthma collaborative decided to implement a centralized, Web-based asthma registry. Key measures of effective control and management of asthma (based on the National Heart, Lung, and Blood Institute's guidelines) are captured via a self-reported clinical assessment form and decision support tool completed by parents and physicians at the point of care. The questions address missed schooldays and workdays, parent's confidence in managing asthma, health resource utilization (e.g., emergency room visits), parent and physician rating of disease control, and other topics. In

Case Example 54. Managing care and quality improvement for chronic diseases (continued)

Proposed Solution (continued)

addition, the clinical assessment form facilitates interactive dialogue between the physician and family during office visits.

The Web-based registry allows real-time reporting at the patient, practice, and network level. Reporting is transparent, with comparative practice data that support the identification of best practices and shared learning. In addition, reporting functionalities support tracking of longitudinal data and the identification of high-risk patients. The Web-based registry also provides access to real-time utilization reports with emergency room visit and admission dates. All reports are available to participating practices and physicians at any time.

Results

The registry provides essential data for identifying best practices and tracking improvement. The network has documented improvement against standard process and outcome measures.

Key Point

Registries can be useful tools for quality improvement initiatives in chronic disease areas. By collecting standardized data and sharing the data in patient-, practice-, and network-level reports, registries can track adherence to guidelines and evidence-based practices, and provide information to support ongoing quality improvement.

For More Information

Mandel KE, Kotagal UR. Pay for performance alone cannot drive quality. Arch Pediatr Adolesc Med. 2007;161(7):650–5.

Case Example 55. Use of reporting tools to promote quality improvement

Description	The Quality Oncology Practice Initiative (QOPI®) is a quality assessment and improvement program for oncology practices.
Sponsor	American Society of Clinical Oncology (ASCO)
Year Started	Pilot program started in 2002; registry launched for full ASCO membership in 2006
Year Ended	Ongoing
No. of Sites	801 registered practices
No. of Patients	Approximately 50,000 patient charts per year

Challenge

The 1999 Institute of Medicine report "Ensuring Quality Cancer Care" identified the opportunity for quality improvement initiatives in oncology. A clear path to nationwide impact was identified, starting with individual practices. The report set forth recommendations including to "measure and monitor the quality of care using a core set of quality measures." In order to promote this endeavor, a methodology and a registry were needed.

Proposed Solution

In 2002, ASCO, in conjunction with a community of oncologists, developed QOPI, a voluntary pilot program to allow participants to assess and improve cancer care within their own practices. The oncologist-led program created quality measures, developed methodology for data collection and analysis, and tested the feasibility of the pilot program before offering access to the registry to all Society members in 2006. The registry provides comparison data to practices on more than 100 quality metrics that practices and practitioners can use to compare their performance to that of their peers, at both the practice and practitioner level. A team of oncologists, researchers, and staff select, adapt, and develop metrics based on clinical guidelines and expert consensus opinion. Practices and institutions register and manually submit abstracted patient chart data through a Web-based

Case Example 55. Use of reporting tools to promote quality improvement (continued)

Proposed Solution (continued)

interface during twice-per-year data collection periods. Once the data collection periods close, the data are analyzed and practices can view reports showing their performance and scores based on quality measures for that round.

Results

Approximately 600 practices representing nearly 15 percent of U.S. practitioners have now contributed data to the registry. Changes in performance rates have been compared among metrics surrounding the following domains: core, end of life, symptom management, breast cancer, colorectal cancer, and Non-Hodgkin lymphoma. For example, in a 2010 analysis of registry data, practices completing multiple data collection cycles with the registry had better performance on care of pain for end-of-life care (63%) when compared with practices participating in the registry for the first time (47%). Registry participants who participated in multiple data collection cycles also demonstrated better performance in the rate of documenting discussions of hospice and palliative care, and higher rates of hospice enrollment, when compared with participants who participated in just a single cycle.

Key Point

Access to performance reports can inform physician behavior or be used to demonstrate the need for process improvements within a practice. A registry can provide a systematic approach to data collection to support the ongoing use of self-assessment and benchmark performance reports to facilitate quality improvement.

For More Information

http://qopi.asco.org/

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Case Example 56. Using registries to drive quality improvement in chronic conditions

Description	The National Parkinson Foundation Quality Improvement Initiative is a registry-based quality care program that captures longitudinal data on clinical interventions and patient-reported outcomes to identify, implement, and disseminate best practices for the treatment and management of Parkinson's disease.
Sponsor	National Parkinson Foundation
Year Started	2009
Year Ended	Ongoing
No. of Sites	20 centers across United States, Canada, and internationally
No. of Patients	5,000 patients as of May 2012; 20,000 targeted enrollment

Challenge

Parkinson's disease (PD), an incurable, progressive neurogenerative disorder associated with a high burden of disease, presents unique challenges for quality improvement initiatives. Treatments for PD generally focus on reducing patients' symptoms and improving quality of life. Unlike other chronic conditions where improvement can be measured in terms of well-defined outcomes such as survival or cardiovascular events, quality improvement in PD can best be measured using patient-based outcomes. However, identifying appropriate patient-based outcomes for this disease can be a challenge. In addition, variability exists in the clinical diagnosis, management, and treatment of PD. Studies have shown that PD patients treated by a neurologist experience better outcomes, such as a decrease in hip fractures or nursing home placement. However, the specific management and treatment strategies used by these specialists have not been studied or well-described. The lack of evidence-based treatment standards warranted a data-driven approach to identify and understand best practices that improve the quality of care and quality of life for PD patients.

Proposed Solution

In 2009, the National Parkinson Foundation launched an initiative to improve the quality of care in PD. To support an evidence-based approach, the foundation initiated a PD registry to capture clinical interventions and patient-reported outcomes over time from multiple centers across the United States, Canada, and internationally. The initiative, led by a steering committee of movement disorders neurologists, is a unique effort in PD research because of its ability to collect long-term, longitudinal data from multiple centers and its focus on patient-based outcomes data, rather than process of care measures. The aims of the registry are to accelerate clinical discovery, promote collaborative science, and drive advancements in clinical practice toward patient-centered care.

Results

As of May 2012, the registry included more than 5,000 patients from 20 centers; second- and third-year data were available for 3,000 and 500 patients, respectively. Patients' encounter-based data, including demographics, comorbidities, hospitalizations, falls, medications, treatments, and outcomes, are collected annually on brief data collection forms. The registry database includes a diverse population of PD patients, and analyses have confirmed variation in practice patterns across centers. The registry data have yielded important findings, including enhanced understanding of factors and predictors of patients' quality of life and caregiver burden. Additional cross-sectional and longitudinal analyses are planned, using physician care and patient outcome data to describe practice patterns across the registry, identify and improve understanding of best practices, and support the development of guidelines.

Many neurologists were initially doubtful about the value of a registry in this disease area. For the most part, their past experience was with mortality-based registries based around interventions or fatal illnesses; these failed to

Case Example 56. Using registries to drive quality improvement in chronic conditions (continued)

Results (continued)

model a disease with complex, heterogeneous symptomology, where the pathology could not be directly measured. Increasingly, providers have recognized the value of the statistical power and nuanced insight that can be leveraged in this large and detailed registry of expert care.

Key Point

Registry-based quality improvement programs can be useful in many clinical settings, from in-hospital care (e.g., heart failure) to chronic progressive diseases (e.g., PD). The design of the registry and the quality improvement initiative must reflect the nature of the disease and the state of existing evidence. For chronic, progressive diseases, registries can be useful tools for identifying, developing, and disseminating guidelines for best practices to improve quality of care.

For More Information

http://www.parkinson.org/Improving-Care/Research/Quality-Improvement-Initiative

Okun MS, Siderowf A, Nutt JG, et al. Piloting the NPF data-driven quality improvement initiative. Parkinsonism and Related Disorders 201;16: 517-21.

Case Example 57. Clarifying the Federal regulatory requirements for quality improvement registries

Description	The National Neurosurgery Quality and Outcomes Database (N^2QOD) is a prospective, longitudinal registry designed to measure and improve neurosurgical and spine surgical care as it exists in the real-world health care setting.
Sponsor	American Association of Neurological Surgeons (AANS)
Year Started	2011
Year Ended	Ongoing
No. of Sites	30 U.S. neuropractice groups expected in the first year
No. of Patients	7,000 patients expected in the first year

Challenge

N^2QOD was formed with the aim of measuring the quality of real-world neurosurgical and spine surgery care, and the registry defined that "quality" as safety and effectiveness. Given this definition, a patient outcome–centered approach to data collection was necessary. This patient-centeredness is aligned with the priorities of groups such as the Patient-Centered Outcomes Research Institute and the Agency for Healthcare Research and Quality, and reflects a wider trend in quality improvement (QI) science, moving away from processes and process-based measures to patient outcomes and outcome measures.

This move towards patient outcomes necessitates a shift in the way QI registries interact with patients. It also presents challenges for institutional review boards (IRBs) reviewing these projects. IRBs can determine that these projects are either "health care operations" or "human subjects research," as defined by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Common Rule. If an IRB determines that a registry constitutes "health care operations" (i.e., data collection used for issues such as clinical care, administrative use, or quality assessment), then neither IRB approval nor informed consent is required. If an IRB determines that a registry constitutes "human subjects research," the registry falls under IRB purview, and the IRB may determine that informed consent is required of registry participants, or it may grant a waiver of informed consent.

Case Example 57. Clarifying the Federal regulatory requirements for quality improvement registries (continued)

Challenge (continued)

Whether an IRB determines a registry to be "health care operations" or "human subjects research" can have profound operational and analytic impacts on the registry. In particular, QI registries designated by an IRB as research and required to collect informed consent from participants can experience a reduction in enrollment numbers, and are exposed to the risk of selection bias being introduced into the registry population.

The registry was introduced to neurosurgical practice sites in January 2011, and was initially reviewed by 11 IRBs over a 4-month period. Six of those evaluations resulted in classifications of the registry as quality improvement (QI). The remaining five IRBs classified the same project description as human subjects research, and insisted on full IRB oversight and the requirement for informed consent.

Proposed Solution

Given this mixed interpretation of Federal regulations from local IRBs, the AANS approached the Department of Health and Human Services' (HHS) Office of Human Research Protections (OHRP) in May 2011 to request a formal review of the registry. AANS and OHRP engaged in regular communication over the course of several months, and convened a multistakeholder meeting at the White House that included representatives from OHRP, the Office of the President, Centers for Medicare and Medicaid Services, U.S. Food and Drug Administration, Department of Veterans Affairs, HHS Office of Civil Rights, and three clinical specialty societies, including neurosurgery.

Results

In August 2011, OHRP clarified that, based on these communications and an examination of the registry, the sites participating in N^2QOD were not engaged in human subjects research, and therefore the regulations requiring IRB oversight did not apply. This communication from OHRP is now provided to sites enrolling in N^2QOD to support their IRB review process.

At the time of this writing, 28 IRBs have formally reviewed or re-reviewed the registry. To date, 27 of the IRBs have classified it as health care operations and have waived the requirement for IRB review. The remaining IRB has classified the same project description as research, and has issued a waiver of consent for the project. Approximately 30 additional sites are still in various stages of institutional review. In summary, the OHRP opinion strongly influenced local IRB analyses of the registry.

In July 2011, OHRP released an Advanced Notice of Proposed Rulemaking (ANPRM) for Revision to the Common Rule. These revisions are intended to improve human subject research while also reducing burdens, delays, and ambiguity for investigators and research subjects.

Key Point

QI registries that are focused on patient outcomes should be aware of the complexities around varied interpretation by multiple IRBs and should plan sufficient time and resources to address these complexities.

For More Information

http://www.neuropoint.org

Department of Health and Human Services. Office of Human Research Protections. "ANPRM for Revision to Common Rule." http://www.hhs.gov/ohrp/humansubjects/anprm2011page.html. Accessed 20 June 20, 2012.

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Chapter 23. Registries for Medical Devices

1. Introduction

Medical device registries are critical for the identification and study of medical devices outcomes. Device registries are used for many purposes, including short- and long-term surveillance, fulfillment of postmarket observational study commitments for regulatory bodies, and comparative safety and effectiveness assessments, including those in under-studied subpopulations. (See Chapter 1 for extensive discussion on the definition and purposes of registries in general.) Medical device registries play an increasingly important role in bridging the gap between device performance in clinical trials and their use in routine practice over time. Unlike clinical trials, device registries allow assessment of medical device performance in a real-world setting. Registries contain data on large numbers of patients receiving care in diverse clinical settings and include clinical outcomes over time, thus providing a critical platform for capturing the experience with a medical device throughout the device and patient lifecycle. Moreover, by linking device exposures and long-term outcomes, registries permit followup that can span decades.

While devices share some similarities with drugs, several major issues unique to devices require special consideration in order to construct and use a medical device registry successfully. Outcomes associated with medical devices can be affected not only by underlying patient factors and device factors (such as biomaterials), but also by user interface (e.g., surgical technique or surgical preference and experience) and ancillary technologies (e.g., choice of imaging). Adverse effects of devices can be localized (e.g., stent thrombosis), but may be more systemic (e.g., toxic, allergic, autoimmune effects). Furthermore, additional hazards may be related to human factor errors such as poor design or adverse interactions (e.g., drug-device or electromagnetic interference). Finally, reasons for device malfunctions may be very diverse, ranging from manufacturing problems and design-induced errors to environmental factors (e.g., humidity) and poor maintenance. Also, although certain malfunctions or device performance issues may appear to be similar, their root cause may vary.

Special challenges related to registry design, data collection, and analysis include the need for unique identification of devices, including device modifications and device components; information on user interface (e.g., surgical technique); information on ancillary technology and therapies (e.g., drug exposures); detection of device performance issues; the need for followup; and the impact of health care provider experience and learning.

This chapter will address two topics related to medical device registries: challenges in design and data collection and potential uses of emerging technology. The chapter begins with a discussion of the major considerations that influence the design of device registries and the data that must be collected. Potential approaches to address a variety of design challenges are described. The chapter then discusses emerging technologies that will potentially allow integration of automated device data capture into registry data sets. Case Examples 58, 59, 60, and 61 offer descriptions of medical device registries.

2. Differences Between Drugs and Devices

Regulatory oversight of the approximately 1,700 marketed device types in the United States is achieved through the use of regulatory controls and a classification process to assure reasonable device safety and effectiveness. The U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health regulates a wide range of products. These are identified into classes I, II, and III, based on the level of control necessary to ensure the safety and effectiveness of the device and the intended use and indications for use of the device. The Total Product Life Cycle[1] follows

products from concept to obsolescence and incorporates post-approval and surveillance information, such as rare adverse events or issues within subpopulations, back into these new product generations. This useful framework establishes a solid baseline for understanding effectiveness and safety in devices.

Differences between drugs and devices persist throughout the Total Product Life Cycle. Drug modifications occur slowly, if at all, whereas device technologies often experience rapid and continuous changes over time, potentially driven by user feedback and involving the use of new materials and approaches.[2, 3] In addition, device performance is affected by factors beyond the device itself, such as operator skill and experience.[4]

3. Design and Data Collection Considerations

As with all registries, the primary purpose of a medical device registry will guide design options. Many factors related to registry design are similar to those discussed in Chapter 3, such as selection of a study design and sample size considerations. However, some distinctive features of a medical device registry require additional planning. It is critical that the registry is adaptable to various needs that arise during the lifecycle of device innovation. Some challenges include the lack of unique device identifiers, including model/version control and component identification; the need to adequately capture device malfunctions and failures; the need for longer followup; and the impact of provider experience, training, and choice of device. It is informative that some device registries have been developed from procedure registries, with the addition of device identification modules. In these cases, likely risks of device failures may be identified prior to consequential clinical signs and symptoms, allowing for device fixes before harms are experienced by the patient. This chapter will provide general suggestions for addressing these challenges, and although each device registry is unique and will require a solution appropriate for its specific purpose, general principles apply in many cases.

3.1 Device Identification

Currently, although Unique Device Identifiers (UDI) are available for some medical devices (in the form of GTIN or HIBC identifiers, which are numbers located under bar codes), they are not routinely captured in observational data sources like billing claims data or registries, as is the case with National Drug Codes, which permit universal drug identification. The inability to identify specific devices affects registry design and data collection and poses challenges for researchers and regulators. Compounding the problem is the fact that device modifications are frequent and part of the business model for manufacturing and innovation. Researchers may connect safety and effectiveness to a class/subset of devices, rather than to the device generally. Hence, it is critically important to identify an individual device accurately. Related challenges include the lack of standardized definitions and of attribute (descriptor) creation based on specific device product codes; difficulties in data collection, such as transmitting information from electronic medical records (EMR) to registries or automated data capture, such as those related to barcode scanning accuracy;[5] and hurdles in maintaining master product lists.

Based on a congressional mandate (Section 226 of the FDA Amendments Act of 2007 and Section 614 of the FDA Safety and Innovations Act), FDA recently issued a draft rule detailing the requirements of manufacturers to have UDIs for their products, and to have this requirement phased in over several years. This FDA initiative eventually will assist with many of the challenges posed by the current lack of standard identifiers for medical devices. In the meantime, several approaches may be used to capture identity in the absence of a UDI that is unique across all devices. For example, some devices have identifiers, such as catalogue, model, serial, and lot numbers, that are unique to a particular manufacturer's device. While these are not standardized and there may be several components from different manufacturers with similar catalogue or model numbers, these numbers can facilitate device identification and tracking when combined.

Thus, prior to full UDI adoption and implementation, researchers must be creative in collecting device information and taking advantage of UDI-like data to fill the gap created by the lack of identifiers. For example, the Society of Thoracic Surgeons Adult Cardiac Database developed a data collection form with an exhaustive list of various heart valve devices. This checklist enables registry participants to collect any information that could be relevant to their practice. Orthopedic registries worldwide are taking advantage of catalogue numbers and lot or serial numbers in order to classify and uniquely identify products. An inefficient but at times appropriate solution is to include device photos in the registry. This strategy is most applicable in settings with few devices on the market that have marked differences in design that can be captured with photographs.

3.2 Device Performance

Devices exhibit numerous types of performance issues, so that it is difficult to capture all potential performance issues, failure modes, and adverse events in a single device registry. The performance issues may be related to software, hardware, biomaterials, sterility, or other issues. Additionally, similar performance problems (e.g., pacemaker oversensing) could have various root causes, some of which may manifest clinically (e.g., breast implant rupture) while others may not. Importantly, although clinical trials may provide some knowledge of failure rates and timing, knowledge of the propensity of these failures to develop is limited during the registry design phase. Adverse-event reporting for device registries should follow the regulatory requirements for reporting.[6] Researchers should consider methods of adjudication and verification of issues with device performance during the design phase in order to ensure collection of all data elements needed to inform those discussions. It is also important to consider how potential performance issues will be detected for the particular device.

