

Registry Transitions

Draft White Paper for Third Edition of “Registries for Evaluating Patient Outcomes: A User’s Guide”

Introduction

Most, if not all registries, should undergo periodic critical evaluation by key stakeholders to ensure that the objectives are being met and to assess the need for a registry transition. A wide variety of factors may drive the decision to proceed with a registry transition. For example, a registry may need to transition to a new technology platform to remain functional for its participants, or a registry that was designed to study the natural history of a disease for which there was no effective treatment may change its purpose when a new product or therapy becomes available in the market. Other scenarios in which a transition may be necessary include changes in funding sources and stakeholders (e.g., funding for a government-sponsored registry may end resulting in transition to private ownership, such as to a professional association) or the introduction of new regulatory requirements (e.g., adapting a registry to fulfill a post-marketing commitment). Because many different factors may contribute to a registry transition, transitions are highly variable in scope and resource requirements.

This paper focuses on issues that are of particular significance in a major registry transition, defined as a change in the 1) purpose, 2) sponsor, and/or 3) technology platform, all of which will have a substantive impact on the ongoing conduct of the registry. Less ambitious transitions (e.g., changes in data elements on preexisting case report forms) are not specifically covered herein; however, parts of this paper (e.g., data analysis) are pertinent to such transitions.

While the considerations for a major registry transition are similar to those for the launch of a new registry, there are several distinguishing features. First, a registry transition is facilitated by an existing registry and the collective experience of conducting that registry. The existing registry can essentially serve as the starting point for creating a prototype of the revision. The planning and design of the registry transition should also benefit from lessons learned in operating the existing version of the registry. What has worked well and what has been problematic? What challenges have been encountered at every level, from staff entering data at the participating sites to the analyst creating reports? Indeed, one or more of

these issues may be contributing factors in the decision to proceed with the registry transition. Even if this is not the case, the transition provides an opportunity to address these issues. Registry transitions also present unique challenges that are distinct from the development of a new registry. In particular, transferring data collected in an existing registry to the revised registry (i.e., data migration) can be a complex and resource-intensive process.

Despite these differences, the steps in the execution of a major registry transition are analogous to those involved in the launch of a new registry. Therefore, the paper is organized in accordance with the general framework for developing a new registry, with a planning and design phase, an implementation phase to carry out the project plan, and an assessment of the potential impact on data management and analysis.

Planning and Design

The planning and design of a registry transition begins with an assessment phase, in which the need for a transition is considered. Articulating the purpose(s), determining if a major registry transition is an appropriate means of achieving the purpose(s), and assessing the feasibility of a registry transition are important considerations, as such projects require a significant commitment of resources and have associated risks. The “Planning a Registry” chapterⁱ describes the assessment phase for a new registry, much of which is directly relevant to the consideration of a major registry transition. If the assessment leads to a decision to move forward, then the planning and design of the transition can proceed with the formation of a transition team and development of a comprehensive project plan that encompasses governance, ethical and legal issues, and technology considerations.

Forming a Transition Team

The creation of a project charter is often a useful starting point in assembling and focusing a transition team. A project charter typically includes the following information:

- Overview of the transition
- Purpose/justification for the transition
- Goals and objectives of the transition
- Business case for the transition (if applicable)

ⁱ Chapters referenced in this document can be found in the second edition of “Registries for Evaluating Patient Outcomes: A User’s Guide,” available at: <http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%20nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf>.

- Identification of major stakeholders
- Assumptions and constraints (organizational, environmental, and external)
- Potential risks
- Milestones/deliverables or high-level timeline
- Budget
- Transition team members
- References to source documents, if applicable (e.g., new clinical practice guidelines)

The next step is to assemble the transition team, which will be responsible for planning and implementing the registry transition. It is important to include key stakeholders and to think broadly about the talent and expertise needed to accomplish a successful transition. In general, the transition team should include the following members:

- Sponsor/funding organization representative: ensures that the team has the resources necessary to complete the project and keeps the sponsor apprised of any issues that may affect the timeline or budget for the transition.
- Project manager: accountable for all aspects of the transition, including timely escalation of issues for resolution.
- Clinical expert: provides guidance on changes that affect the clinical content of the registry (e.g., changes in purpose and data collection) and provides input on data migration, as needed.
- Epidemiologist/biostatistician: provides guidance on changes that affect the study design and analysis plans (e.g., changes in purpose, data collection, data management, and data migration).
- Data management expert: provides guidance on changes that affect data collection, data storage, or data quality assurance.
- Legal/ethical expert: provides guidance on how changes affect the legal and ethical construct of the registry (e.g., contract with funding source(s), contracts with participating sites, contracts with vendors, and data sharing agreements) and identifies any ethical issues (e.g., need for institutional review board review, changes to informed consent documents, need to re-consent participants).
- Other representatives: depending on the nature of the transition, other representatives may be included on the transition team such as 1) a principal investigator or study coordinator from a participating site to provide guidance on feasibility and burden of data entry, 2) a technical expert to help guide a transition to a new technology platform, and/or 3) a patient advocate to gain the patient perspective.

Once the transition team has been assembled, it is critical to achieve consensus on the rationale and the overarching goal(s) for the registry transition. Open discussion at this stage may identify unanticipated barriers, which can be addressed proactively in the transition planning. Gaining the full support of the transition team will increase the likelihood of a successful registry transition.

Developing a Project Plan

The next step for the transition team is to develop a detailed project plan encompassing timeline and budget. The transition project plan should be thoughtful, complete, and realistic. As with all projects of this magnitude and complexity, disagreement among stakeholders over scope, cost overruns, and time delays may occur. These predictable issues should be anticipated, as much as possible, and risk mitigation strategies considered. The project plan should also consider other sources of risk specific to the transition (e.g., unexpected issues with technology compatibility, delays in obtaining institutional review board approval, and disputes related to ownership issues). The “Planning a Registry” chapter provides more information on project planning considerations.

The project plan should also address staffing issues. The transition may require new expertise and skills that alter staffing requirements. Training existing employees or hiring appropriately skilled personnel may be necessary. Planning for additional workload on the registry staff during the actual transition is also an important consideration, as they may be operating and supporting the existing registry while working on the transition to the modified registry.

Other issues that should be considered in transition planning relate to governance, ethical concerns, legal matters, data collection, and technology. These issues are discussed in more detail in the following sections.

Governance Issues

Nearly all registry transitions will require an internal and external governance structure to manage and approve changes, whether the transition relates to the scientific objectives of the registry, technology changes, or data access. The transition team is one important component of the governance structure. The “Planning a Registry” chapter reviews the governance considerations for the planning of a new registry, many of which are relevant to a registry transition. Some additional considerations are addressed below.

Scientific Advisory Board Governance during the Transition

Many registries have scientific advisory boards that oversee the conduct of the registry. These boards may also play a role in governance during a registry transition and provide external perspective for the considerations and future objectives for a registry transition. Membership of the scientific advisory board should be reviewed to ensure the key stakeholders that are involved in the transition are represented. During the registry transition, the scientific advisory board can also act as an advocate of change by publicly supporting the transition and helping to engage and motivate clinicians at the participating centers. External stakeholders, such as patient advocacy groups and regulatory agencies/health authorities, may also be informed of the transition and, depending on the goals of the transition, potentially enlisted as additional public advocates for the registry transition.

Governance of Data Access

Registry transitions will also require revisiting the data access policies and procedures. If a data access committee is already in place, the committee should be charged with 1) determining how changes in the registry will affect the policies and procedures for accessing data, and 2) reviewing the operational plan for executing analysis plans with respect to the registry transition. Furthermore, if the transition involves a change in registry stakeholders, the procedures for conducting analyses and developing publications should be re-examined. New stakeholders may need to be involved in the prioritization of analysis plans, conduct of analyses, and/or the review of scientific abstracts and manuscripts.