Automated surveillance within the registry is an advanced approach to identifying select performance issues with a device (i.e., those that manifest uniquely and clinically). When implemented correctly, it can permit real-time evaluation of performance issues within a large sample or population. Surveillance, however, is a complex endeavor, and standardized data elements and collection procedures are required, likely across multiple institutions or registries. There are several examples of successful registry implementation for surveillance in cardiovascular disease. The Data Extraction and Longitudinal Trend Analysis (DELTA) network study was the first computerized safety surveillance proof-of-concept study for cardiovascular medical devices. This multicenter prospective observational study was designed for safety evaluation of drug-eluting coronary stents, embolic protection devices, and vascular closure devices used during percutaneous coronary intervention.[7] The study facilitated aggregation of safety events across institutions by using standard data elements from the American College of Cardiology National Cardiovascular Data Registry (NCDR®).

3.3 Device Systems and Components

In many cases, the device of interest for a registry is either part of a larger system of devices or contains multiple components that are considered devices themselves. Issues around the lack of unique identifiers persist and are accompanied by the additional challenge of determining which component is responsible for the performance issues. Sometimes, FDA approves or clears device components separately. When a registry is designed to understand effectiveness and safety, and the device of interest is dependent on accompanying devices included in the same system, information on all components must ideally be captured in enough detail to assess how well the device of interest is functioning.

In some instances, FDA approves devices as full systems rather than singular components. Examples of this include implantable pacemakers, implantable cardioverter defibrillators, and hip and knee implants. In these cases, surgeons may “mix and match” multiple manufacturers or multiple brands into one system. Such mixing presents a data collection issue as well as an analytical challenge. Heterogeneous devices may need to be grouped together in order to perform analysis.

In addition to the actual device, some implantable devices require assistance from procedural devices, including other commodity devices or operative instruments, or ancillary devices, such as imaging equipment. In these cases, clinically relevant additional information should be collected. For example, in hernia repair, information on the method of mesh adhesion, such as staples, glue, or sutures, may need to be collected, as these adhesives could interact with a specific type of mesh and affect device performance. Researchers should consider the role of these factors and how they can be captured in the data collection process.

3.4 Drug/Device Combinations

Device/drug combinations have become increasingly common over the past decade. Because the development processes for drugs and devices differ, combination products face different challenges. For example, drug-eluting stents (DES) are an example of a product where the device, a bare-metal stent, has been enhanced by the addition of an immunosuppressant or mitotic inhibitor[8] and its elution polymer coating. In 2003, FDA approved the addition of drugs to stents for a subset of cardiac patients with uncomplicated coronary lesions.[9] In these patients, there was a decrease in coronary restenosis requiring repeat revascularization 9 months after stent implantation, compared with bare-metal stents. However, as the adoption rate of DES increased, the population of patients in which they were implanted changed—they tended be sicker patients. Moreover, stent thrombosis, a rare but serious adverse event, was higher in DES patients at 1 year compared with bare-metal stent patients.[10-12] Stent thrombosis represented a localized device failure mode with serious and unique clinical manifestations. In cases like this, registries are a critical tool for understanding the long-term safety and effectiveness of the technology.[13, 14] Special considerations in registry design include separate collection of concomitant drug dosing information and attention to the medications that the patient is taking during and post implantation in order to flag possible drug interactions. It is also important to prospectively collect concurrent medications that the patient is using over time, again in order to understand potential interactions.

3.5 Obtaining Sufficient Followup Information

Obtaining sufficient followup information and as complete as possible case ascertainment are issues for all studies, and many of these challenges are addressed in Chapters 3 and 10. However, long-term followup is a particular concern with implantable devices, as well as other products such as ablation and radiation therapy devices. Clinical trials have relatively short followup for implantable devices that are expected to stay in the body indefinitely or until replaced with a similar device. These devices are typically studied for less than 5 years premarket, but are intended to work for decades. While followup time in the initial period of implantation is useful, an indefinite followup registry imbedded within a clinical practice has the ability to answer questions concerning device safety and effectiveness over the full product lifecycle. Only a few registries have sufficient followup for endpoints of device performance, continuous effectiveness, and safety. One of the best examples is Australia's National Joint Replacement Registry,[15] which has followup of more than 10 years.

A unique challenge for device registries is that once a device is implanted, a patient does not have to return to the doctor if he or she does not have any issues, in contrast to a therapeutic situation in which patients return for prescription refills. As a result, collecting followup data both directly from patients and through the health care provider is a useful tool for patient retention. Loss to followup differentially for patients who do not experience complications is a risk, and underscores the importance of achieving reasonably complete followup on all patients through delivery settings well designed for continuity of care.[16] Long-term data on medical devices also can be obtained through linking registries with administrative billing data, electronic health records, or other clinically rich data sources, although data

limitations such as lack of test results or reasons for procedures may remain.

3.6 Provider Experience and Training

Provider experience and training can influence the selection of device, device performance, and patient outcomes, particularly for implantable devices. Surgeons generally have a preference in terms of selection of devices, and although sometimes this preference is based on clinical appropriateness, it also can be based on marketing or familiarity with a particular brand. Group purchasing organizations, cost, provider contracts, reimbursement, and other market forces may also influence selection and, in some of these cases, surgeons may not have a choice of device. Additionally, provider experience and surgical/procedural skill can greatly influence the effectiveness and safety of devices.[17]

Device-specific training is an important element of a medical device registry that is not an issue in a drug registry. Device premarket studies are typically smaller than drug studies. Post-approval, regulatory agencies are concerned about training program quality. Often, an observational study is required to formally evaluate the appropriateness of physician training. Regardless of whether regulators have mandated this type of study, they recommend integrating training information into data collection. The importance of this training varies based on device type. For example, physicians with experience using balloon-expandable or self-expanding stents may not need additional device-specific training to use a new carotid stent. In contrast, prior experience may not be translatable to use of a new percutaneous valve; in this case, specific training on the delivery technique required for that specific valve is important. The amount of training required to ensure safe application of a technology is often unclear.[9]

Experience-related factors also should be considered in analyses and training evaluation: practitioner annual volume; practitioner lifetime volume; facility volume; and facility characteristics such as academic teaching status. It is important to distinguish between these factors because each has a threshold effect. Some factors, particularly lifetime volume, have not been well documented or analyzed. For others, such as hospital volume and academic teaching status, relationships with complications, revision surgery, length of hospital stay, and mortality are well documented.[18-20] It is ideal to have training and volume information in the registry, but this may not always be realistic. If this is deemed critical, information needs to be collected on provider experience and training at registry initiation and supplemented if any training programs occur during the registry development.

Registry design teams should consider how provider training and learning curves can be handled during analysis. Particularly for devices with few qualified surgeons, clustering may be an issue in analysis. Sample size may need to increase, and statistical methods that account for clustering, such as generalized estimating equations, should be used. Adjustment by surgical volume, either on the hospital or provider level, might also be appropriate.[21] For example, some studies have shown that categories integrating both of these components as one adjustment variable (e.g., high-volume hospital and surgeon; high-volume hospital with low-volume surgeon; low-volume hospital with high-volume surgeon; both low volume) are useful.[22]

3.7 Summary of Design and Data Collection Considerations

Although device registries are similar to other registries operationally, the challenges outlined above are critical to consider during the registry design phase. Careful review of the unique features of medical device registries can result in high-quality, useful studies of device performance. Medical devices must be identified accurately and their attributes classified according to standard nomenclature. Minimum recommended identity variables include manufacturer, product name, lot number (where applicable), catalog number, serial number (where applicable and with appropriate consideration for protected health information), description of device, and device attributes. These implant characteristics can then be linked to

patient, surgeon, hospital, and procedural data along with outcomes of interest. For these reasons, diligence in information security is warranted when identity variables are being collected, and these data should not be included in limited data sets. (See Chapter 7 for a full discussion of the implications of collecting individually identifiable data within a patient registry.) Device identification and attribute classification require constant maintenance as new devices are introduced into the market. In the future, UDIs will significantly facilitate this process. A standard minimum data set targeted toward device registries would be useful to support strong registry designs and to facilitate linkages with other data sources.

The definition and validity of device performance issues is another important element. In developing a device registry, the modes of failures and definitions must be clearly defined. Pragmatic systems for outcome verification need to be in place. It is also crucial to track all device components in case a single component fails. Collecting information to track drug/device interactions is also critical. Finally, sufficient followup of patients must be established in order for registries to provide longitudinal outcomes.

4. Regulatory Uses and Considerations

FDA has for a long time been actively engaged in the use and development of registries for both pre- and postmarket assessments of device safety and effectiveness. For premarket considerations, device registries have: (1) provided data to support the development, design, and use of comparators (both concurrent and historical) in clinical trials (e.g., the National Heart, Lung, and Blood Institute's (NHLBI) Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS™], heart valves); (2) provided access to products (outside of IDE [investigational device exemption] trials) (e.g., PFO [patent foramen ovale] occluders); (3) enhanced safety assessments via broader analysis of adverse events (e.g., adhesion barriers); and (4) expedited approval of device modifications or labeling (e.g., intraocular lenses). Postmarket applications of device registries have included frequent use in FDA-mandated studies (e.g., drug-eluting coronary stents), use in enhanced passive surveillance efforts (e.g., INTERMACS; the Department of Veterans Affairs' Clinical Assessment, Reporting, and Tracking System for Cardiac Catherization [CART-CL]), use in exploratory efforts to expand FDA Sentinel capabilities, both in active surveillance and data source linkage (e.g., DELTA), and use in discretionary applied research as noted below.

Over time, various stakeholder communities have increased their efforts to foster the development of clinical registries as a valuable postmarket tool for capturing utilization of devices, identifying early signals, and studying postmarket performance of medical technology. Some of these efforts transformed what were primarily procedure registries into procedure/device registries for certain targeted devices of interest. Examples of longstanding collaborative efforts include those between FDA and professional society databases such as the American College of Cardiology NCDR.[23] This collaboration resulted in one of the largest observational studies on hemostasis devices using NCDR registry data.[24] In addition, FDA collaborated with Duke University and the Society of Thoracic Surgeons to study the outcomes of transmyocardial revascularization procedures using the Adult Cardiac Surgery Database.[25] More recently, the national multistakeholder community, including professional societies, FDA, and the Centers for Medicare and Medicaid Services, worked together to establish the first national transcatheter valve therapy (TVT) registry to capture transcathether aortic valve replacement therapies.[26] This effort aims to foster both pre- and postmarket uses for future TVT devices and indications. In the orthopedic arena, FDA led the development of the International Consortium of Orthopedic Registries to advance the methodological infrastructure for studying performance and clinical outcomes of orthopedic implants.[27]

FDA continues to foster the development of registries in key product areas. It also recognizes the need for a national perspective on device registry development that considers how best to:

(1) leverage existing experience and expertise; (2) establish common data elements across registries; (3) share evolving methodological tools; (4) enhance interoperability between standard electronic health records and registries; (5) create sustainable business models; and (6) adopt robust and transparent governance practices.

5. Potential Uses of Emerging Technology

Registries may soon be able to take advantage of emerging technology for data transmission. New technologies can enable medical devices to transmit data directly to electronic medical records and other patient management systems. Ultimately, this type of data may be sent directly to a patient registry, reducing the burden of data entry and increasing the timeliness of registry data.

These new technologies are currently at various stages of development. Automatic measurement and adjustment of programming to provide optimal settings is a potential area of innovation that would provide efficiencies in the use of pacemakers and other implantable devices. Feasibility for this has been demonstrated by the AUTOMATICITY registry, which aims to evaluate physicians' acceptance of automatic algorithms for ventricular capture, automatic sensing, and automatic optimization of sensor settings.[28, 29] The AUTOMATICITY team concluded that project team followup and avoidance of reprogramming due to the automated programming can increase effective use of hospital time and resources. This would be a useful technology for registries because all automated changes can be collected at one followup time point, rather than collecting each change ad hoc as it occurs.

Diagnostics for implantable devices are another area of technical improvement. Implantable devices, such as implantable cardioverter defibrillators, pacemakers, and cardiac resynchronization therapy devices, can track heart rate, heart rate variability, respiration rate, atrial tachyarrhythmia and ventricular tachyarrhythmia recurrence and duration, intrathoracic impedance, symptom markers, and patient activity.[30] This diagnostic information can be provided directly to EMRs and fed into registries, in many cases continuously. Although the clinical application of this capability is still being examined, the benefits in efficient, timely data capture are clear.

The fascinating pace of emerging medical technologies and information science applications are expected to further shape health care research. Further development and integration of device-based registries into the national postmarket infrastructure creates opportunities for novel methodology developments, harmonization, sharing, and combining of data.

6. Summary

Medical device registries can be designed for a variety of purposes. They can provide useful information on long-term effectiveness and safety of devices, as well as the impact of factors such as surgical technique, surgeon, hospital, and patient characteristics. Like all observational studies, medical device registries have some limitations. Failure to control for often complex confounding variables and the inability to take into account device version changes, surgical technique, and other unique factors can lead to erroneous conclusions. However, design and analysis of medical device registries can often provide critical information for decisionmaking by regulators, clinicians, patients, and policymakers.

Case Examples for Chapter 23

Case Example 58. Designing a registry to study the effectiveness of a device training program for providers

Description	The Carotid Artery Stenting with Emboli Protection Surveillance Post-Marketing Study (CASES-PMS) was designed to assess the outcomes of carotid artery stent procedures for the treatment of obstructive artery disease during real-world use. The primary purpose of the registry was to evaluate outcomes in the periapproval setting, including the use of a detailed training program for physicians not experienced in carotid artery stenting.
Sponsor	Cordis Corporation
Year Started	2004
Year Ended	2006
No. of Sites	74
No. of Patients	1,493

Challenge

In 2004, the sponsor received approval for a carotid stent procedure from the U.S. Food and Drug Administration (FDA), largely because of the results of the Stenting and Angioplasty With Protection in Patients at HIgh Risk for Endarterectomy (SAPPHIRE) clinical trial. The SAPPHIRE trial studied the results of stent procedures performed by experts in the field. While the trial provided strong data to support the approval of the carotid stent, FDA and the Centers for Medicare & Medicaid Services (CMS) both questioned whether the outcomes of the trial were generalizable to procedures performed by physicians without prior experience in carotid artery stenting.

To respond to the FDA and CMS requests, the sponsor needed to design a study to confirm the safety and effectiveness of carotid artery stenting in a variety of settings. The study needed to gather data from academic and nonacademic settings, from physicians with various levels of carotid stenting experience, from settings with varying levels of carotid stenting volume, and from a geographically diverse mix of sites. The study would also need to examine the effectiveness of a training program that the sponsor had designed to teach physicians about the stenting procedure.

Proposed Solution

The sponsor designed a comprehensive training program for physicians and other health care professionals. The training program, which began in 2004, included didactic review, case observations and simulation training, and hands-on experience. Depending on their prior experience with carotid artery stenting, physicians received a 2-day in-person training plus online training; online training only; or no additional training. To study the effectiveness of the training program and to provide data on the clinical safety and effectiveness of carotid stenting in a variety of settings, the sponsor designed and launched the registry in 2004.

The registry was a multicenter, prospective, observational study designed to assess stenting outcomes in relation to the outcomes of the SAPPHIRE trial (the historic comparison group). The study enrolled 1,493 patients from 74 sites, using inclusion and exclusion criteria that matched those of the SAPPHIRE trial. The patients in the study were high-surgical-risk patients with de novo atherosclerotic or postendarterectomy restenotic obstructive lesions in native carotid arteries. Study participants completed clinical followups at 30 days and again at 1 year after the procedure. The 30-day assessments included a neurological examination by an independent neurologist and an evaluation of adverse events. The study defined the 30-day major adverse event rate as the 30-day composite of all deaths, myocardial infarctions, and strokes.

Case Example 58. Designing a registry to study the effectiveness of a device training program for providers (continued)

Results

The 30-day major adverse event rate of 5.0 percent met the criteria for noninferiority to the outcomes of stented patients from the pivotal SAPPHIRE trial. Outcomes were similar across levels of physician experience, carotid stent volume, geographic location, and presence/absence of the training program. The initial findings show that a comprehensive, formal training program in carotid stenting enables physicians from multiple specialties with varying levels of experience in carotid stenting to achieve outcomes similar to those achieved by the experts in the clinical trial.

Key Point

An observational registry can provide the necessary data for a postmarket evaluation of devices that are dependent on newly acquired skills. The registry can provide data to assess both the clinical safety of the device and the effectiveness and success of a training program.

For More Information

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Yadav JS, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med. 2004;351:1493–501.

Case Example 59. Identifying and responding to adverse events found in a registry database

Description	The Kaiser Permanente National Total Joint Replacement Registry (TJRR) was developed by orthopedic surgeons to improve patient safety and quality and to support research activities. The TJRR tracks all Kaiser Foundation Health Plan members undergoing elective primary and revision total knee and hip replacement. The purposes of the registry are to (1) monitor revision, failure, and rates of key complications; (2) identify patients at risk for complications and failures; (3) identify the most effective techniques and implant devices; (4) track implant usage; and (5) monitor and support implant recalls and advisories in cooperation with the U.S. Food and Drug Administration. The TJRR uses an electronic medical record (EMR) system to collect uniform data at the point of care. Data are abstracted from the EMR to the registry, and followup data are collected through several methods.
Sponsor	Kaiser Foundation Health Plan
Year Started	2001
Year Ended	Ongoing
No. of Sites	350 surgeons at 50 medical centers
No. of Patients	140,000 total joint replacements

Challenge

The registry collects standardized total joint preoperative, operative, and postoperative data to supplement administrative data collected through the EMR. The registry database includes information on patient demographics, implant characteristics, surgical techniques, and outcomes. As a result, the registry provides opportunities for total joint replacement surveillance and monitoring, but the depth and breadth of the data make manual data reviews for adverse events (AEs) too resource intensive and time consuming.

Proposed Solution

Electronic screening algorithms were developed to detect AEs in the registry database in a timely, efficient manner. The algorithms use ICD-9 codes and CPT codes to identify complications of joint replacement surgery, such as revisions, reoperations, infection, and pulmonary embolism. All complications picked up by the screening algorithms are validated with a chart review. The screening algorithms are run and the results monitored on a regular basis to identify trends.

The registry can also run specific queries to respond to physician concerns. For example, if physicians at participating medical centers notice a problem with an implant or hear about a problem from colleagues, they can request an ad hoc query of the registry database. The query can identify all patients receiving a particular implant and assess outcomes. When the outcome of interest is not part of the registry database, the registry staff may perform additional followup through chart review. The staff may also check the U.S. Food and Drug Administration's Medical Product Surveillance Network (MedSun) to validate their findings against other data sources.

Case Example 59. Identifying and responding to adverse events found in a registry database (continued)

Proposed Solution (continued)

Once an implant has been recalled or when there is an advisory or concern, the registry can immediately generate a list of all patients who received that implant and notify their physicians. The registry can also identify complications and assess revision rates among its patients who received that implant. Registry staff continue to monitor outcomes of patients who undergo revision surgery, until the patient dies or is lost to followup.

Results

Since its launch in 2001, the registry has assisted participating physicians with their responses to several implant recalls and advisories. Data from the registry were used to identify surgical techniques that resulted in higher revision rates. The registry staff shared this information with physicians, resulting in reduced use of these techniques.

Key Point

Electronic screening algorithms offer an efficient method of identifying potential AEs in large data sets in a timely manner. For such algorithms to be effective, the registry database must collect detailed information on the implants' lots and catalog numbers, and must be updated frequently as new and modified products become available. In addition, when using medical codes, it is important to validate the results of the screening algorithm to ensure that coding errors have not affected the findings.

Case Example 60. Receiving data from medical imaging devices

Description	The Dose Index Registry collects data on radiation doses administered during computed tomography (CT) examinations. Facilities can compare their average radiation dose for a particular examination (e.g., CT head examination) to that of similar facilities and to the national average. Such comparisons help facilities identify examinations for which their dose indices may be higher than others and adjust their protocols accordingly. Because it does not collect patient outcomes, the registry is considered a registration registry rather than a patient registry. The example is presented to illustrate the ability to use medical devices to report information directly to registries or other databases.
Sponsor	American College of Radiology
Year Started	2011
Year Ended	Ongoing
No. of Sites	Over 200
No. of Patients	Over 1,000,000 CT examinations

Challenge

Safety concerns over the effects of ionizing radiation exposure from diagnostic imaging have been described in numerous publications and summarized in a Joint Commission Sentinel Event Alert posted August 24, 2011 (Issue 47). To address some of these concerns, the American College of Cardiology established the Dose Index Registry to collect and compare data on radiation doses administered during CT examinations. For the data collection system to be a viable tool for participating facilities, it was imperative that the data be collected without interrupting the workflow at the facility (i.e., without adding additional workload for the CT technologist). The biggest challenge facing the registry was to automate and standardize the collection of dose information provided by several CT manufacturers in a variety of formats.

Proposed Solution

The sponsor worked with the organization Integrating the Healthcare Enterprise to develop the Radiation Exposure Monitoring (REM) profile. This profile describes the way dose information should be transmitted across different health care settings and specifies that information should be transmitted to a registry in the form of a Radiation Dose Structured Report (RDSR). However, only the most recent versions of CT scanner models and software support RDSR. In order to accept dose information provided by older scanners, the registry developed software that could convert the data into the RDSR format. The software that collects dose information also removes patient identifiers before sending data to the registry.

The second hurdle in standardization was the development of a common nomenclature for CT examinations. Different names are used for the same examination both within and among imaging facilities, and the registry needed a standard terminology for meaningful reporting. While it would have been possible to develop a new standard, the registry was aware of other lexicons under development, such as the Radlex Playbook. Conversations between the registry and the Radlex Playbook developers allowed the two groups to understand and meet each other's needs, and the registry was able to adopt the Radlex Playbook as the standard terminology for exam names. For facilities that submit data using non-standard terminology, these terms are mapped to Radlex Playbook terminology using a mapping tool developed by the registry.

Case Example 60. Receiving data from medical imaging devices (continued)

Results

To date, the data collection system has collected information related to CT radiation dose from over 200 facilities nationwide and has collected dose information from over 1,000,000 CT examinations. In addition to allowing comparison of dose indices between facilities, data collected from the registry will also be used to establish national benchmarks for CT dose indices.

Key Point

While not a patient registry, this example demonstrates that registries that collect information from medical devices may be able to reduce data entry burden by incorporating data transmitted directly from the device. When considering this option, registries may benefit from communicating with industry to find solutions that are not manufacturer specific and that can be implemented within a reasonable timeframe. Registries may also benefit from working with existing standards to determine if they can be modified to fit the registry's use case.

For More Information

http://nrdr.acr.org

Case Example 61. Combining registry data with EHR data to measure real-world outcomes of implantable devices

Description	Members of the Cardiovascular Research Network (CVRN) are conducting a longitudinal study of the characteristics, clinical outcomes, resource utilization, and costs among "real-world" patients receiving implantable cardioverter defibrillators(ICDs) for primary prevention of sudden cardiac death.
Sponsors	National Heart, Lung, and Blood Institute (NHLBI), Agency for Healthcare Research and Quality (AHRQ), American College of Cardiology Foundation, Heart Rhythm Society
Year Started	2009
Year Ended	Ongoing (planned completion of outcome ascertainment in 2013)
No. of Sites	Seven health care systems, with 15 participating hospital partners
No. of Patients	3,600

Challenge

ICDs have revolutionized the approach to treatment for hundreds of thousands of patients in the United States with left ventricular systolic dysfunction who are at risk for sudden cardiac death. Despite broadened indications for ICD therapy, use varies across patient subgroups. Most existing data on complication rates, mortality, morbidity, and cost of primary prevention ICD therapy come from clinical trial samples, which enroll subjects who may not be representative of patients cared for in routine practice. Baseline data on patients and devices are available in the National Cardiovascular Data Registry's (NCDR) ICD Registry, but longitudinal outcomes are not routinely included in the registry system. Evaluation of longitudinal, real-world data is needed, but following large groups of patients in community care settings can present logistical challenges.

Proposed Solution

CVRN is a national research collaborative funded by NHLBI that leverages expertise, populations, and data sources from a consortium of 14 health plans in the United States. Seven sites in the CVRN are sponsored by NHLBI, AHRQ, the American College of Cardiology Foundation, and the Heart Rhythm Society to conduct a longitudinal study of patients receiving ICDs for primary prevention of sudden cardiac death. The aims of the study are to (1) evaluate the extent to which patients receiving ICDs for primary prevention meet guideline-based eligibility

Case Example 61. Combining registry data with EHR data to measure real-world outcomes of implantable devices (continued)

Proposed Solution (continued)

case criteria; (2) assess longitudinal outcomes, including complications, hospitalization, mortality, and delivery of device therapies among primary prevention ICD patients; and (3) identify the characteristics associated with these outcomes in real-world community practice. To achieve these goals, the study developed a new database, which links a national device registry with information from health system medical records archived in electronic and other forms.

Baseline information is obtained from the NCDR ICD Registry, which captures national data on primary-prevention ICD implants for Medicare beneficiaries, although most participating hospitals, including the study facilities, submit data to the registry for all ICD recipients regardless of insurance status. Clinical and administrative followup data for three years post-implant are collected through the electronic health record (EHR) systems of the health plans participating in the CVRN. Finally, a new repository of arrhythmic episodes treated by ICD is being generated through review and abstraction of archived device followup records at the study sites.

ICD patients have periodic followup visits which include downloading data from their devices; this data can include the number and type of arrhythmic episodes detected by the device since the last check, what therapy (e.g., shock) was administered by the device, and the outcome of that therapy. The health systems download the device data from patients during an office visit or via remote transmission over the telephone. The device followup data are then incorporated into the health system medical record archives. Since the study includes devices from a variety of manufacturers and includes device followup records in a variety of formats, study staff have created a standardized format for collecting therapy data so they can be adjudicated and analyzed. All three data sources are then combined into a single analytic data set for addressing the study's specific aims, using a unique subject identifier to link all data elements together for the same subject.

Results

The study includes 3,600 subjects with primary-prevention ICDs implanted from 2006 through 2010. Data collection began in 2009. A report on the study methods and the baseline characteristics of the study population has been published, demonstrating that important demographic and clinical characteristics of patients receiving ICDs in real-world clinical practice are significantly different from the population enrolled in the landmark clinical trials conducted on ICDs in the early 2000s.

Key Point

Existing registries and EHR data can be valuable data sources for measuring the long-term outcomes of devices in real-world settings. This is especially true for implantable devices, where data may be downloaded automatically from the device to an EHR system.

For More Information

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Chapter 24. Public-Private Partnerships

1. Introduction

As both government and private groups have shown increased interest in patient registries, public-private partnerships (PPPs) have become more common as a means to develop and support patient registries and data linkage projects. These types of partnerships may become more common, as recent legislative actions have suggested PPPs as a potential approach to registry development.[1] More information is needed on what types of public-private partnerships are possible, what issues should be considered when using such a partnership to develop or support a registry, and what characteristics and practices are likely to enhance the success of such efforts. This chapter defines PPPs in the context of patient registries, provides examples of existing PPPs, discusses considerations for setting up and operating PPPs, and reviews key factors for successful partnerships. While the discussion in this chapter focuses primarily on PPPs within the United States, some considerations for international partnerships are also reviewed. Case Examples 62, 63, and 64 offer descriptions of PPPs for registries.

2. Definition of a Public-Private Partnership

"Public-private partnership" is a broad term that refers to any partnership in which at least one entity is a public agency (e.g., a government entity) and at least one other entity is a private organization. The scope can range from partnerships at the local level, including local and regional health agencies, to national and international health agencies and other private institutions or organizations (e.g., professional associations, patient advocacy groups). In a research context, a partnership implies some joint collaboration to achieve a common scientific goal. Partners may contribute intellectual capital, funding, data, or other services.

3. PPP Models

PPPs may take many forms. Some possible models include partnerships among Federal agencies to examine safety and effectiveness (e.g., INTERMACS™); partnerships among health agencies from several countries on an international level to describe the clinical course of a disease and understand whether there are any effective treatments (e.g., Avian Flu Registry); partnerships with State agencies for quality improvement (e.g., Get With The Guidelines®); and partnerships for evidence development for coverage decisions (e.g., Centers for Medicare and Medicaid Services). These models are described below, as case studies.

3.1 INTERMACS

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is the U.S. national registry for patients who have received durable, U.S. Food and Drug Administration (FDA)-approved mechanical circulatory support device (MCSD) therapy to treat advanced heart failure. This registry was devised as a joint effort of the National Heart, Lung, and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the FDA, clinicians, scientists, and industry representatives. The goals of the registry are to—

- Facilitate the refinement of patient selection to maximize outcomes with current and new device options;
- Identify predictors of good outcomes as well as risk factors for adverse events after device implantation;
- Develop consensus "best practice" guidelines to improve clinical management by reducing short and long term complications of MCSD therapy; and
- Use registry information to guide clinical application and evolution of next generation devices.

A major challenge to INTERMACS was to create a registry with sufficient data quality, regulatory rigor, and sophistication to be able to achieve these goals. INTERMACS used the quality of a high-level clinical trial as its standard, realizing that it could never totally meet these standards but could emulate them as closely as possible in a structured, protocol-driven manner. See Table 24–1 for a listing of the regulatory, data quality, and scientific components of a clinical trial, and an indication of which of these components are contained in INTERMACS.

Table 24–1. Regulatory, data quality, and scientific components of a typical FDA clinical trial and INTERMACS[a]

	Typical FDA Clinical Trial	INTERMACS
DSMB	✓	✓
Informed consent	✓	✓
IRB approval	✓	✓
Data use agreement	✓	✓
Human subjects training	✓	✓
Information security	✓	✓
Active Web site	✓	✓
Protocol	✓	✓
CLIA certification	✓	✓
Adjudication	✓	
Local principal investigator certification	✓	✓
Data freezes	✓	✓
Audits	✓	✓
Complete enrollment	✓	✓
Complete data	✓	✓
AE definitions	✓	✓
Inclusion/exclusion	✓	✓
Nurse monitors	✓	✓
Site training	✓	✓
Site reports		✓
Standardized data sets	?	✓
Medical device reports to FDA	✓	✓
Mandatory data entry	✓	✓
Planned analyses	✓	✓
DAAP: research requests	?	✓
Annual meetings	✓	✓
Committees	✓	✓

AE = adverse events; CLIA = Clinical Laboratory Improvement Amendments; DAAP =Data Access. Analysis, and Publications Committee; DSMB = Data Safety Monitoring Board; FDA = U.S. Food and Drug Administration; IRB = Institutional Review Board.

[a]Copyright 2014 INTERMACS. Table reprinted with permission.

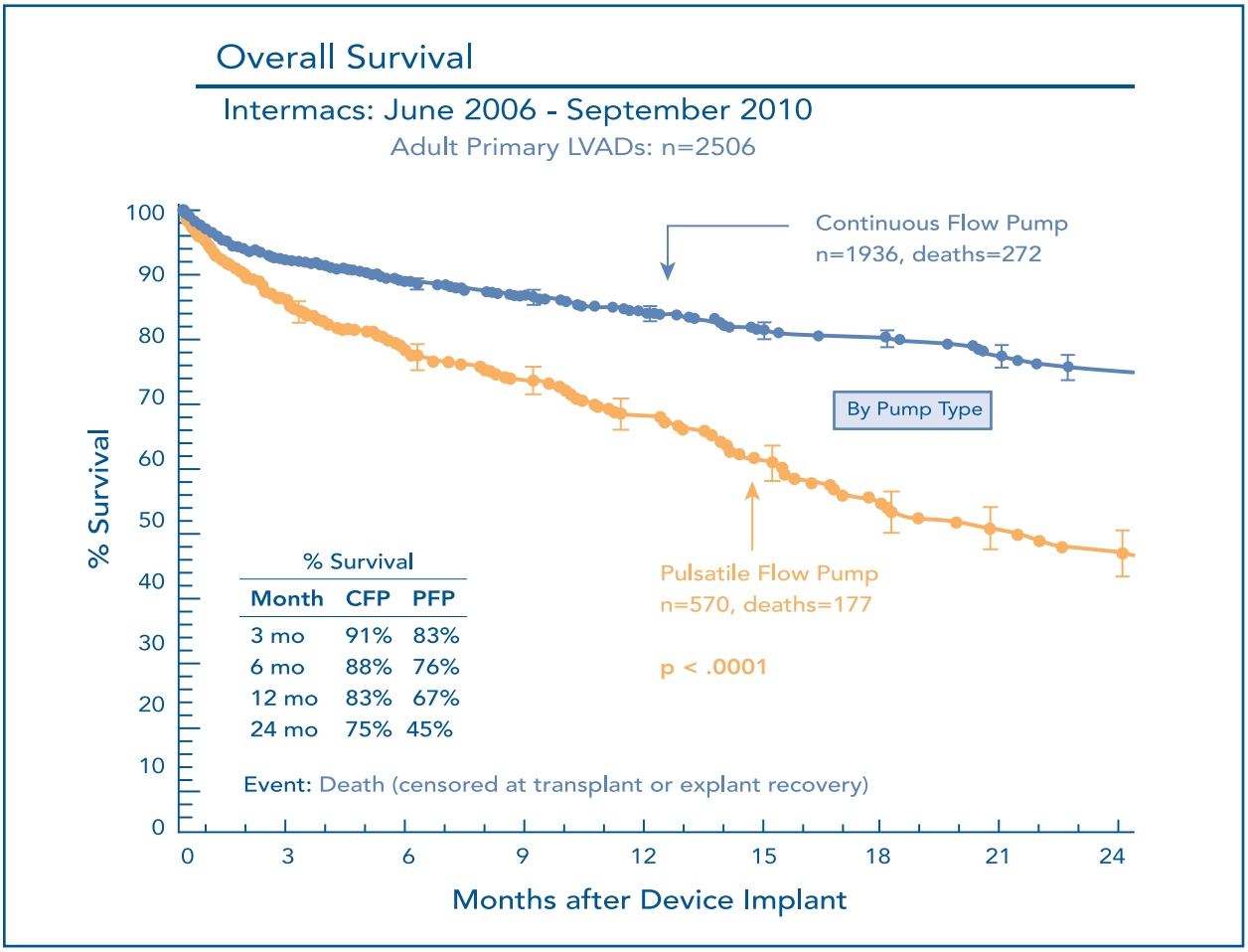
Another major challenge to INTERMACS is to maintain focus on its mission while many tangential efforts and registry "byproducts" have appeared. For example, INTERMACS has offered a new regulatory pathway for industry, as FDA approval is sought for new devices. It also has provided the control arm for one FDA pre–market-approval trial, and is in the process of providing control data for several ongoing and new trials. While these efforts were not part of the initial goals and contract deliverables of INTERMACS, they do, in general, fit its mission of moving the field forward.

In 2005, the original contract between NHLBI and the Division of Cardiothoracic Surgery at the University of Alabama at Birmingham specified a target enrollment of 40 to 60 hospitals. As of July 2011, 120 hospitals have enrolled and have entered data on more than 5,000 patients.

The complexity of managing a patient with a mechanical circulatory assist device requires a similarly complex registry. Implantation of a left ventricular device, a right ventricular device, and/or a total heart replacement device must be captured along with subsequent device explants, multiple adverse events, functional capacity, and quality of life. The INTERMACS clinical research forms are numerous and detailed, with more than 1,500 data elements.

A unique feature of INTERMACS is that it is assessing a rapidly changing clinical and technological field. INTERMACS must be poised to quickly assess newly approved devices and to quantify the evolution in patient selection. Figure 24–1 shows survival based on two types of devices. These devices correspond to eras, with the intracorporeal continuous flow pump being the most recently approved MCSD. The improvement in survival is dramatic, and INTERMACS has been the best way to quantify this improvement.