Ethical and Legal Issues

The major ethical and legal issues for registries focus on data privacy, patient confidentiality, and ownership of and access to the data. These issues, covered comprehensively in the “Principles of Registry Ethics, Data Ownership, and Privacy” chapter, should also be carefully considered during a registry transition. It is important to note that interpretations of the pertinent laws and regulations are numerous and varied, leading to inconsistent application among institutions, which may affect multicenter registries.¹ Hence, input from legal counsel and regulatory authorities should be sought when planning a registry transition. Some common legal or ethical concerns that may arise during registry transitions are reviewed below.

Institutional Review Boards/Ethics Committees and Informed Consent

An early step in the registry transition planning process is consideration of the need for institutional review board (IRB)/ethics committee (EC) review. If the purpose of the registry is unchanged and no new data are being collected, IRB/EC review may not be necessary – subject to ethical guidelines and the requirements of the individual IRBs/ECs. However, IRB/EC review would likely be required in certain

transitions, such as if new data will be collected through contact with patients, if the new data that will be collected includes identifiable personal information, or if the data will be used in a different manner than previously communicated to patients (45 CFR §46.102(f)).

A registry transition may involve extending the follow-up period of the initial cohort. In these circumstances, re-contacting patients or using their identifiers may be necessary to collect the longer-term data. This may require modification of informed consent documents and amended protocols. For example, a cardiac assist device registry may have been established initially to determine perioperative safety. However, new safety concerns associated with longer-term implantation may prompt a change in the purpose of the registry. Medical records, death indices, and patient interviews may be required to collect the longer-term follow-up data. This new data collection effort would likely require IRB/EC review.

Consideration should also be given to whether any changes will be required in the informed consent process (e.g., obtaining revised consents from existing subjects, obtaining new consents for registries that do not currently have such consents). If consent was obtained for registry participation initially, re-consenting may be needed, especially when the registry transition will result in (1) longer or otherwise different follow-up than what was originally agreed to by patients, (2) direct contact with patients to obtain new data, (3) collection of biological samples or linkage of existing specimens to registry data, (4) the use of data from deceased participants, or (5) linkage of the participant's data to other databases. If the planned registry modifications involve patients for whom the feasibility of obtaining consent would require unreasonable burden or situations where the consenting process would potentially introduce an unacceptable level of bias,^{2,3,4} discussions with local IRBs/ECs should be undertaken to see if the consent can be waived. The "Informed Consent for Registries" chapter discusses these issues in more detail.

Data Collection

A major component of the registry transition project plan should be a thorough evaluation of current and future data collection needs. The project plan should allocate time for epidemiologists and clinical experts to jointly review the current registry case report form (CRF). It is of paramount importance that the relevance of the current set of data elements is reviewed, in light of what is known about new hypotheses to be tested. During this review, some data elements may be deemed irrelevant and may not be required moving forward. When considering the collection of additional covariates and outcomes, particular attention must be given to balancing the scientific relevance of the new data elements with the logistical burden on participating centers.

Additional considerations may arise if a registry transition involves one of the following specific circumstances.

Collection of Biological Samples

Biobanks, defined as facilities that store biological material (e.g., serum, genomic material, pathology specimens) from humans, are increasingly popular additions to registries.⁵ The addition of a biobank raises many logistical issues, which are outside the scope of this paper. However, it should be noted that the addition of a biobank will likely require changes in the informed consent. Some biobanks have used general consents to cover future analyses of the biological material and integration into the registry, but there is significant concern about these broad consent documents. Some commentaries on this issue have suggested that such broad consents are more appropriate when limited to a specific disease entity, thereby allowing for studies examining diagnosis, mechanisms of disease, risk factors, and treatment outcomes.^{6,7,8} The “Informed Consent for Registries” chapter discusses these issues in more detail.

Pediatric Registries

If a registry enrolls pediatric participants and the registry transition involves extending the follow-up period, consideration should be given to whether participants need to be consented when they reach an eligible age. This is particularly important for those registries that plan to add a biobank or link to other databases as part of the transition process. There is considerable debate regarding the ethics of parents enrolling their children in research studies. More discussion on this topic can be found in the “Informed Consent for Registries” chapter. It is also important to note that for all registries, the right to withdraw is inherent;^{9,10} see the “Principles of Registry Ethics, Data Ownership and Privacy” chapter.