Figure 24–1. Overall survival of adult INTERMACS subjects receiving primary left ventricular assist devices, by pump type[b]



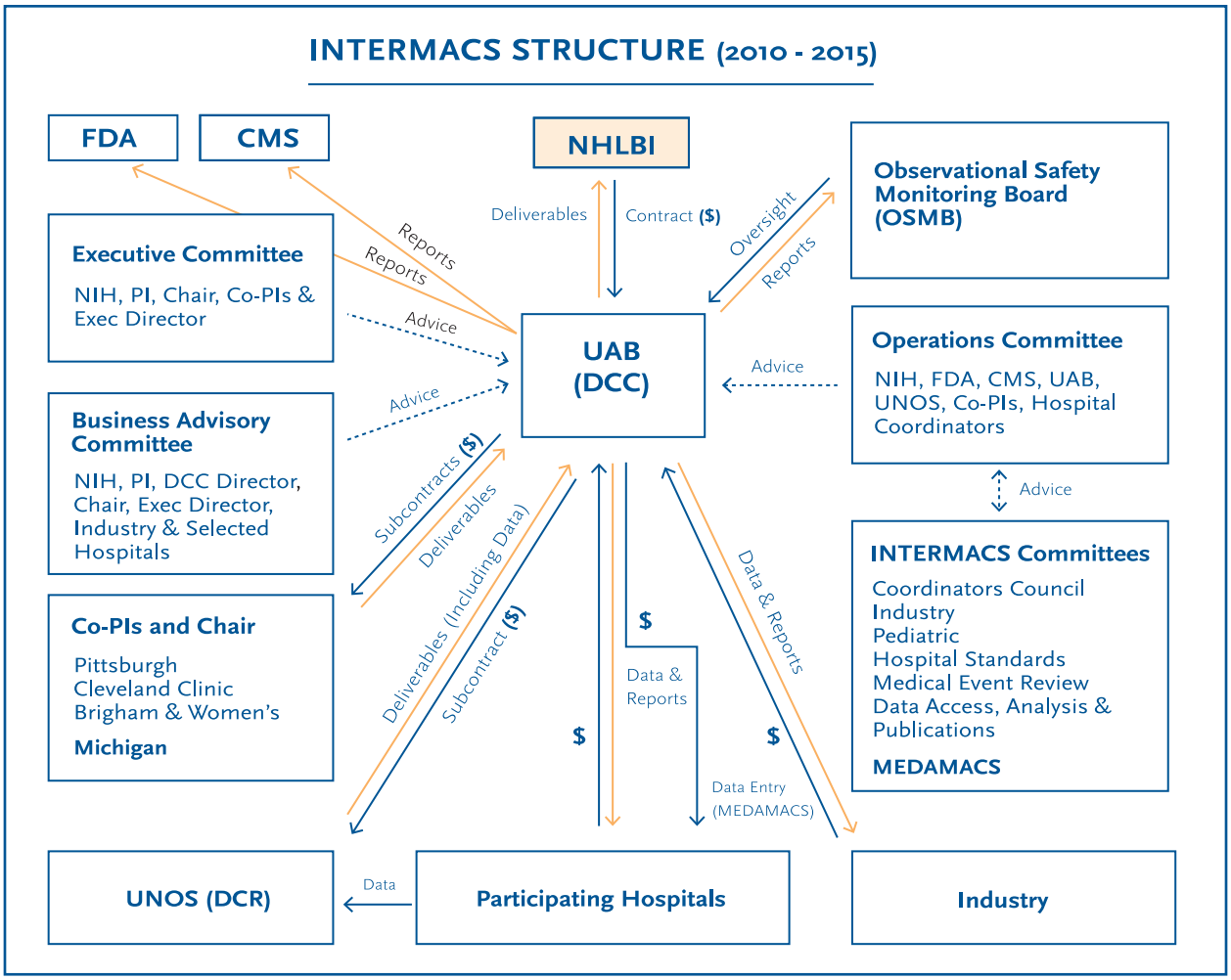
CFP = continuous flow pump; LVAD = left ventricular assist device; PFP = pulsatile flow pump

[b]Reprinted from the Journal of Heart and Lung Transplantation. Vol. 30, Kirklin J, Naftel D, Kormos R, et al. Annual Report: The evolution of destination therapy in the United States, Pages 115-123, Copyright 2011, with permission from Elsevier.

Initially, INTERMACS was the result of an NHLBI initiative in collaboration with FDA and CMS. Other stakeholders quickly joined in the planning stage, and they have continued to be INTERMACS partners. These multiple partners each have their own agenda and their own reasons for participating in INTERMACS. While their goals do not always align, there is considerable overlap, and INTERMACS has been able to fulfill most needs for each partner. At the intersection of these agendas are the common goals of assessing current devices and contributing to the development of new devices by analyzing registry data. The ultimate goal for all of the partners is to improve patient outcomes.

Figure 24–2 is a schematic representative of the partners involved in INTERMACS. The relationships are necessarily complex and must be managed by clear expectations, deliverables, standard operating procedures, and lines of authority.

Figure 24–2. Structure of INTERMACS partnerships[c]



CCD = Continuity of Care Document; CMS = Centers for Medicare and Medicaid Services; Co-PIs = Co-Principal Investigators; DCC = data coordinating center; EHR = Electronic Health Record; FDA = U.S. Food and Drug Administration; NHLBI = National Heart, Lung, and Blood Institute; NIH = National Institutes of Health; UAB = University of Alabama at Birmingham; UNOS = United Network for Organ Sharing.

[c]Copyright 2014 INTERMACS. Figure reprinted with permission.

3.1.1 Stakeholders

NHLBI. As the sponsoring agency, NHLBI is both the primary partner and primary regulator of the registry. In addition to its oversight role, NHLBI has been involved in many of the day-to-day activities of INTERMACS, including the important role of ensuring scientific and regulatory integrity and patient protection.

FDA. Through their regulatory role in approving and monitoring new devices, the FDA functions as the "gatekeeper" for devices. INTERMACS benefited from early interactions with FDA in developing the specifications of data elements and definitions of adverse events. As INTERMACS evolved, it worked with two separate components of FDA. The premarket personnel at the Center for Device and Radiological Health (CDRH) helped create a registry that would build on the previous premarket approval studies of MCSD. INTERMACS also worked with the postmarket approval personnel of CDRH to explore ways to facilitate the analyses of approved devices. The partnership with FDA has evolved as

INTERMACS has become a major postmarket study vehicle for approved MCSDs, as evidenced by the collaboration with Thoratec and FDA to perform the post-market studies for HeartMate II, the first FDA-approved adult non-pulsatile pump.

CMS. When INTERMACS began, CMS was reimbursing hospitals for FDA-approved MCSDs that were implanted as destination therapy (DT) at approved centers. One of the requirements of the reimbursement was that data on implanted patients be entered into a national database. By the third year of INTERMACS, CMS changed the requirement to explicitly specify INTERMACS as the data repository and stated that a certified DT center must be in good standing with INTERMACS. This partnership with CMS has been critical to the development of a comprehensive database that captures the vast majority of approved durable devices implanted as DT or as bridge-to-transplant therapy.

Joint Commission. The Joint Commission is responsible for certifying hospitals as DT centers. INTERMACS collaborates with CMS, The Joint Commission, and hospitals to assist in the quantitative summaries necessary for certification.

Industry. Essentially every company that manufactures approved MCSDs or is in the process of gaining approval for an MCSD has been involved with INTERMACS. Industry was "at the table" during the meetings to develop INTERMACS. Many companies saw great potential for using INTERMACS in both premarket clinical trials and postmarket studies. The FDA has encouraged companies to work with INTERMACS. Some of these activities fall outside of the strict deliverables of INTERMACS but do fall within its goals.

Hospital collaborators (physicians, surgeons, coordinators, administrators, and quality assurance officers). The scientific and clinical energy of INTERMACS comes from physicians who care for heart failure patients and surgeons who implant the devices. The hospitals, via their coordinators, provide the data that populates the registry. INTERMACS serves as an important resource for the hospitals in activities related to mechanical circulatory support. For example, hospitals can submit requests for scientific studies, obtain their own electronic data from INTERMACS, and participate in an INTERMACS forum (the Coordinators Council) for coordinator feedback and discussion of relevant mechanical circulatory support topics. INTERMACS provides quarterly reports to participating hospitals that summarize and analyze their patients and provide benchmarking against registrywide data. Patient-level reports that provide a chronological history of the patient's MCSD-related events are also available. These clinical summaries are an important tool in the data quality process.

Other entities. In addition to the formal partners of INTERMACS, a number of other entities have requested collaboration. These include regulatory bodies of foreign governments, scientific societies, foreign hospitals, insurance companies, investment firms, and the media. Each request for collaboration is handled on an individual basis and considered within the framework of the goals and regulatory structure of INTERMACS.

3.2 Avian Flu Registry

Highly pathogenic infectious diseases continue to emerge, with substantial public health and financial tolls. Three features of newly emerged communicable diseases are immediately salient to registry development and use:

- Communicable diseases do not respect international borders.
- Communicable diseases, by their very nature, usually constitute a significant public health threat.
- Emerging communicable diseases usually enjoy a high media profile and are the subject of significant interest to the public.

Consider the recent H1N1 influenza pandemic and SARS (severe acute respiratory syndrome) as examples. In addition, while many newly emerged infections first manifest themselves in exotic or tropical locations, this is not an invariable rule, as shown by the emergence of legionellosis in Philadelphia.

The facility with which communicable diseases are able to cross international borders means that they typically receive global attention, especially in our

current era of mass international travel and globalization of trade. The fact that newly emerged infections usually represent a threat to public health means governments and their agencies usually become involved in their investigation and management, typically at an early stage. Public concern, often fueled by the news media, may add to pressures on public health authorities to react and to be seen as reacting to newly emerged threats. As a consequence, entities wishing to investigate newly emerged infections will generally need to engage with public health authorities, typically at a national government level.

A prime example of such a collaboration is the Avian Flu Registry, set up to investigate infection with influenza A/H5N1, a disease with almost 90 percent mortality if untreated.[2, 3] The registry, which began in 2007, is a multicountry, observational study of the diagnosis, treatment, and outcomes of human cases of the A/H5N1 virus. Data are collected from health care professionals, and information abstracted from detailed, published case studies are also included. The registry has built a multinational, multicenter collaboration that houses the world's largest collection of human avian influenza cases and has made important contributions to the understanding of the treatment effectiveness for this highly lethal disease.[4, 5] Its success has been built upon recognition of the unique nature of emerging infections, recognition of the differing needs of developing countries and collaborators, and adoption of a flexible and pragmatic approach. Its success is also attributable at least in part to the establishment of successful collaborations with national public health agencies in a number of countries.

However, the establishment of such collaborations is not always a straightforward matter, especially when initiated by the private sector.[6] Newly emerged infections usually become politicized quite soon after their initial appearance. The classic example of this phenomenon is HIV, but SARS and pandemic influenza were also politicized rapidly after emergence. This politicization is seen in both economically developed democracies and developing countries. Further and deeper politicization may ensue when the newly emerged infection is viewed by afflicted countries as stigmatizing them in some way or is seen as a matter of national security; the response of some governments to avian flu exemplifies these types of responses. Similar reactions were seen in Indonesia with H5N1 and in China with the early stages of SARS. Developing countries may also be sensitive to the fact that their health care systems do not offer the same level of care as is available in developed countries. These countries may also lack developed disease surveillance systems and may feel uncomfortable at the exposure of this deficiency.

Considering these sensitivities, the establishment of registries to study newly emerged infections may require a different approach to that typically adopted in other disease areas. An understanding of local sensitivities and a willingness to attend to local needs and to answer local questions will be helpful. An avoidance of a "one size fits all" approach should also prove helpful, with flexibility to react to different countries in different ways being important. A useful guiding principle in the establishment of such multinational collaborations is to place the needs of the collaborator first, rather than the needs of the entity establishing the registry. While national public health authorities may well understand the altruistic nature of much global public health research, their constituencies remain local, and they are answerable to their local political masters and public. Working in this type of environment adds an additional layer of complexity, but one which has to be successfully navigated if success is desired.

The Avian Flu Registry provides a good example of these political issues and how they might be surmounted. A complaint frequently heard when approaching ministries of health for collaboration was that such previous efforts had yielded little or no benefit to the participating country, with little or no feedback once collaboration had been agreed and data entry completed. The Avian Flu Registry, from inception, took pains to ensure prompt feedback to collaborators of data analyses and registry findings and to respond to requests from collaborators for further analyses in a positive and timely manner.

The funding for the Avian Flu Registry came from a pharmaceutical company that had a marketed product for treatment of seasonal influenza. Since hardly any information was available about avian influenza, the registry sponsor wanted to learn more about the illness with an eye toward understanding if their product would be effective for this more lethal flu strain. While some may see primary funding from industry as a disadvantage, the apolitical nature of this funding may actually have been advantageous. The relationship between the funder and the scientists charged with building the registry was clearly established at the earliest stage of planning and documented in a clearly worded binding contract. It was in the interests of the industry sponsor to step back from operational issues, allowing the investigators to build an international collaboration with the sole purpose of understanding the disease, with the expectation this would be done as efficiently as possible and with findings to be shared with all participants.

In addition, the registry was created in its earliest stages to conform to principles of good practice for registry science, including formal ethical review, a steering committee, and various other governance structures that proved useful throughout the program. A complexity of the registry was its broad global reach, which included collaborators from 13 different countries. Regulations varied by country and by collaborator, but were in all instances compatible with the founding documents of the registry, as enshrined in the agreement between the industry funder and the investigators, and as presented to an independent ethics review board. A formal memorandum of understanding outlined all the key principles for data sharing, protection of privacy, ethical review, et cetera. Original documents guaranteed protection of the identity of individual reporting countries, a restriction that was later lifted by mutual agreement once it become apparent that country-specific factors like viral clade and barriers to access to care tempered treatment effectiveness. The Data Access and Publications Committee also proved to be useful by providing a formal mechanism for recording, reviewing, and prioritizing research questions that were posed to the registry.

3.3 Get With The Guidelines®

Get With The Guidelines® is a hospital-based quality improvement program operated by the American Heart Association. The program aims to improve in-hospital care for patients by providing tools to support adherence to clinical practice guidelines. Hospitals pay a fee to participate in the program, which involves collecting and submitting data on patients. The program uses the data to generate benchmarking reports and to provide real-time feedback on adherence to the clinical practice guidelines. The program has been successful at demonstrating sustained quality improvement at participating hospitals.[7]

State-level departments of health also have an interest in improving quality at hospitals within their State. However, the development of a comprehensive quality improvement program is often not feasible, given resource and staff constraints. In several cases, State departments of health partnered with the American Heart Association to sponsor hospitals in the Get With The Guidelines program. The State agencies paid the program fee for participating hospitals and, in return, received reports on hospital performance on a quarterly basis. Hospitals agreed to share their performance data, which the program would normally keep confidential, in return for receiving free access to the Get With The Guidelines program.

3.4 CMS Coverage With Evidence Development

In 2006, CMS issued a guidance titled "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development"[8] that presented a new option for CMS when determining whether a drug or device would be covered under Medicare or Medicaid. In addition to the existing possible decisions of "no change in current coverage," "non-coverage," and "coverage without special conditions," CMS could now grant "coverage with special conditions," in which:

"The medical evidence is adequate to conclude that the item or service is reasonable and necessary […] only under one or more of the following circumstances:

a. The item or service is covered only for patients with specific clinical or demographic characteristics.
b. The item or service is covered only when provided by physicians and/or facilities that meet specific criteria.
c. The item or service is covered only when specific data are submitted in addition to claims data to demonstrate that the item or service was provided as specified in the [national coverage determination]."[8]

Registries are particularly suited to this type of prospective data collection. This new Coverage with Evidence Development (CED) requirement spurred the creation of multi-stakeholder registries to facilitate data collection for drugs and devices receiving CMS coverage conditional on evidence development. In 2012, CMS published a draft guidance for the public, industry, and CMS staff on CED in the context of coverage decision, further clarifying best practices in an attempt to improve the application of CED.[9] Aside from CMS, which provides the incentive for the data collection, major partners in CED studies often include professional associations (which contribute scientific guidance) and industry (which contributes funding). Registries that have been created or adapted to meet CED requirements include the National Oncologic PET Registry for the use of positron emission tomography to treat certain types of cancers[10] and the ICD Registry for the use of implantable cardioverter defibrillators.[11]

4. Considerations for Setting Up a PPP

4.1 Governance

A public-private registry is, by definition, a collection of stakeholders who have different purposes and agendas that hopefully overlap at the intersection of clinical science and improved patient care The registry needs a central authority to keep it focused. Often, this authority is the principal investigator (PI), who oversees the registry and is responsible for developing consensus among stakeholders. The PI is also responsible for ensuring that the registry and the analyses of the registry data remain scientifically relevant and unbiased. The PI's scientific and operational oversight can be augmented by an Advisory Committee, which can include co-PIs and representatives from various partners in the registry (e.g., funding sources, reporting entities, or subcontractors that handle operational aspects of the registry).

4.2 Involving Patients

As with many other types of outcomes research, there is a growing trend to involve patients and patient advocacy groups in the planning and operation of patient registries. Working with patients brings certain unique considerations, and varying levels of patient involvement may be appropriate and/or feasible for different PPPs. For example, some diseases such as influenza A/H5N1 lack a cohesive patient population or advocacy group, because of the disease's rarity and high mortality rate. However, patients can offer valuable contributions to PPPs when it is feasible for them to do so, especially around such areas as user burden (e.g., when the registry is collecting patient-reported outcomes), registry feasibility, and training and support needs.

4.3 Operational Decisions

Many registries are complex in nature with operational components including regulatory, financial, informed consent, data entry software, progress reports, periodic meetings, and scientific analyses. These registries are essentially small businesses that require intense day-to-day operations that should be conducted as a well-structured effort. The structure of the registry efforts should be clear, with well-defined lines of authority and responsibility. The structure should also have the flexibility to adapt to changing science and the changing national landscape of regulatory requirements, such as the periodic updates to the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule.
A representative Operations Committee that meets regularly to review the ongoing progress of the

registry and to address issues as they arise may be desirable. This group can make decisions by consensus rather than a formal vote. Documentation (i.e., meeting minutes) should be created and distributed to memorialize decisions and actions taken.

4.3.1 Plans for Transparency and Communication

Transparency and ongoing communication are vital to the success of any complex registry, especially a PPP. An important vehicle for transparency can be a registry's public Web site, which can contain regulatory documents including the protocol and user's guide (see http://www.uab.edu/medicine/intermacs/). The public face of the Web site for the Avian Flu Registry contains the registry prospectus and information about data security, along with an updated list of published scientific articles and presentations (see https://www.avianfluregistry.org/), including many of the actual posters and slide sets for public viewing. Other options for engagement, transparency, and communication include periodic public stakeholder meetings, newsletters, and email listservs.

4.3.2 Dispute Resolution

Disagreements, or even disputes, are inevitable when a group of diverse stakeholders collaborate on a single registry. As with any complex endeavor, the key to symbiotic working relationships lies in the initial formulation of the goals and expectations of the registry and of each collaborator. The responsibility of mediation and dispute resolution can be assigned to a leader within the registry, such as a Study Chair or PI, or can be handled by committee, as in the Avian Flu Registry.

4.3.3 Data Security

The data contained in any registry must be managed according to strict rules for data security, which can include secure password-protected access to data entry, secure transmission of data, background checks on personnel, personnel training on data security, virus scans of all computers, and offsite backup of data. Anyone creating a new registry is strongly advised to collaborate with information security experts, who can lead the registry through the data security requirements and can create protocols for security breaches. Additional information on data management, data quality, and data security can be found in Chapter 11.

4.4 Data Ownership, Data Access, and Publications

As discussed in Chapter 7, ownership of registry data is a complex issue. In many registries, the registry sponsor owns the registry data. However, PPPs may have multiple sponsors and multiple stakeholders. Because of these complexities, it is important for the registry to specify clearly in registry partnership agreements and contracts who will have ownership rights to the registry data.

4.4.1 Data Access

A related question is who has access to the data. While some registries may rely on a scientific advisory board or other governing body to handle data access requests, PPPs should consider a formal Data Access and Publications Committee (DAPC). A formal DAPC can develop policies and manage requests for data access in a transparent, consistent way that is agreeable to all stakeholders. All data access should conform to HIPAA regulations, informed consent documents, and data use agreements between contributing sites and the registry. Many entities may request access to registry data, including some listed below:

- *Data provider or participating site*. Typically, the data use agreement between the site and the registry specifies that the site can request to receive all of its own data at any time, but may not request identified data from another site.
- *Registry sponsor*. The registry sponsor owns the data and therefore has complete access to all data. When the registry ends, the entire database is often transferred to the sponsor.
- *Regulatory agency (e.g., FDA, CMS)*. A government regulatory agency may request registry data to fulfill safety reporting requirements or other obligations. In particular, if a sponsor has a marketed product that is used by any patients in the registry, that sponsor is subject to mandatory safety reporting

requirements (see Chapter 12).

- *Industry*. Pharmaceutical companies or device manufacturers may request data of patients who receive their products, or may request registry data to use as controls for a clinical trial.
- *Investigators (within or outside the registry)*. Investigators may request registry data for a particular research project; each request should be reviewed by the DAPC so that only the necessary data elements for the research project are shared.
- *Public*. Although rare, data requests from the media or the public are possible. Any information released to the public by the registry (via newsletters, public Web site, or other methods) should be reviewed prior to release, to ensure that data confidentiality is not compromised.
- *Standardized data sets*. Some registries produce de-identified, standardized data sets that are available to researchers on a periodic basis. These data sets contain no protected health information, no product or treatment brand names, and no site identifiers, and they are often constructed to provide the information believed to be most helpful to researchers. The actual content of these standardized data sets and the policy for distribution should be governed by the DAPC, with approval by the registry sponsor.

4.4.2 Process for Publications

As noted above, PPPs may find it particularly useful to form a DAPC to prioritize research projects and handle data access requests. The committee should meet regularly to formally review, prioritize, and evaluate the requests based on the potential impact on clinical practice and the amount of data available to answer the research question. The DAPC can also work directly with an advisory or operations committee to identify and facilitate internal research projects that directly address the stated research goals of the registry.

4.4.3 Process for Analyses

Depending on available resources, a registry can either conduct analyses to support publications in-house, contract with an outside agency to conduct analyses, or leave this task to the data requestors themselves. If an outside agency or data requestor will be conducting analysis on registry data, a secure mechanism should be in place for sending the data to them. The DAPC should retain oversight of these activities, especially those that are intended to be used for manuscripts submitted to peer-reviewed publications.

4.4.4 Formal Documentation of Roles and Responsibilities

Whether a registry resembles a traditional PPP (i.e., a group of stakeholders who come together to create and fund a registry) or a more unusual structure (i.e., a series of contracts and subcontracts that have precise deliverables), each entity is a collaborator in the sense that each partner provides something to the registry and receives something from the registry. For example, each hospital participating in INTERMACS provides the local effort for participation and data entry. The hospital also pays $10,000 per year for participation. In return, the hospital receives many deliverables and benefits such as quarterly quality assurance reports, clinical summaries on each patient, electronic copies of their data, participation in research projects, and representation on the INTERMACS committees.

Because each entity may have numerous functions within a registry, it is important that roles and responsibilities be clearly defined and documented at the beginning of the registry. An operations committee can be charged with producing the roles and responsibilities document and updating it periodically as needed.

4.5 Funding

Registries can obtain their funding from a variety of sources. For example, INTERMACS was initially funded by a contract from NHLBI. During its second 5-year contract (December 2010–November 2015), NHLBI asked the University of Alabama at Birmingham to develop a cost-sharing plan that would allow NHLBI to significantly

decrease their contribution while obtaining funding from private sources. The primary goal of this new arrangement was to obtain the necessary ongoing funding in order to achieve sustainability. This transition in funding is not unique to INTERMACS. Changes in funding are particularly common in PPPs, where funding often comes from multiple sources. When funding sources change, it is often necessary to revisit the roles and responsibilities and data access policies to ensure that all stakeholders are represented appropriately.

4.6 Ethics

4.6.1 Conflicts of Interest

Because of the variety of stakeholders involved, a plan for identifying and managing actual and perceived conflicts of interest (COI) is essential. In this context, COIs can be financial or intellectual. The plan should clearly spell out the timeline and process for obtaining completed COI and financial disclosure forms from participating members and for reviewing and managing any potential conflicts, particularly given any unique working relationships with the Federal government, academic institutions, or industry. The plan should also define what constitutes a problematic COI, and this definition should be reviewed on a periodic basis and revised if needed. It is suggested that the PI, co-PIs, study chair, operations and steering committee members, subcommittee members, and individuals named on the contract (including subcontractors and their staff) be required to complete annual COI forms. Once collected, the forms can be reviewed by registry staff and any conflicts forwarded to the operations committee for review. Any individuals that have a financial disclosure identified through the COI review process should declare it prior to participation in any scientific meetings, government meetings, presentations at sites, registry annual meetings, steering committee meetings, et cetera.

4.6.2 Informed Consent

The informed consent documents are key elements in determining the unique relationship between a patient's medical information and the ultimate use of this information in achieving the goals of the registry. The document must contain an explicit description of who will see what data and how confidentiality will be maintained. For registries with many partners as is common with PPPs, it is desirable to have a common informed consent form. This document can be combined with a HIPAA authorization to use or disclose protected health information for registry purposes. (See Chapter 7 for additional information on HIPAA authorization requirements.) If a common form is not used, the reasons for the different forms should be documented and transparent to all key parties. The data coordinating center for INTERMACS created an informed consent template in collaboration with NHLBI that contains the necessary elements as determined by NHLBI and the institutional review board at the data coordinating center. Chapter 8 discusses informed consent in detail.

5. Evolution of PPPs

Registries that are PPPs may undergo many changes over their lifetime. The registry goals and roles of stakeholders may change, and new stakeholders may become involved. A registry not initially set up as a PPP may later evolve into one. The general topic of registry transitions is covered in Chapter 14, but there are several changes and transitions that are unique to PPPs.

For example, INTERMACS began as a collaboration between NHLBI, FDA, and CMS. The other partners currently involved in INTERMACS (and shown in Figure 24–2) joined later, and each brought their own agenda and goals for the registry. As these new partners joined, INTERMACS had to evaluate the many different goals they brought to the table, identify areas of overlap, and determine how INTERMACS could meet the needs of each partner while remaining focused on the ultimate goal of the registry: to improve patient outcomes.

Sometimes a registry is not initially organized as a PPP but later evolves into one. This often happens when potential stakeholders do not see the value of being involved in a registry in the beginning stages, particularly when the registry has not yet published any results or provided proof of concept.

In these situations, it is incumbent on the registry originators to operate the registry and produce results that will entice stakeholders to participate. For example, the Avian Flu Registry (funded by industry and operated by a private contract research organization) found much more success in partnering with international ministries of health after the Registry published its results in peer-reviewed journals and presented abstracts at well-known scientific conferences. Similarly, Get With The Guidelines was able to partner with State-level health departments only after consistently demonstrating its success in improving patient quality of care.

6. Considerations for Managing a PPP

6.1 Stakeholder Engagement

Once a PPP has been established, it becomes critical to focus on proper management of the project. Major stakeholders may be involved, including clinicians, payers, patients/consumers, Federal agencies, and industry/manufacturers. Inclusion of varying perspectives ensures balance, yet decisionmakers from different sectors may have conflicting priorities. Engaging each of these groups with the common goal of improving health care quality and patient outcomes through sharing of data and other resources is vital to the achievement of the partnership. Such collaborations have occurred successfully in several industries where no single entity had the resources or expertise to drive an entire field.[12, 13] Eliciting trust among decisionmakers combined with advice and/or participation from reputable associations are valuable incentives for maintaining the interest and engagement of collaborators.[14-16] Successful collaborations satisfy the needs of multiple stakeholders, providing immediate value and long-term returns, while driving innovation and efficient productivity and leading to the development of best practices.

It is also vitally important to set appropriate expectations for the participation of each group within the partnership. The utility of preproject meetings involving discussion of priorities and policies that will govern the collaborative efforts cannot be overemphasized.[17, 18] Roles and responsibilities must be clearly defined and mutually agreed upon so that all stakeholders benefit equally.[19] Evaluation of the available literature may reveal which practices have worked for other partnerships. Establishing guidelines that dictate partnership activities, including conflict of interest procedures, will allow accountability.[16, 19] Identifying a PI with strong leadership skills, a project manager to drive timelines, and other properly trained team members will ensure successful execution of project goals.[14] Establishing agreement between participating groups on the time commitments required of them from the beginning will help set appropriate expectations. Resources that increase ease of communication and minimize time commitments, such as shared Web sites or databases,[14] can speed development and improve participation. Although the importance of timelines is paramount, the ability to be flexible is also important in the changing landscape of health care policies and for PPPs that add partners and collaborators and adapt over time.[20]

6.2 Communication

Communication tools for generating and maintaining interest among stakeholders and participants are beneficial when used effectively. Initiation of interactive workshops or exchange forums between public and private sectors, dissemination of publications and news releases, and updates at professional meetings are all effective ways of communicating the necessary information to drive the partnership forward.[21] Periodic updates and exchanges of data have been shown to have positive effects on collaborations.[15] Overly frequent distribution of printed communications, required teleconferences, or excessive meetings will generate unwanted frustration or lack of continued support/participation. However, the value of a reasonable number of written updates, fairly regular calls (monthly, for example), and at least two in-person meetings (at onset and before distribution of results) are essential for building strong team morale, maintaining commitments, and achieving successful outcomes. Clearly these processes must

be adapted to accommodate national and regional cultural sensitivities.

6.3 Visibility

Visibility of results and the breadth of dissemination of information to be obtained through the partnership should be discussed in the early planning phase of the project. Preparing results for wide dissemination requires considerable time and effort, which may not fall within the scope of the project team. However, if such a distribution is desired and the funding and resources are available, the results can benefit a more widespread audience. Visibility of potential and perceived conflicts of interest should also be discussed at the onset of the partnership. An internal and/or external monitoring committee can reinforce ethical standards and trust among stakeholders.[16] The priorities with respect to transparency and diffusion of information will depend on the nature of the partnership, the initial agenda, and the resources available.

6.4 Change Management

Anticipating and planning for change is good practice for all patient registries. Because of their nature and the variety of their stakeholders, PPPs in particular may be more subject to changes in registry goals, stakeholders, budget, processes, and other areas. For this reason, it is important for PPPs to have a plan for how change will be managed. Tools that can assist in change management planning include a manual of procedures, a governing body, infrastructure for ongoing personnel training, and a plan for communicating change.

Protocols, governance documents, and other related documents may change from time to time as a registry matures and adapts. Documents should be reviewed periodically and updated as needed. Resubmission for ethical review may be required, depending on the extent of the changes. The use of versioning (e.g., naming a protocol "Registry Protocol v1.0") can reduce miscommunications and ensure that all stakeholders refer to the same document. It is also important to document major decisions that will affect the scope or budget, or otherwise impact the registry, and to share information about these decisions with key stakeholders. For more information on managing change in registries, see Chapter 11, Section 2.6, and Chapter 14.

7. Special Considerations for International PPPs

International PPPs face some unique challenges, in addition to the usual challenges of language and cultural barriers. While some investigators may complain about the burden of compliance with regulation in developed countries, the opposite problem may exist in some less-developed jurisdictions. The absence of a clear regulatory framework within which to operate may create problems in both the investigator's home country and in the host collaborating country. One example may be lack of clarity in determining the responsible office for establishment of collaborations; another example may be changes in the local political landscape that alter this locus of responsibility. An issue that should be clarified in advance is the right to publish findings and to confirm authorship. Early attention to these details will avoid later issues.

8. Key Factors for Success and Potential Challenges

8.1 Key Factors for Success

A PPP represents a valuable business model for the development of multi-stakeholder registries. The shared-risk and shared-benefit nature of PPPs presents an ideal opportunity for attracting involvement from risk-averse elements in any sector, but these benefits coincide with challenges that may derail the success of a project as a whole.

A PPP starts with an identified public health issue in need of a solution. There is no shortage of strong, scientifically valid and important topics relating to the delivery of medical care and use of medical products; the challenge is in prioritizing these issues and focusing on pragmatic solutions for high-impact projects. For example, a registry tracking care patterns for a well-understood rare disease would likely generate less support than one

that would collect acute and chronic data on a novel treatment for a highly prevalent condition. To ensure success of a given PPP, it is vital to communicate with a broad array of stakeholders early in the process to ensure that the problem is appropriately conceptualized and that the goals mesh with priorities of stakeholders.

While PPPs represent a variety of interests and viewpoints, the value of a strong leader cannot be overstressed. Because of the nature of professional life, few people have the necessary time to devote to the difficult task of managing not only the scientific aspects of developing a registry, but also the equally challenging task of developing and managing an interdisciplinary team with diverse interests and leading it toward a common goal. The presence of a trusted and dedicated individual who is willing to commit substantial time to the development of a PPP is critical to the success of the project. This individual needs to be a recognized expert voice and have skills as a moderator, mediator, business developer, and salesman. Individuals who are open to pragmatic approaches that accommodate stakeholders without sacrificing the scientific integrity of the project will have a high likelihood of success. Similarly, an active and dedicated core team that represents an array of stakeholders is also necessary to support the goals of the PPP.

Many PPPs, like any project, are started with small conversations that grow into grand ideas. The formative stages of a PPP involve many steps of developing and refining the issues and potential solutions long before the first data entry form is ever filled out, and often consist of preparing documents, attending calls, holding workshops, and other collaborative activities. While talk is indeed cheap, there comes a point where the project cannot move further without some substantial funding. It is good practice to begin development of a funding strategy early, often alongside the development of the scientific strategy. Funding options should not depend solely on any one source or sector. A broader base of support is more likely to be a sustainable funding model, and has the added benefit of potentially reducing the appearance of conflicts of interest.

If one views the PPP as a business model, the necessity to provide accurate and timely reports to shareholders becomes more readily apparent. In the planning process and throughout the development of the project, it is important to set goals and produce meaningful deliverables within a reasonable time frame. Projects that appear to drag on, or that have a dearth of outputs for an extended period, are likely to lose support and jeopardize funding. Likewise, reporting of the progress of a project is critical to sustain interest and support. For PPPs that involve professional or academic societies, the annual scientific sessions of these organizations often provide an ideal opportunity to update the community.

Clear communication in open forums that encourage and allow for buy-in and feedback is another critical component of success in a PPP environment. A registry is a unique application of the PPP model in that successful implementation of the final project is heavily dependent on individual hospitals and practitioners. Having stakeholders represented at the leadership levels of organizations is necessary for good governance; however, communicating with the physicians, hospitals, nurses, and associated staff to address their concerns will promote enrollment. Further, the case must be made to this group that the registry will add value to their organizations, and not just represent a further drain on their already sparse time.

Some registry characteristics that increase the probability of success include—

- The registry should have goals that address a clear and current clinical need in a well-defined population. These goals become the rallying point for the diverse partners.
- The expectations of each partner should be explicitly numerated, pragmatic, transparent, and measurable.
- The registry should return value to all partners who are financial contributors. As much as possible, the value should equal or exceed the financial contribution for each partner.

- The registry should have strong, respected leaders who have national or international reputations. Mutual respect among all partners is also necessary for a strong working relationship.
- High quality data is essential to the success of the registry. Data must be collected consistently, using agreed-upon definitions. Protocol-driven efforts to assess compliance with the registry protocols and well-defined efforts to repair any deficient areas are critical.
- While the registry should be built for consistency, it still must have an element of flexibility to allow it to react to changes in the clinical landscape.
- The registry should have policies and procedures in place to support transparency and ongoing communication to partners and participants.

8.2 Common Challenges

The first challenge is involving stakeholders in designing the registry and implementing the registry procedures (e.g., governance, operational management, analysis). The second challenge is creating a data collection plan and registry procedures that are realistic and will capture the data necessary to meet the goals, but flexible enough to accommodate change when necessary. The third challenge is adhering to the registry procedures and data collection plan. If a registry is successful, many spinoff projects and additional uses of the registry may appear. Maintaining focus on the original goals of the registry while responding to increasing registry demands is clearly a challenge. Creating a business plan that will allow for sustainability of the registry is one of the biggest challenges. Assessing quality of life and other patient-reported outcomes, including clinical assessments (e.g., neurocognitive assessment) is a challenge because direct interaction with the patient is required. The biggest challenge is to provide daily high-level effort that simultaneously focuses on regulatory and data quality issues while continuing the scientific mission of the registry.

9. Summary

PPPs are increasingly being used as a model for operating patient registries in the United States and internationally. Government regulators and payers are increasingly requiring evidence development to inform decisions about approval, coverage, and expanded indications, and patient registries governed by PPPs are in a unique position to fulfill those requirements. In the future, PPPs that include international partners will continue to be important. While there are special considerations for planning and operating PPPs, they offer a unique way for varied stakeholders to contribute their particular strengths to achieve a common scientific goal.