National to International Registry

Some registry transitions may extend the geographic scope of a registry. For example, a U.S.-based registry may add participating sites in Europe. When the registry scope extends beyond national borders, additional ethical and legal concerns must be addressed. Each country may have different legislation and restrictions for the collection and processing of subject information and its use for research. Adequate time and additional resources to investigate these requirements should be factored into the project plan. Moreover, if Federal funds are used in the registry transition, additional steps may be involved in the expansion of the registry. In particular, some registries may be collecting data on vulnerable international populations for which additional privacy protection safeguards may be necessary. Federal guidelines for performing international research should be consulted as part of the planning process.

Data Ownership and Licensing

A number of scenarios exist in which ownership of registry materials must be delineated, including the interface, platform, infrastructure, and data. During a registry transition, particularly one involving a change in stakeholders, a careful review of agreements or contracts should be performed to determine if modifications are needed. In some cases, the registry transition may involve moving data from one platform to another. Hence, data ownership may need to be clarified. For example, a professional organization may determine that the vendor maintaining its registry is performing below expectations and may select a new vendor to house and run the registry. Depending on the terms of the prior agreements, it may or may not be possible to import the historical data into the new vendor's system.

Registry data are often collected using electronic or paper CRFs that may have intellectual property protections, including copyright, trademark, and patent. Measures should be taken to ensure that the appropriate permissions for use are still applicable when the registry transitions if continued use of these forms is planned.

Data Access

In addition to data ownership, ongoing and future data access is an important consideration. The new and ongoing registry stakeholders should consider whether the previous stakeholders should have access to the previously collected data as well as to the data collected in the future. Federal and academic stakeholders may need to execute technology transfer agreements (e.g., material transfer agreements) or other contractual agreements in order to access the data.

Changes in Funding

Registry transitions may also include changes in funding. For example, a registry that was initially funded through a government grant may be transitioned to a professional association or industry partner. When funding sources change, the role of the funding entities should be clearly delineated to ensure that there is no real or perceived threat to privacy or data confidentiality.

In some cases, a change in funding may require contract modifications in anticipation of potential conflicts between the new stakeholders and the remaining stakeholders. For example, industry may elect to partially fund a registry that is also receiving Federal funding from a regulatory agency. Contracts may need to be modified to clearly delineate how each set of funds will be spent. The new chapter on public-private partnerships provides more information on these issues. As with all contracts involving Federal funds, attention should be given to regulations governing their appropriate use. Additionally, changes in

funding may raise new ownership issues. It is important to have unambiguous conversations with stakeholders and associated contractual agreements that clearly delineate the rights of the funding entities.

When data are transferred from one owner/sponsor to another, the liability associated with the protection of subjects' information should be clarified. Consideration should be given to indemnification clauses in data transfer agreements. Oftentimes, the data transfer agreements detail that the new sponsor of the registry will accept all liability for use of the data previously collected by the transferring sponsor. The data transfer agreement should also contain a clause that the new sponsor agrees to use the data properly. In these circumstances, the liability would be assumed by the new sponsor if there was a breach of information whereby subject-level information is relayed to an outside party. If the new sponsor is a Federal entity, however, there are regulations that prohibit the Federal government from indemnifying others (e.g., Anti-Deficiency Act).

Contracts with Vendors

Issues may arise with vendors (including inadequate performance of duties, loss of financial solvency, or escalating cost of renewing the contract), necessitating a transition to a new vendor. In light of these potential outcomes, it is necessary to draft contracts that consider these scenarios and contain provisions to address them. For example, if a registry is being transitioned to a new, fledgling company, consideration should be given to establishing an escrow account for the registry. This account would cover the cost of ensuring that the data remain accessible to the sponsoring body. Moreover, it prevents the registry from being part of the estate if the company is unable to meet its contractual obligations. Establishing the escrow account would increase the cost of the initiative for the sponsor, the vendor, or both and should be considered when planning the transition. In addition, contracts should contain explicit clauses that guarantee the transmission of data to a new vendor when the contract expires or if the vendor defaults on the contract.