Case Examples for Chapter 24

Case Example 62. Developing a public-private partnership for comparative effectiveness research

Description	The Registry In Glaucoma Outcomes Research (RiGOR) is a prospective observational study comparing the effectiveness of treatment strategies for open-angle glaucoma.
Sponsor	Agency for Healthcare Research and Quality (AHRQ)
Year Started	2011
Year Ended	Ongoing
No. of Sites	47 community and academic ophthalmologic practices
No. of Patients	2,625

Challenge

In 2009, the Institute of Medicine disseminated a landmark report, "Initial National Priorities for Comparative Effectiveness Research," which listed research priorities for the newly enacted American Recovery and Reinvestment Act (ARRA). Among the 100 priority research topics identified was evaluating the different treatment strategies for primary open-angle glaucoma. Since the disease disproportionately affects African-Americans, understanding the effectiveness of treatment strategies in minority populations was also of special interest. With ARRA funding, AHRQ sought to develop high-quality scientific evidence to inform decisionmaking by clinicians and patients. An approach was needed to obtain continued and expanded input from the various stakeholders while addressing existing evidence gaps.

Proposed Solution

A diverse group of stakeholders was assembled to implement the registry, provide scientific guidance, develop dissemination plans, and further key research based on study findings. The principal investigator and co-principal investigators represent AHRQ, the American Academy of Ophthalmology (AAO), the University of California at Los Angeles (UCLA) Jules Stein Eye Institute, and the Outcome DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Center. AHRQ provides oversight and financial support to the project, with scientific leadership from the principal and co-principal investigators; the Outcome DEcIDE Center manages the operational aspects of the study; AAO and UCLA engage sites and investigators and provide guidance on clinical issues. The stakeholder committee is comprised of individual clinical advisors and representatives from the Glaucoma Research Foundation, American Glaucoma Society, National Medical Association, and State-level health care organizations.

Developing the study protocol, initiating startup activities and decisions, and analyzing and reporting the findings require continued communications among all stakeholders. A communication plan was developed to outline project team roles and organizational structures for each stakeholder. Regular stakeholder committee meetings have created a forum to discuss design issues, share study status, solicit input on unexpected challenges, and discuss future research. Site- and patient-recruitment efforts were designed to maximize geographic diversity and enrollment of minority populations. Quarterly study newsletters and investigator meetings coinciding with the AAO annual meeting were also implemented to maintain site interest.

Results

Launched in 2011, RiGOR is a prospective, observational, cohort study designed to compare the effectiveness of treatment strategies for primary open-angle glaucoma. Different treatment strategies studied in the registry include laser surgery, other procedures (such as incisional surgery or other glaucoma procedures), and medications. All treatment decisions are at the discretion of the treating physician according to their usual practice. Data collection includes

Case Example 62. Developing a public-private partnership for comparative effectiveness research (continued)

Results (continued)

patient demographics, medication, visual measures, glaucoma severity, surgical characteristics, adverse events, and patient-reported outcomes, and occurs at baseline, 3 months, 6 months, and 12 months.

The registry has been successful in meeting its objective of enrolling a high percentage of minority patients. An interim report describing baseline findings is currently in process, and full analyses are expected to be published in 2013. The current AHRQ funding will allow RiGOR to operate through 2013. A future challenge for the registry will be identifying and transitioning to a new funding source once the initial funding ends.

Key Point

The public-private partnership model can be an effective approach to engaging multiple stakeholders in an effort to address a comparative effectiveness research question. When working with multiple stakeholders, it is critical to clearly identify roles and communicate regularly with all stakeholders to address any design, operational, or analytical issues, solicit input from all contributors, share study findings, and maintain stakeholder engagement.

For More Information

http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=841.

Case Example 63. Leveraging a public-private partnership for a postmarketing commitment

Description	The Longitudinal Study of Urea Cycle Disorders is operated by the Urea Cycles Disorder Consortium (UCDC). Its primary purpose is to collect data on the natural history, disease progression, treatment, and outcomes of individuals with urea cycle disorders (UCD). The Orphan Europe Carbaglu Surveillance Protocol is a mandated postapproval registry that is collaborating with the study to monitor the long-term safety and effectiveness of Carbaglu, a treatment for UCD.
Sponsor	Orphan Europe, UCDC, National Institutes of Health (NIH)
Year Started	2011
Year Ended	Ongoing
No. of Sites	14
No. of Patients	1

Challenge

Orphan Europe is the manufacturer of Carbaglu, a drug used to treat hyperammonemia (high blood ammonia levels) due to N-Acetylglutamate synthetase (NAGS) deficiency, a type of UCD. In 2010, the U.S. Food and Drug Administration (FDA) approved Carbaglu for use in the United States and mandated a 15-year postmarketing surveillance program to monitor its long-term safety and effectiveness. The sponsor recognized that data collection for this rare disease would be difficult because of the small number of NAGS patients in the United States and the extended timeframe for data collection; thus, the sponsor sought to meet FDA's commitment while avoiding redundancy in research efforts and overburdening the small patient population.

Proposed Solution

NIH established UCDC in 2003 as part of the Rare Diseases Clinical Research Network. The UCDC is governed by a steering committee and maintains relationships with 16 clinical sites, a data monitoring and coordinating center, and patient advocacy groups. One of the functions of the UCDC is to operate the Longitudinal Study of Urea Cycle Disorders, initiated in 2006 and now

Case Example 63. Leveraging a public-private partnership for a postmarketing commitment (continued)

Proposed Solution (continued)

containing baseline and longitudinal data on 515 patients.

Orphan Europe recognized the value of the UCDC study's existing database and infrastructure and pursued collaboration with the Consortium. After initial discussions, it became clear that the data elements already being collected in the study would need to be supplemented by only a few additional elements in order to fulfill the sponsor's postmarketing registry commitment to FDA. A protocol was written for the registry to specify which study data the sponsor would have access to in their registry and which new data elements would be added to the study for registry purposes.

One unique challenge encountered early on related to the execution of a legal agreement on which to base the collaboration. Because the UCDC does not have a legal entity, it was not possible to contract directly with them. Thus, the sponsor contracted with the Children's Research Institute at Children's National Medical Center, which served as a coordinating center for the remaining sites and had existing contractual agreements in place with them. The Institute then executed data use agreements with the sites for participation in the postmarketing registry.

Results

The registry has been operating since 2011 and includes 14 active sites. To date, one patient has been enrolled in the registry. By collaborating with UCDC, Orphan Europe was able to operationalize the registry in a shorter timeframe and at a lower cost than building a new, independent registry. Collaboration with UCDC also resulted in only a few more data elements required from sites and patients participating in the UCDC study; this represents a smaller data collection burden on the already limited patient population. Future challenges for the registry include sustainability, as NIH funding for the UCDC study is expected to end in 2014. UCDC and Orphan Europe are in the process of collaborating with the European Registry and Network for Intoxication Type Metabolic Diseases (E-IMD), a registry collecting information on this patient population in Europe.

Key Point

Even after FDA approval, rare disease treatments can face logistical and financial challenges in fulfilling postmarketing obligations. Collaborating with existing studies that are collecting longitudinal data on the patient population can reduce the burden on participants and streamline the operationalization of a registry.

For More Information

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http://rarediseasesnetwork.epi.usf.edu/ucdc/index.htm

http://clinicaltrials.gov/ct2/show/NCT00237315

http://www.e-imd.org

Case Example 64. Public-private partnerships for rare diseases

Description	The American Thrombosis and Hemostasis Network (ATHN) is a nonprofit organization operating the ATHNdataset, a registry that serves as a secure resource of longitudinal, individual-level demographic, clinical, and genetic information from U.S. patients with rare bleeding and clotting disorders. The data are used for research, outcomes analysis, public health surveillance, and advocacy.
Sponsor	Initial infrastructure development: Novo Nordisk, Inc. Project-specific extensions and applications: public sector partners such as Centers for Disease Control and Prevention (CDC), National Heart, Lung, and Blood Institute, Health Research and Services Administration (HRSA) Maternal and Child Health Bureau; as well as private-sector sponsors from industry, treatment centers, and the patient community (e.g., Baxter Bioscience, Hemophilia of Georgia, Indiana Hemophilia and Thrombosis Center)
Year Started	2010
Year Ended	Ongoing
No. of Sites	129
No. of Patients	12,154 as of September 6, 2012

Challenge

In the late 1970s, the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA), a branch of the U.S. Department of Health and Human Services, established a network of hemophilia treatment centers across the United States. As HIV became a concern for these patients in the 1980s, CDC also lent its support to this network. Today, more than 130 centers in the network deliver comprehensive care to patients with rare bleeding and clotting disorders, offering the multidisciplinary services of care teams that include hematologists, nurses, physical therapists, and social workers. Care coordination often includes orthopedists, dentists, genetic counselors, obstetrician-gynecologists, infectious disease practitioners, and emergency departments.

While the network provided nationwide geographical coverage, centers were organized into independent regions that functioned as informal collaborations. Research often required pooling data from different regions in order to obtain a sample size sufficient for meaningful analysis, but these efforts were often hampered by the fact that treatment centers in different regions used different electronic data capture systems.

A series of meetings was held at which government agencies and representatives from the network centers agreed that there was a clear need for standardized data to support the many data requests being received by the centers. There was also a need to efficiently use the limited resources available to these centers.

Proposed Solution

In 2006, ATHN was established as a nonprofit organization, with initial motivation for startup supplied by CDC and the federally funded network centers, which continue to be supported by HRSA. After actively seeking a partner for ongoing, long-term funding, in 2007 ATHN secured support from Novo Nordisk, Inc. One of its first actions was establishing a new standards-based electronic infrastructure, followed by the ATHNdata.quality.counts program, which provided funding to individual centers to increase data management capacity. Legacy data on more than 700,000 visits related to 101,610 patients was standardized and migrated to the new platform. Following the donation from Baxter Bioscience of the first electronic system for

Case Example 64. Public-private partnerships for rare diseases (continued)

Proposed Solution (continued)

logging bleeds and infusions, patient self-reported data was integrated and made accessible to treatment centers in the same infrastructure.

In 2010, the ATHNdataset registry was created, with the goal of providing a consolidated, nationwide, longitudinal data resource that can be used for research, public health surveillance, and reporting. The registry is designed to study blood product safety, natural history of disease, effectiveness of care, prevention strategies, treatment patterns, and patient outcomes. Individual treatment centers execute Data Use Agreements and Business Associate Agreements, designating ATHN as the steward of data collected at the site, and allowing the data to be used for research purposes. Data are collected by the individual centers using a common electronic data capture system that also includes provider-focused Web-based tools and integrated electronic patient self-reporting systems. Data are stored as a limited data set (LDS) as defined by the HIPAA Privacy Rule, and the registry obtains authorization from patients for use of their data. Indiana Hemophilia and Thrombosis Center, Hemophilia of Georgia and other affiliated sites contributed to the design and testing of the registry, governance processes, and fundraising.

Results

Currently, 129 centers, representing about 12,154 patients, are contributing data to the registry. ATHN provides a library of report templates and study management tools to participating centers, introducing efficiencies that allow the centers to devote more resources to providing care. ATHN itself has also received grants to conduct public health surveillance that leverages the registry data set, and recently received research funding from CDC to conduct a cross-sectional analysis on cardiovascular disease in older men with hemophilia.

Key Point

PPPs can be especially valuable models for registries in rare diseases, where resources are scarce and research efforts may not be well coordinated. PPPs can provide the resources needed to create a common electronic infrastructure, data standards, and centralized data management and research functionalities, allowing disparate data sources to be combined for meaningful analysis.

For More Information

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Section VI
Evaluating Registries

Chapter 25. Assessing Quality

1. Introduction

As described throughout this guide, registries are created for many purposes, including scientific, clinical, and policy. Registries may also serve more than one purpose and potentially may add or change purposes over time. This leads to variations in design, operations, or quality assurance that are sometimes viewed as methodological inadequacies. It is not generally appreciated that the attributes important for some purposes may be less important for others. As a result, it is important to distinguish these purposes with respect to recommending particular practices.

For example, in describing a very rare disease or small subgroup of patients for whom there is little other information, some relevant data from a registry are better than no data. Further, even registries that fall short of including many of the essential elements of good registry practice described in this chapter may still provide valuable insights for some purposes. As a general rule, quality should be evaluated by elements that directly impact the ability of the registry to achieve its main objectives. In other words, a registry must be fit for its purpose.

Nonetheless, while all registries can provide useful information, there are levels of rigor that enhance validity and make the information from some registries more useful for guiding decisions than others. For example, there are certain practices that enhance the validity and reliability of registries intended to evaluate safety and comparative effectiveness in terms of design and confirmation of key outcomes.

Prior to the publication of the first edition of this User's Guide,[1] no criteria had been developed to guide evaluation of registries. Research into the quality aspects of registries, whatever their purpose, remains relatively sparse, especially when compared with the rich information available to guide quality in clinical trials. The aim of this chapter is to provide a simple and user-friendly listing of attributes and practices that allow registries to be described and evaluated for their essential elements and enhancements in the context of the purpose for which they are conducted. Information is presented to help distinguish between—

- Essential registry practices that are desirable for every study.
- Practices that could enhance scientific rigor and that are particularly important for certain purposes, but may not be achievable because of practical constraints.

The items listed as "essential" elements of good practice are applicable to all patient registries. While it may not be practical or feasible to achieve all of the essential elements of good practice, it is useful to consider these characteristics in planning and evaluating registries. It is also important to remind readers that some of the fundamental differences between clinical trials and registries affect how quality is evaluated. For example, a clinical trial will have a rigorously maintained schedule of visits and assessment. A clinical trial patient who does not adhere to the schedule may be viewed as noncompliant with the protocol and potentially could be discontinued from the trial. In a registry, treatments and assessments may be recommended, but the registry participant who does not adhere to the schedule typically is allowed to remain in the registry, and this is considered good practice. Moreover, some argue that the kind of data produced by registries may be more valid for inferences needed in clinical decisionmaking because few exclusion criteria are used and inferences are drawn from measurements customarily used by clinicians.[2]

The information described in this User's Guide, and particularly in this chapter, is also designed to be used in reporting registry study results, much as CONSORT (Consolidated Standards of Reporting Trials) guidelines have been used to improve reporting of clinical trials,[3] and STROBE (Strengthening the Reporting of Observational

Studies in Epidemiology) guidelines are being used for observational studies.[4, 5]

2. Defining Quality

This chapter has adapted a definition of quality that was developed for randomized controlled trials;[6] the term is used to refer to the confidence that the design, conduct, and analysis of the trial or registry can be shown to protect against bias (systematic error) and errors in inference—that is, erroneous conclusions drawn from a study.[7] As used here, quality refers both to the data and to the conclusions drawn from analyses of these data. For more information about the types of biases that can affect observational studies, as well as strategies for addressing and even avoiding these biases to the extent feasible, see Chapters 3 and 13. For more information about bias, validity, and inference, readers are encouraged to consult epidemiologic textbooks.[8-11]

3. Measuring Quality

There are two major difficulties with assessing quality in registries:

- It can often be difficult to differentiate between the quality of the design, the study conduct, and the resultant information available.
- There is a lack of empirical evidence for evaluating the parameters purported to indicate quality and their impact on the utility of the evidence produced from registries.

Evaluations of the quality of any registry must be done with respect to the essential elements of the registry and those aspects that are important in the context of the registry's main purpose and the purpose for which the data are being used. Both the internal and external validity of the data must be taken into account along with considerations of cost and feasibility.

The most commonly used method to assess quality of studies is a quality scale; there are numerous quality scales of varying length and complexity in existence, with strong opinions both for and against their use.,[6, 8,12] Different scales emphasize distinctive dimensions of quality and therefore can produce disparate results when applied to a given study. In most situations, a summary score is derived by adding individual item scores, with or without weighting. This method, however, ignores whether the various items may lead to a bias toward the null (suggesting the erroneous interpretation that there is no effect) or tend to exaggerate the appearance of an effect when none really exists, and the final score produced does not reflect individual components.[13] Furthermore, validation of the scales is difficult; studies have found wide variation in the scores for a particular study both by different reviewers and the same reviewers at different times.[14]

The approach suggested here is to undertake a quality component analysis, which involves an investigation of the components that may affect the results obtained. In the quality component analysis, a differentiation is made between two domains: research quality, which pertains to the scientific process (in this instance, the design and operational aspects of the registry), and evidence quality, which relates to the data/findings emanating from the research process.[15-17] According to Lohr,[18] "[t]he level of confidence one might have in evidence turns on the underlying robustness of the research and the analysis done to synthesize that research." The individual items highlighted as essential elements of good practice and evidence quality can be used to guide the evaluation of registries, though there are no criteria as yet as to what proportion of elements must be satisfied in order to be considered "good enough" for various purposes.

To select the quality components for analysis, several key elements identified in previous research studies, among many consulted, were Guidelines for Good Pharmacoepidemiology Practice,[19] the ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) Guideline on Good Clinical Practice,[20] the Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Ethical Review of Epidemiological Studies,[21] standards developed for the conduct of registry

studies for patient-centered-outcomes research,[22] various reports on rating scientific evidence from observational studies[12, 23] and surveillance systems,[24] Goldberg's review of registry evaluation methods,[25] the MOOSE (Meta-analysis of Observational Studies in Epidemiology) proposal,[26] the EULAR (European League Against Rheumatism) task force on biologic registers,[27] and Guidance for Reporting Observational Studies maintained by the Equator Network.[28] Special purpose quality guidance documents, including the GRACE principles for observational studies of comparative effectiveness (see http://www.graceprinciples.org),[29] were also reviewed.

The results of the quality component analysis must be considered in terms of the registry purpose and in the context of the disease area (See Table 25–1.) For example, a disease-specific registry that has been designed to look at natural history should not be deemed low quality simply because it is not large enough to detect rare treatment effects.

Table 25–1. Overview of registry purposes

- Determine clinical effectiveness, cost effectiveness, or comparative effectiveness of a test or treatment, including evaluating the acceptability of drugs, devices, or procedures for reimbursement.
- Measure or monitor safety and harm of specific products and treatments, including conducting comparative evaluation of safety and effectiveness.
- Measure or improve quality of care, including conducting programs to measure and/or improve the practice of medicine and/or public health.
- Assess natural history, including estimating the magnitude of a problem; determining the underlying incidence or prevalence rate; examining trends of disease over time; conducting surveillance; assessing service delivery and identifying groups at high risk; documenting the types of patients served by a health provider; and describing and estimating survival.

4. Quality Domains

The quality domains shown here reflect the domains described earlier in this User's Guide and have also been adapted from work undertaken for clinical trials. For research, the quality domains are research design and processes and procedures, which address planning, design, data elements and data sources, and ethics, privacy, and governance. Table 25–2 shows the essential elements of good registry practice for research, and Table 25–3 shows optional indicators of quality that may enhance registry validity and reliability, subject, of course, to feasibility and applicability.

For evidence, the quality domains are external validity, internal validity, and analysis and reporting. Table 25–4 shows the essential elements of good registry practice for evidence, and Table 25–5 shows optional further indicators of quality, including those important for selected purposes. It is important to weigh efforts to promote the accuracy and completeness of evidence in balance with the public health urgency of a problem, the types of interventions that are available, and the risks to public health from coming to a wrong conclusion. These lists of components are most likely incomplete, but the level of detail provided should be useful for high-level quality distinctions.

Most importantly, the essential elements of good practice, as well as the optional further indicators of quality depend, to a great extent, on the resources and budget available to support registry-based research.

Table 25–2. Research quality—essential elements of good practice for establishing and operating registries

Research Design

- Develop objectives and/or research questions (main and supporting, as needed).
- Identify the target population, eligibility, and inclusion and exclusion criteria. For registries where practice characteristics may influence outcome, seek to include diverse clinical practices. Where possible, a broad range of patients (few exclusion criteria) is desirable to facilitate subgroup analysis.
- Identify important personal identifiers, exposures, risk factors, and mitigating (or protective) factors, and seek those that are reasonably feasible to collect. Use the literature to inform the choice of data elements.
- Choose outcomes that are clinically meaningful and relevant to patients and to the medical community for decisionmaking. Define patient outcomes clearly, especially for complex conditions or outcomes that may not have uniformly established criteria (e.g., define "injection site reaction" in operational terms). Consider whether these outcomes will be collected from medical care providers, patients, or other observers.
- Use validated scales and tests when such tools exist for the purpose needed.
- Understand the followup time required to detect events of interest and whether or not the objective is feasible to achieve. Ensure that the followup time planned is adequate to address the main objective.
- Plan the main analyses, including specification of exposure and effect measures.
- Consider the size required to detect an effect should one exist, or to achieve a desired level of precision. Consider whether or not the sample size requirement can be achieved within the available time and budget constraints.
- Consider the most efficient and reliable means to consistently collect data of sufficient quality to meet the registry's purpose and whether existing data can be used to supplement or minimize active data collection.
- Plan to report safety events according to regulatory requirements.
- Plan the data analysis to address the key objectives or research questions, including what comparative information, if any, will be used to support study hypotheses or objectives.

Processes and Procedures

- At the outset, reach agreement on key aspects of the registry and document them, including the goals, design, target population, methods for data collection, data elements and sources, high-level data management and data quality review, and how human subjects will be protected. It may be helpful for stakeholders to have input to ensure clinical relevance and feasibility.
- Establish a process for documenting any modifications to the plan, since the main objective may change over time as knowledge accumulates, and the plan for data collection and followup may need to be adapted.
- Carefully consider the issues of protection of human subjects—including privacy, informed consent, data security, and study ethics—and address them in accordance with local, national, and international regulations. Obtain review and approval by any required oversight committees (e.g., ethics committee, privacy committee, or institutional review board, as applicable). If linkage of registry data to other sources is planned, consider the additional issues of protection of human subjects.
- Define the role of any external sponsor, including data access and use.
- Provide clear, operational definitions of outcomes and other data elements. Establish a data and coding dictionary to provide explicit definitions and to describe coding used. Whenever possible, use standardized data dictionaries, such as the International Classification of Diseases, and use coding that is consistent with nationally or internationally approved coding systems to promote comparability of information among studies.
- If linkage of registry data to other sources is planned, consider any additional requirements that may influence successful linkage, such as selection of data elements and definitions used.
- Plan subject and physician recruitment targets and methods to achieve those targets, and plan the means for monitoring enrollment and retention.

Table 25–2. Research quality—essential elements of good practice for establishing and operating registries (continued)

Processes and Procedures (continued)

- Plan to expend reasonable efforts to ensure that appropriate patients are enrolled systematically and followed in as unbiased a manner as possible.
- Identify appropriate personnel and facilities, including those for secure data storage. Identify the individual(s) responsible for the integrity of the data, computerized and hard copy, and make sure these individuals have the training and experience to perform the assigned tasks.
- Develop standard instructions for use in training data collectors. For safety studies, create a process for identifying and reporting serious events that is consistent with regulatory requirements. Plan training for study personnel about how to identify serious events, including:
  - Asking about complaints or adverse events in a manner that is clear and specific (e.g., solicited vs. unsolicited).
  - Knowing if and how information should be reported to manufacturers and health authorities.
- Create a quality assurance plan that addresses data editing and verification. Plan an approach for handling missing data (e.g., go back and collect those data or make a plan as to how "missing" data will be coded in the data files.)
- Anticipate how study results will be communicated on completion.

Table 25–3. Research quality—further indicators of quality for establishing and operating registries (optional)

Research Design

- Formalize the study plan as a research protocol.
- For comparative effectiveness and safety—
  - Use concurrent comparators, since they may offer an advantage over historical or external comparison groups, especially in situations where treatments are evolving rapidly. The comparator cohort should be as similar as possible to the exposed cohort, aside from the exposure under study, and should reflect current clinical practice.
  - Use formal statistical calculations to specify the number of patients or patient-years of observation needed to measure an effect with a certain level of precision or to meet a specified statistical power to detect an effect should one exist, although the desired size may not be achievable within the practical study constraints. Temper considerations about precision and power with budgetary and feasibility constraints, while also giving heed to the importance of conducting research in areas where little information exists.
- Develop formal analysis plans.
- Collect information to permit linkage (and therefore validation) with external databases such as the National Death Index, electronic health records, or claims data sets, as appropriate.
- Post the registry on a public registry of registries (e.g., at the Registry of Patient Registries) or trials listing (e.g., at ClinicalTrials.gov).

Processes and Procedures

- Undertake a feasibility study or pilot test (e.g., when studying hard-to-reach populations, when sensitive data are sought, and when critical registry methods are new or have not otherwise been tested).
- When capturing composite scores, collect and record core components, if possible.
- Collect information on start and stop dates of treatments of interest and dose (if relevant) or other means to discriminate between high and low exposure.
- Use similar methods of followup for exposure and comparison cohorts, and for all subjects in each cohort, to the extent feasible.

Table 25–3. Research quality—further indicators of quality for establishing and operating registries (optional) (continued)

Processes and Procedures (continued)

- To enhance transparency, consider using an advisory board, particularly a board that includes members who are external to the clinician, center, or company that sponsors the research. An advisory board or steering committee can promote clinical and public health relevance and may assist with governance and communication. If using an advisory board, consider rotating membership and/or term limits.
- Specify publication policies in advance of collecting data and reevaluate at regular intervals (e.g., annually).
- Develop a plan for stopping or transitioning the registry, including any archiving or transferring of data and notifying participants, as appropriate.
- Consider when and how to allow third parties access to data, if feasible, and the process for any such data access.
- For safety and comparative effectiveness—
  - Data collection methods should not limit site participation to the extent that the representativeness of sites is compromised. Although a single method of data collection is most efficient, multiple methods of data collection may be desirable for some purposes.
  - Loss to followup should be monitored and characterized to ensure that followup is sufficiently complete for the main objective and to see if there is differential loss to followup by characteristics that may affect the likelihood of achieving the main objectives. Reasonable resources should be devoted to minimizing loss to followup.
  - Quality assurance (QA) may include review or monitoring of a sample of data and/or data review by an adjudication committee for complex conditions or endpoints for which established procedures and/or coding are not used. For most purposes, a risk-based strategy should be used for QA, focused on detecting and quantifying the most likely causes of error and the types of error most likely to affect the registry purpose, with QA activities adapted based on observed performance (e.g., increase QA for sites that appear to be having difficulty in study conduct or data entry).
- For safety, comparative effectiveness, and quality improvement—
  - Maintain appropriate documentation, such as an audit trail, to ensure proper handling of information and to support transparency.
  - Establish processes and standards for creating analytic data files and maintaining such files to support publications and presentations, since registry analyses may be performed on live data (data that may change as the registry continues to collect and verify information through various quality control procedures) or on data that have been locked and have undergone formal review and editing.
  - Use open standard approaches to interoperability when health information systems are used for active data collection to permit more efficient collection of data from multiple systems.

Table 25–4. Essential indicators of good evidence quality for registries

External Validity • External validity was demonstrated by showing that registry participants were similar to the target population and, to the extent feasible, efforts were devoted to minimizing selection bias (e.g., rules for sequential enrollment were developed and codified in a manner that worked for all sites). • Completeness of information on eligible patients was evaluated and described.
Internal Validity • For safety studies, a clear and specific approach was used (e.g., solicited vs. unsolicited) to ask about complaints or adverse events. • Necessary information was collected for relevant key exposures, risk factors, and mitigating or protective factors. • Exposure data used to support the main research questions were as specific as possible. For example, a specific product, including manufacturer, was identified to the extent feasible. • Data checks were employed using range and consistency checks. • For comparative effectiveness and safety— – Followup period was reasonably sufficient to capture the main outcomes of interest. – Comparators reflect current practice. – A sample of data was validated with patient records, (e.g., 10–20% of patients' records were compared with registry data). – Followup was reasonably complete for the registry purpose.
Analysis and Reporting • The report describes the methods, including target population and selection of study subjects, compliance with applicable regulatory rules and regulations, data collection methods, any transformation of variables and/or construction of composite endpoints, how missing data were handled, statistical methods for data analysis, and any circumstances that may have affected the quality or integrity of the data. The information was reported with enough detail to allow replication of the methods in another study. • Results were reported for all the main objectives, including estimates of effect for each. • Accepted analytic techniques were used; these may have been augmented by new or novel approaches. • Followup time was described to enable assessment of the impact of the observation period on the conclusions drawn. • The role and impact of missing data and potential confounding factors were considered. • The report includes a clear statement of any conclusions drawn from the analysis of the registry's main objectives and any implications of study results. Alternative explanations for the observed results were considered; a variety of factors, including the strength of the association, biases, and temporal relations, were considered before drawing any causal inferences. The practice of making inferences about causation largely on the outcome of tests of statistical significance is discouraged. • The consistency of results was compared and contrasted with other relevant research.

Table 25–5. Further indicators of registry evidence quality (optional)

External Validity • Eligibility (inclusion and exclusion criteria) was confirmed on enrollment. • Selection bias was evaluated by describing the representativeness of the actual population in terms of how it was selected, how well the characteristics of the actual population match those of the target population, and to whom the results apply.
Internal Validity • Results that can be confirmed by an unbiased observer—such as death, test results, and scores from validated measures for patient-reported results or clinical rating scales—were used to enhance accuracy and reliability. • For safety and quality reporting (to third parties)— – Potential sources of error relating to accuracy and falsification were rigorously evaluated and quantified to the extent feasible (e.g., through database and/or site reviews). – Reproducibility of coding was evaluated.
Analysis and Reporting • Validated analytic tools were used for the main analysis. For example, commercially available analytic packages were used. The data elements used in any models were described. • Effect estimates among meaningful subgroups were described. • Appropriate statistical techniques were used to address confounding. • Sensitivity analyses were used to examine and quantify the effect on the association between the a priori exposure of interest and the outcome(s) by, for example, varying the definitions of exposure, potential confounders, and outcomes. • For safety studies, the risks and/or benefits of products, devices, or processes under study were quantitatively evaluated beyond simply evaluating statistical significance (e.g., rates, proportions, and/or relative risks, as well as confidence intervals, were reported). • For studies of comparative effectiveness and safety, contemporaneous data were collected for one or more comparison groups that reflect current clinical practice, when other reasonably accurate and relevant comparative data were not available.

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The findings and conclusions in this document are those of the contributors and reviewers. The contributors and reviewers participated as individuals and not necessarily as representatives of their organizations. No statement in this document should be construed as an official position of any organization represented here.

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Appendixes

Appendix A. An Illustration of Sample Size Calculations

As a general principle, sample size calculations depend on the study design, the study question, and the scale of measurement of the variables being measured. Indeed, one of the benefits of performing a sample size calculation is the requirement that each of these elements be specified, thus increasing the likelihood that the proper variables will be measured on the proper patients in the proper manner.

For concreteness, assume that the outcome of interest is a dichotomous variable measured for each patient, such as the presence/absence of a complication associated with carotid endarterectomy (CE). Typically, this literature considers complications within 30 days of the procedure. Nothing essential changes for outcome variables measured on other scales, such as continuous or survival data. The dichotomous outcome (i.e., presence or absence of a complication) is then aggregated across patients into a complication rate (e.g., 9 complications for 300 patients equals a 3-percent complication rate).

For CE, some registry-based designs and study questions that might be of interest include the following. For the purpose of this discussion, case-mix adjustment is the incorporation of various patient characteristics believed to influence complications of CE into a mathematical model used to predict the likelihood of these complications. The most natural such model is a logistic regression.

Design 1: For patients at high risk of stroke, perhaps using an operational definition of "symptomatic with 70–99 percent stenosis of the carotid artery," the study question is whether the surgeons within a larger entity (e.g., a national chain of hospitals) are, in aggregate, experiencing complication rates similar to those who participated in the randomized trials demonstrating the efficacy of CE. The reason this is an open question is that the surgeons and institutions in these randomized trials have undergone a high degree of selection, so that there is a concern that their surgical outcomes may be better than could be expected in usual practice.

The patient inclusion criteria for the registry are selected to be as close as possible to those of the randomized trials; thus, while various characteristics might be collected on each patient, no formal case-mix adjustment is required.

Further, suppose that the 30-day complication rate of CE in the randomized trials was 3 percent. The study question can then be translated into a statistical hypothesis of a one-sample comparison of an observed complication rate versus a prespecified value. In other words, the null hypothesis is that surgeons within the larger entity are, in aggregate, experiencing complication rates that are the same (3%) as those of surgeons who participated in the randomized trials. The final input required to perform the sample size calculation is the complication rate under the alternative hypothesis. For example, if it is determined that the goal of the registry is to have high power to flag results as statistically significant if the true complication rate is 6 percent or higher, then the complication rate under the alternative hypothesis is 6 percent.

In general, the value of the complication rate under the alternative hypothesis is derived using a combination of quantitative and qualitative reasoning. The precise methods used are context dependent and thus not discussed in detail here. In the present example, a cost-effectiveness analysis might suggest that complication rates of 6 percent and above would call into question the efficacy of CE. Given these inputs, it can be shown that the effect size is 0.21, and the sample size required for 80-percent power is approximately 370.

Design 2: Continuing to follow patients at high risk of stroke, now suppose that the goal of the registry is to compare complication rates across hospitals. For simplicity, we continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required.

Design 2 is a simple form of benchmarking application. For example, the CE complication rates for each hospital might be reported to a regulatory agency and/or the general public, on the presumption that statistically significant differences between complication rates can be used to identify hospitals with differences in quality of care. The particular danger in this design is that the complication rate for any particular hospital might be estimated with relatively little precision, thus generating results that have more noise than signal. Another danger, discussed later, is that case-mix adjustment is required and not performed, or performed, but not adequately.

We assume that the benchmarking will focus on comparing specific hospitals—i.e., in the underlying statistical model, hospital will represent a *fixed* rather than *random* effect. The null hypothesis is that the complication rates for all the hospitals are identical, and the alternative hypothesis is that the complication rates follow some pattern other than being identical. In this design, specifying the alternative hypothesis of interest is a potentially formidable task. One way to formulate this hypothesis is to focus on outlier hospitals. For example, suppose that there are 10 hospitals in the registry, the overall complication rate among 9 of these is expected to be 3 percent, and the complication rate at the tenth hospital is 10 percent. This information, along with expected number of cases in each hospital, is sufficient to calculate an effect size and thus perform the sample size calculation.

When comparing complication rates among specific hospitals, some adjustment may be made for multiple comparisons—that is, in any group of hospitals, there will always be a hospital with the highest complication rate, and focusing on differences between the outcomes of this particular hospital versus outcomes of the others will overstate the level of statistical significance. The initial statistical test used to assess the homogeneity of complication rates across all the hospitals in the registry implicitly takes this multiple-comparison problem into account. Subsequent tests, in particular those tests that compare apparent outlier hospitals with others, should include an explicit adjustment for multiple comparisons, and the sample size calculations should reflect the fact that an adjusted comparison is being made.

In practice, the approach to this design might reasonably depend on whether registry data are being collected electronically or manually. If data are being collected electronically, the most sensible policy is to collect information on all CE procedures performed within each hospital and to use the sample size formula as an assessment of whether the registry as a whole is likely to produce results that are sufficiently accurate to support decisionmaking. This assessment can be framed in terms of statistical power, as discussed above, or in terms of precision.

Considering precision, a 95-percent confidence interval for a nonzero complication rate for any hospital is $p \pm 1.96 \text{ sqrt } (pq/n)$, where p is the observed complication rate, $q = 1- p$, and n is the sample size. Supposing that $p = 3$ percent and $n = 300$ per hospital, within any particular hospital, the width of this confidence interval is expected to be approximately ±1.9 percent. If data are being collected manually, and thus the marginal cost of data collection per patient is high, a reasonable policy would be to collect data on a sufficient number of patients in each hospital so that the precision of the estimates of the complication rate within a given hospital would be considered adequate.

As with hypothesis testing, the analysis to derive the width of the confidence interval usually applies a combination of qualitative and quantitative insights. In particular, the question can be reframed as the following: For what values of the complication rate will my decision (whether taken from the perspective of clinical medicine, public health, etc.) be the same? For example, if the decision is the same regardless of where the complication rate falls within the range of 2 to 4 percent, an interval of this width is sufficiently precise.

Unless sample sizes are large, using registries to compare individual hospitals is potentially quite problematic. Although determining the inputs to

the power calculations is not always a straightforward task, performing this analysis is quite useful, even if the result is only to suggest extreme caution in the interpretation of differences between hospitals.

Design 3: Continuing to follow patients undergoing CE, now suppose that the goal of the registry is to compare two different versions of the surgical procedure. For simplicity, continue to assume that patients are sufficiently similar to the comparator patients that no explicit adjustment for case mix is required. The following discussion (after including an adjustment for case mix, if appropriate) also applies to comparisons of two different versions of a medical device and similar applications. The key distinctions between this design and Design 2 are that in Design 3 the primary comparison or comparisons can be stated ahead of time and the number of comparisons is relatively small, so that the issue of multiple comparisons can be ignored.