Technology Considerations

A registry designed to collect long-term follow-up data will inevitably undergo technology changes. Platforms for electronic data capture (EDC) may be upgraded (such as version updates within a system), or the registry sponsor may select a different third party vendor to host the EDC system. Upgrading the EDC system and technology platform may enable more frequent data entry from participating centers, rather than annual or semi-annual data reporting under previous technology environments. Such changes have implications on training plans for participating centers (see below). Technology considerations relevant to linkage of a registry to an electronic health (medical) records (EHR/EMR) or other database and for collection of patient reported outcomes are covered elsewhere in this volume.

In transitioning to a new registry technology platform, it is important to clearly define software requirements to avoid design flaws, which are costly to correct after project completion. Soliciting input from various stakeholders (e.g., data entry personnel, clinical experts, data analysts) may be helpful to validate the proposed design of the new registry. The proposed design should be presented to them in an easy-to-understand format (e.g., a prototype) rather than a detailed requirements document, which may be more difficult to comprehend. Setting aside time for user acceptance testing (UAT) or pilot testing may also be useful to identify issues before the transition is complete.

One of the earliest and most important decisions in transitioning to a new technology platform is whether to develop the platform in-house or to use an external vendor. Each approach has advantages and disadvantages. The in-house approach requires personnel with the appropriate expertise and the infrastructure to support such a project. Development tools widely used by software companies should be employed, if possible, to mitigate the risk of experiencing shortages of qualified personnel for ongoing support and maintenance of the application. Organizations that do not have the internal resources and expertise to develop a registry application in-house usually turn to external vendors. Selecting a registry vendor is an important strategic decision for an organization, particularly for sponsors who anticipate operating the registry for many years. Some factors that should be considered in selecting a registry vendor are outlined in Figure 1 below.

Figure 1: Considerations in Selecting a Registry Vendor

- Develop detailed requirements for the new registry before issuing a request for proposals. The requirements may be modified later to align with the vendor's framework for development, but having complete requirements early in the process will allow for a more accurate timeline and cost estimate.
- Gather as much information as possible about the potential vendor by contacting existing clients and asking detailed questions about communication, timelines, budget, and post-release support.
- Ask an independent expert to evaluate and analyze the technology platforms and technology expertise of the potential vendor.
- Ask the potential vendor to be specific with their cost estimates. Avoid vendors that cannot provide concrete estimates.
- Know the hosting and maintenance fees of the existing registry and compare them to the hosting and maintenance estimates from the potential vendor.
- Assess the security policies and procedures established by the vendor and ensure that they

comply with the industry standards and best-of-breed practices.

- Assess the ability and willingness of the potential vendor to transfer registry data (both transfer of historical data into their registry application and transfer out from their registry application if the registry changes vendors in the future).
- Learn about the vendor's experience in importing data from other sources of medical information using standard interfaces (e.g., HL7, CDISC) and also about their ability to build custom interfaces. A list of existing and emerging standards in the field is maintained by U.S. Food and Drug Administration (FDA) and available at:
<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.
- Consider the vendor's international experience, including translation and help desk support, if pertinent to the planned transition.
- Obtain policies related to data access, including how participating sites can access their own data and how the registry team can obtain datasets for analysis.

Once a vendor has been selected and the features of their technology platform are known, it is important to assess the hardware, software, and browser configurations at the participating sites, as these may affect performance of the registry application. It is also important to ensure that the participating sites have access to the optimal configurations on which the application has been tested and validated. Requesting a technology contact person at each of the participating sites may be helpful to facilitate working through these issues during the transition.

Another technology consideration is transitioning personnel involved in data entry at participating sites from an existing registry to the new registry. This requires an analysis of security levels in order to transfer users to the appropriate permission level in the revised registry. In some cases, users can be transferred electronically from the existing to the new registry application, but in other cases, they must be added manually. The transition team must develop a plan for accomplishing the transfer that minimizes the effort at the participating sites, but ensures only valid users can access the registry at the appropriate permission level. Of note, a registry transition provides an opportunity to assess the activity level of users at the participating sites and their ongoing need to access the registry.