The analytic approach to this design is a logistic regression, with the input file having one record per patient. The outcome variable is the presence or absence of a complication, the categorically scaled control variable is the hospital, and the primary predictor is the categorically scaled coding of the type of surgical procedure (i.e., CE using version A vs. CE using version B). The null hypothesis is that, after accounting for any differences in hospitals, the two different versions of the procedure have identical complication rates. The alternative hypothesis is that the rates differ by a specified amount, this amount being the *minimum clinically significant difference* interpreted to be of concern. Power calculations proceed in the same fashion as for logistic regression with multiple predictors.

The main pitfall in this design is that patients who receive version A of the surgical procedure might differ from those who receive version B of the procedure along some dimension that has an impact on outcomes. (This pitfall is discussed in more detail under Design 4.)

In this application, the null and alternative hypotheses are sometimes structured the same way as in an equivalence trial—that is, differences in complication rates are not expected, and the goal of the study is to demonstrate that complication rates for the two versions of the surgical procedure are similar within a certain level of precision. The structure of the analysis is not fundamentally different. Indeed, sample size calculations for equivalence trials are sometimes not performed within a hypothesis-testing framework but instead by identifying a sample size of sufficient magnitude to make the confidence interval for the difference in the complication rates between the two versions of the surgical procedure a certain width. For simplicity of presentation, let us assume from now on that any equivalence-trial-type calculations can be reframed into confidence-interval format, and thus need not be discussed separately.

Design 4: Continuing to follow patients at high risk of stroke, and continuing to assume that the goal of the registry is to compare two different versions of the surgical procedure, now additionally assume that this comparison will include an adjustment for case mix. Within the logistic regression paradigm, variables used to adjust for case mix are accounted for as covariates (i.e., additional predictors). Alternatively, propensity-scoring methods could be used to adjust for those variables that predict the assignment of patients to particular versions of the procedure. For concreteness, let us focus on logistic regression. In order to perform a sample size calculation for a logistic regression, the analyst must specify the predictive ability of the covariates and the odds ratio associated with the predictor of interest. (For example, version B of the procedure might increase the odds of complications by a factor of 1.5.) Once these inputs are specified, the sample size calculation is straightforward.

Both the logistic-regression and propensity-scoring approaches suffer from the fundamental drawback that they can adjust only for covariates that are observed. In particular, if there are variables that predict outcome that are unmeasured (e.g., a physician's assessment of a patient's likelihood to comply with treatment, or an assessment of "stroke in evolution" not included in the administrative database used as the source of data for the

registry), then the comparison between the two versions of the surgical procedure is potentially biased. Accordingly, before proposing to use a registry to compare complication rates (e.g., across different versions of a procedure or a device) or other outcomes, it is critical to determine that the following three conditions do not all hold: (1) a patient, provider, system, or other characteristic affects the complication rate; (2) this characteristic is unmeasured within the registry; and (3) there is a reasonable likelihood that this characteristic might be differentially distributed across the different versions of the procedure or the device. If all three conditions (in epidemiologic terms, the conditions for *confounding*) hold, use of the registry to compare outcomes is potentially dangerous.

Critical to Designs 1–4 is the assumption that the CE complication rate is stable over time. If this is the case, it is appropriate to use the registry to estimate a single complication rate associated with version A of the procedure, estimate another single complication rate associated with version B of the procedure, and compare the rates. On the other hand, if the technology of CE (e.g., physical materials, surgical technique) is improving, then the registry should continue to monitor the performance of CE over time. Such an ongoing monitoring function seems particularly relevant for medical devices and similar applications.

Even when the associated technology is assumed stable, some registries are intended to provide ongoing assessments of outcomes. For example, in a quality assurance context, CE complication rates might be assessed at individual hospitals on an annual basis (e.g., in order to check for problems that have recently arisen). On the other hand, a registry whose purpose is to assess whether complication rates observed in randomized trials could be achieved in usual practice could be designed with a sunset provision to cease operation once this question is answered. The latter type of registry might, for example, support a coverage decision by the Centers for Medicare & Medicaid Services.

Having an ongoing monitoring function induces additional analytical complications, among others a multiple-comparisons problem. Traditional statistical power calculations are performed under the assumption that the sample size is fixed and that, unless otherwise noted, multiple comparisons are not a major issue. Sequential testing methods associated with randomized trials (where, for example, the type I error of .05 is apportioned into an early test with alpha = .001 and a subsequent test with alpha = .499) are not appropriate for this particular design, since most of these methods assume that the maximum sample size is fixed. Some methods assume that what is fixed is not the number of patients but the number of events, but these methods are also inappropriate for registry applications.

Design 5: Suppose the goal is to estimate the complication rate associated with CE at multiple time points for the foreseeable future. Control chart methodology might reasonably be applied to this class of problems. This methodology, often used in the quality assurance and quality improvement context, was originally developed for industrial applications. In this example, the null hypothesis, under which the system in question is "in control," is that the CE complication rate remains at the desired value of 3 percent throughout the entire followup period. Samples are taken at given points in time (e.g., monthly). As an example, if these monthly samples are of size 100, then the standard error is approximately 1.7 percent. The analyst then creates a *control chart* by plotting these monthly complication rates over time and forming *channels* based on the standard error. In this example, the channel extending from the point estimate to 1 standard error above the point estimate is 3 percent to 4.7 percent.

Once the basic control chart—which goes by different names depending on the scale of measurement of the outcome variable—is formed, the plot is checked for various violations of the null hypothesis of constant complication rates. The set of possible violations to be flagged as statistically significant might include (1) any observation more than 3 standard errors from the mean; (2) two of three consecutive observations more than 2 standard errors from the mean; (3) eight observations in a row that increase or decrease; and (4) eight observations in a row on one side of the mean. These rules of thumb

implicitly take into account the multiple-comparisons problem by requiring noteworthy departures from the null hypothesis in order to be flagged; they are also based on the observed properties of physical machines as they fall out of adjustment: suddenly breaking down and producing an extreme outlier, or gradually heating and thus producing sequentially higher readings. Complication rates of CE might or might not follow the properties of physical machines, but the decision rules from control chart methodology are at least a good place to start.

Appendix B. Copyright Law

Copyright law confers exclusive legal rights on the owner of the copyright.[1] The exclusive rights of copyright may be sold, assigned (transferred), or licensed (limited transfer of rights for use on specific terms or conditions) to others; these rights may also be waived (quit claim). Licensing ordinarily consists of a private agreement governed by contract rather than copyright law.[2]

However, the exclusive rights conferred by copyright to prepare derivative works and distribute copies of a health information registry may be limited by regulatory requirements. Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule restrictions may limit data use, reuse, and disclosures or may require additional patient authorizations for subsequent research use. The conditions of institutional review board (IRB) approval under the Common Rule may also limit reuse and further disclosure of registry data. The terms of patient authorization and consent, a data use agreement, or a business associate agreement may modify the scope and nature of rights protected by copyright law. These limitations can be avoided by the use of de-identified health information, as defined by the Privacy Rule, plus information that is not subject to the Common Rule, if they suffice for the scientific or other purposes of the registry. Without resort to copyright protections, State laws may directly restrict access to registry data, as well as the use and disclosure of data from registries developed by public health agencies.

Formal copyright registration[3] with the U.S. Copyright Office is not necessary but may be desirable for registries anticipated to have commercial value. The owner of a copyright is generally the author[4] or author's employer; ownership of the copyright for a compilation is not ownership of the underlying facts or data.[5] Copyright law presumes that an employer owns the copyright in materials created by an employee within the scope of his or her employment as a "work made for hire."[6] Institutional policies and procedures frequently prescribe whether the registry developer, his or her employer, or a funding agency owns the copyright. Employee manuals often contain an employer's position on the intellectual property created by employees. Research institutions frequently reserve the right to the intellectual property produced by their employees. Intellectual property issues are explicitly negotiated in most sponsored research contracts. Authors of a joint work are co-owners of copyright in the work.[4]

Several factors determine whether the use of a registry protected by copyright for scholarship, research, or certain other purposes is within the statutory fair use limitation on copyright.[7] In general, these factors will support subsequent uses of registry data for research, even though it may be protected by copyright. In any given set of circumstances, a specific analysis of the statutory factors is necessary to determine whether use is likely to be viewed within the fair use limitation on copyright.[1]

Copyright law may provide some legal protections for compilations such as health information registries. The extent of this protection depends on the specific characteristics of the registry. In general, the concept of ownership does not comfortably apply to health information, even when limited to copyright. Nevertheless, some registry developers may want to consider adding the legal protections of copyright to reinforce controls on access to and use of registry data. Registry developers may also encounter copyright protections on health information held by health care providers. Use of health information protected by copyright for research purposes may constitute fair use under copyright law.

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Appendix C. Relevant Entities in Health Information Technology Standards

The Clinical Data Interchange Standards Consortium, or CDISC, is a multidisciplinary nonprofit organization that is focused specifically on medical research and that works toward developing and supporting global, platform-independent data standards that enable information system interoperability. It is a membership organization made up of more than 170 academic research centers, global biopharmaceutical companies, technology and service providers, and institutional review boards.[1] CDISC has established standards to support the acquisition, exchange, submission, and archiving of clinical research data and metadata, such as case report tabulation data definitions, submission data, and operational data modeling; these standards are intentionally vendor neutral, platform independent, and freely available. CDISC has formed key partnerships with other standards bodies, vendors, and research groups to further the creation and use of these and other industry standards. CDISC's Healthcare Link project is an initiative that specifically focuses on the mission of interoperability between health care and clinical research.

Health Level Seven, or HL7, is an American National Standards Institute (ANSI)–accredited nonprofit organization that produces specifications and protocols for clinical and administrative health care data.[2] HL7 is a global organization with corporate and individual membership consisting of providers, vendors, payers, consultants, and government groups. Like CDISC, HL7 does not develop software, but instead creates specifications. HL7's original specification was a messaging standard that enables disparate health care applications to exchange key sets of clinical and administrative data.[3] This standard defines the structure and content of the messages that are exchanged between systems in either batch mode, which facilitates transfer of a collection of individual messages labeled by a single header, or interactive mode, which transmits a single message. HL7 then extended this idea to a Clinical Document Architecture (CDA®), which is designed to support standards for storing and retrieving file-level information such as electronic health records (EHRs).[3] The Reference Information Model then specifies the details, results, and contexts of clinical informatics by defining subject areas, classes, attributes, use cases, and trigger events (such as a followup clinical visit). HL7 also houses important specifications and tools relating to electronic documentation of standards, for example, the Continuity of Care Document.

The Healthcare Information and Management Systems Society, or HIMSS, is an industry membership organization that focuses on knowledge sharing, advocacy, and collaboration among its members. HIMSS is a longstanding advocate of using information management systems to improve health care, and represents a large portion of the industry (more than 20,000 individuals and 350 corporations).[4] HIMSS plays a critical role in this discussion through the HIMSS Electronic Health Record Association, and also through its role in partnering with two other key standards groups: the Health Information Technology Standards Panel (HITSP) and Integrating the Healthcare Enterprise (IHE).

The HIMSS Electronic Health Record Association (EHRA) is a trade association specifically made up of EHR companies. This association is a key player in the interoperability discussion. EHRA focuses on creating interoperable EHRs in hospital and ambulatory care settings by providing a forum and structure for EHR leaders to work toward standards development, interoperability, the EHR certification process, performance and quality measures, health information technology legislation, and other EHR issues.[5]

IHE is an initiative sponsored by HIMSS, the Radiological Society of North America, and the American College of Cardiology.[6] It is designed specifically to bridge the gap between existing standards and the implementation of integrated systems. IHE does this by creating *Profiles*, which specify precisely how standards are to be used in integration implementations. It is important to note that IHE does not develop standards; instead, it provides a link between existing standards and the problems within the industry that need to be solved. The initiative is focused on eliminating ambiguities, reducing configuration and interfacing costs, and ensuring a higher level of practical interoperability for users and developers of health care information technology as they implement standards-based communication between systems and then perform tests to determine that the implementation conforms to the specifications.[7] In recent years, IHE has developed the Patient Identifier Cross Referencing (PIX) Integration Profile, which supports the cross-referencing of patient identifiers from multiple domains,[8] and the Patient Demographics Query (PDQ) Integration Profile, which facilitates the querying of a patient database to retrieve demographics data.[9] Standards from different organizations that achieve the same goal can be inserted into an IHE Profile, and IHE will then produce technical specifications that can be used by developers and vendors to build products compliant with those standards. Because of IHE's practical approach, its value has been recognized by other standards organizations, particularly CDISC. For example, IHE has defined a simple four-step process that carries a specific problem from problem definition, through implementation and testing, to the real world:

1. Identify interoperability problem.
2. Specify Integration Profiles.
3. Test systems at Connectathon (an annual weeklong interoperability-testing event); demo at HIMSS Interoperability Showcase.
4. Implement in real world.

HITSP serves as a partnership between the public and private sectors with the purpose of identifying a widely accepted set of standards for interoperability of health care applications. HITSP is funded by the U.S. Department of Health and Human Services, administered by ANSI, and tightly partnered with HIMSS; Federal agencies are mandated to use interoperability standards that have been harmonized by HITSP.[10]

The Certification Commission for Health Information Technology (CCHIT®) is a private nonprofit organization with the "sole public mission of accelerating the adoption of robust, interoperable health information technology by creating a credible, efficient certification process."[11] It is divided into workgroups that address the standards for specific functional areas such as ambulatory care, behavioral health, personal health records, and cardiovascular care. Since being recognized as a certifying body by the Department of Health and Human Services in 2006, it remains the only federally approved organization to certify health information technology products and systems.

The Regenstrief Institute, Inc., is an informatics and health care research organization and a joint enterprise of the Regenstrief Foundation, Inc., the Indiana University School of Medicine, and the Health and Hospital Corporation of Marion County. Regenstrief is active in developing health care informatics standards, including the widely-used Logical Observation Identifiers Names and Codes (LOINC®) terminology.[12]

Table C–1 provides details about the establishment, membership, and mission of the organizations described above, along with a listing of standards/specifications pertaining to each organization.

Table C–1. Relevant entities in health information technology standards

Group	Year Established	Number of Members	Mission	Relevant Standards/ Specifications
CDISC	2000	>290 (corporate)	Developing and supporting data standards.	CDASH
HL7	1987	>4,000	Producing specifications and protocols for clinical and administrative health care data.	CDA, RIM, CCD
HIMSS	1961	>570 (corporate) >44,000 (individuals)	Knowledge sharing, advocacy, and collaboration	
EHRA	2004	~40 (corporate)	Creating interoperability between existing EHRs.	EHRA Interoperability Roadmap
IHE	1997	>540 (organizations)	Providing a link point between the standards that exist and the problems among the industry that need to be solved.	RFD, CRD
HITSP	2005	>550 (corporate and organizations)	Partnering with public and private sectors to achieve standards to support interoperability among health care software applications.	TP50, C76
CCHIT	2004	94 products certified under 2011/2012 CCHIT criteria	Defines the requirements for an EHR to be certified in the United States.	CCHIT certification criteria (available at ww.cchit.org/certify)
Regenstrief Institute	1969	>50 (investigators)	Improvement of health through research that enhances the quality and cost-effectiveness of health care.	LOINC®

C76 = HITSP Case Report Pre-Populate Component; CCD = HL7 Continuity of Care Document; CCHIT = Certification Commission for Health Information Technology; CDA = HL7 Clinical Document Architecture; CDASH = Clinical Data Acquisitions Standards Harmonization; CDISC = Clinical Data Interchange Standards Consortium; CRD = IHE Clinical Research Data Capture; EHR = electronic health record; EHRA = Electronic Health Record Association; HIMSS = Healthcare Information and Management Systems Society; HITSP = Healthcare Information Technology Standards Panel; HL7 = Health Level Seven; IHE = Integrating the Healthcare Enterprise; LOINC = Logical Observation Identifiers Names and Codes; RFD = IHE Retrieve Form for Data Capture; RIM = HL7 Reference Information Model; TP50 = HITSP Retrieve Form for Data Capture Transaction Package.

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Appendix D. Linking Clinical Registry Data With Insurance Claims Files

A research project is being designed to compare the effectiveness for treating diabetes of one class of medication, or one specific generic medication within the class, to another. The results should provide scientific evidence for patients, physicians, and policymakers to use to make decisions about the use of these drugs.

Registry developer A will collect limited data sets of information on patients discharged with a diagnosis of diabetes from hospitals in three States. These limited data sets do not include patient names or direct identifiers, and so are not considered individually identifiable health information under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The registry developer has institutional review board approval to use the data for research purposes. The hospitals will provide the data sets to group B under a data use agreement that complies with the HIPAA Privacy Rule.

Group B intends to perform probabilistic matching of the registry data to a health insurance claims database to determine diabetes treatment outcomes. Registry developer A and research group B have entered into a formal collaboration for this research project.

The health insurance database will be derived from the claims data of multiple health plans operating in the same three States. The insurers' original data sets include direct beneficiary identifiers and constitute protected health information under the HIPAA Privacy Rule. Because the registry contains only limited data sets, the claims data collected in the insurance database will have to be linked to the registry data using probabilistic matching techniques.

Consequently, the research project will use only a limited data set of health insurance claims data to create the link with the registry data. The health insurance companies will provide the limited data sets of claims information to group B under data use agreements that comply with the HIPAA Privacy Rule.

The common data elements for the insurance database and the registry that will be used for linkage are date of birth, gender, race, hospital ID, State of hospital, date of admission, date of discharge, date of death (if the patient died), ICD-9 (International Classification of Diseases, 9th Revision) code for primary diagnosis for the index hospitalization, primary procedure code for the index hospitalization, and ZIP Code for the patient's address.

In order to protect the identity of the hospitals, the researchers were asked to sign a confidentiality agreement that specifically defined the registry operator's proprietary information. Such proprietary information included the names or other identifiers of hospitals or other health care facilities participating in the registry. The researchers were precluded from using the names or other distinguishing characteristics of the hospitals in any public document, including publications or marketing materials. The confidentiality agreement did allow the researchers to retain an identifier number for each hospital, as long as that number identified only generic characteristics and excluded any information about the hospital that would enable anyone to identify the specific hospital. For example, the researchers could not retain information that classified a particular hospital with a number that identified it as an academic teaching hospital based in a particular State with a certain number of beds, since in many instances the identity of the hospital could be derived from such information. Due to the potential contractual liability that may arise, the possibility of identifying participating hospitals is a critical issue.

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