A final technology consideration pertinent to a transition relates to the closeout of an existing registry. Generally, the closeout should be scheduled well after the anticipated launch of the new registry, as

timelines on such complex projects are often delayed. The existing registry may also be useful in validating successful data migration into the new registry.

Implementation

Once a transition plan has been developed and the decision has been made to move ahead, it is important to communicate with stakeholders about the plans, train registry participants on the changes and support them through the launch, and assess the impact of the transition on data management and analysis activities.

Communication

Communicating with all stakeholders is critical during a registry transition. The transition team should develop a communication plan that defines who is responsible for communicating what and to whom. The frequency and mode of communication should be established with a particular sensitivity to key stakeholders. Since the registry transition will likely disrupt workflow at the participating sites, communicating the rationale for the change, the timeline, and the impact on users is important. Any change in expectations or incentives for participation should be fully explained. It is important to anticipate and respond to questions and concerns from participating sites, knowing that change can lead to stress and anxiety. In most circumstances, the communication plan will focus on retaining participating sites through the transition. However, a registry transition provides an opportunity to evaluate participating centers to decide whether all of them should be retained. A transition may also be an ideal time to recruit additional sites.

Training

The development and implementation of a robust training program prior to the registry transition will facilitate the roll out of the revised registry and improve the quality of data collected. Training needs will vary according to the scope of the registry transition. For example, a technological change that affects the user interface, functionality, and/or organization of the data elements will likely require extensive training, whereas a transition related to a change in purpose with minimal impact on data entry should require less training. When developing a training program, the key elements of adult learning theory¹¹ should be kept in mind, and several questions should be addressed:

- Who is the intended audience? Determining the audience will have a significant impact on the design and implementation of the training program. For example, internal staff training will differ

from that of external registry participants and the training program for clinicians will likely differ from that designed for data entry personnel.

- What are the learning objectives? The learning objectives should drive the development of the curriculum. What do the people involved in the registry need to know to be successful during and after the transition? The focus should be on what will change and why, and the impact of the changes on registry participants.
- What information is needed to meet the learning objectives? High-level overviews and detailed documents are useful to help participants with varying levels of interaction with the registry understand the changes. The creation of a reference guide that clearly describes what changes were made and why each change was made will be extremely helpful to some registry participants.
- What are the best mechanisms for disseminating the information? People respond differently to various learning environments and techniques. Depending on the size of the registry, training may be offered in various ways, some of which are described below:
 - Conference calls can be effective for smaller groups and allow for open discussion.
 - Webinars can be useful when larger groups are involved and the training activity includes visual presentation.
 - Face-to-face meetings are frequently effective since the learner is less likely to be distracted.
 - One-on-one training sessions are usually well received, since the training can be customized to the individual learner. However, this approach is costly.
 - User's guides, manuals, FAQs, and other documents can be posted on a website, or hard-copy materials can be distributed to participants.
- What is the best approach to ensure that learning has occurred? It is important to confirm that the training program is successful, in order to avoid issues with retention and data quality after the transition launch. Learning assessment approaches include tests (e.g., the completion of a sample data collection form or other task), surveys, and direct feedback. Feedback from the learning assessments should be incorporated into the training program, as needed. Pilot testing may also be useful for refining and strengthening the training program before launch.

Supporting Participants through the Registry Launch

In addition to a robust training program, sufficient personnel and resources should be assigned to respond to input and inquiries from registry participants following the launch of the revised registry. Accessibility of the support team is very important during this critical period of the transition. Planning for the registry

launch should delineate how users can submit questions or concerns (e.g., by e-mail or calling a support desk), who will be the first responders, and how complex issues will be escalated for further evaluation. Many straightforward questions (e.g., problems logging on) can be resolved quickly and efficiently. However, it is important to carefully assess all input from participants since they may uncover problems with the revised registry that have been missed during testing. Such problems may require immediate attention not only from support personnel, but also from the developers of the registry application. At some defined point in time (e.g., 1 to 3 months after launch), a broader analysis of all of the questions and comments from participants may be helpful in prioritizing any further changes to the registry.

Data Management

Technological changes may require a change to the database/data warehouse used to store the registry data. Database or data warehouse transfers are complex processes that involve a number of steps, including creating a new database layout, mapping the legacy data to the new database layout, and transferring the data with rigorous quality controls to ensure that the transfer is successful. Database transfers also need to be conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 and any regional IRB or EC approvals to ensure that the privacy of any patient-level data is maintained. The size and complexity of the registry as well as the extent of the changes in the CRFs will determine the complexity of the data mapping process. The data fields known to users of the registry might be collected in different contexts (e.g., with added specificity or new dependencies between data elements on CRFs) and these differences must be considered in the data mapping process. Relatively small changes in the wording of a question on the CRF, or creating an additional category on an existing item (e.g., expanding categories of ethnicities) may introduce ambiguities in mapping the existing dataset to the new environment. In other instances, significant changes to the definition of an outcome variable will typically require review and adjudication of prior cases to establish longitudinal consistency across the dataset (for further detail, please refer the section below on “Impact on Existing Cases of an Outcome”). For these reasons, input and evaluation of the impact of the migration on future registry outcome analyses from subject matter experts, including epidemiologists and clinical experts, along with documentation of decision rules that were established during the epidemiological and clinical review, will be needed in the data mapping process. The effort and expense involved in the data migration is often underestimated and adequate time must be allocated during the project planning and in establishing timelines. Despite careful attention to detail, this activity often becomes an iterative process, with data mapping, data importation, and quality control checks that lead to corrections in the data mapping, re-importation of the data, etc.

Many practical issues should be considered when transferring a database. First, it is important to document the rationale for adding, modifying, or deleting data fields, so that this information can be communicated to stakeholders and registry participants. Second, carefully consider the future impact of changes. Certain changes may make it difficult to link prior datasets with the new datasets. For example, adopting a new, broader definition may mean that data can only be linked in one direction, as shown in Figure 2.

Figure 2: Impact of Definition Changes on Data Linkage

Old Definition	New Definition	Linkage Direction
Death: A mortality that occurred in the hospital within 30 days of the procedure.	Death: a mortality that occurred within 30 days of the procedure, whether in the hospital or not.	Deaths in the old dataset fall within the parameters of the new definition. However, deaths according to the new definition would not necessarily apply to the old definition since they include mortalities post-hospitalization.

When making changes to the data structure, the following questions should be considered:

- Will existing queries (i.e., questions raised by a data manager and issued back to the participating centers regarding a data entry issue) need to be rewritten for the new dataset?
- Will existing reports (e.g., percent of patients with a lab value above a certain number) need to be revised for the new dataset?
- Will more server space be needed to house the data?
- How can the impact of the changes on the processes affected by the new data structures be minimized?

It is also important to determine what metadata (e.g., long name, short name, data type/data format, and permissible values) are important to capture for each field and how the transition will affect the metadata.

Data Analysis

A registry transition may introduce many data analysis considerations that require the input of epidemiologists and/or biostatisticians. Transitions that involve new hypotheses or technological changes can present enormous challenges to the continuity and validity of the analyses. The issues range from the handling of new data elements to the introduction of selection bias or recall bias if the cohort definition evolves during the transition.

Changes in Cohort Definition

A registry transition may involve a change in the inclusion or exclusion criteria for patient participation, thus shifting the definition of the study cohort. These changes can occur under a number of scenarios, such as if the registry moves from a disease-based cohort (i.e., no inclusion criteria for receiving a particular treatment) to focusing on a cohort of patients with the disease who receive a specific therapy or class of therapies (i.e., inclusion criteria now requires patients to be receiving a treatment). Cohort definitions may also change based on geography (e.g., if a registry transitions from a national to a global catchment area). This introduces the possibility of geographic differences in disease severity or treatment patterns, which may require thorough documentation of baseline clinical status in order to stratify or perform covariate adjustment, if necessary.

Other changes in the cohort definition may occur if the registry transitions from having broad participation by centers to a limited set of centers (e.g., physicians who are associated with large specialty care clinics). A registry transition that results in such a change in the cohort definition has the potential to introduce selection bias into the registry by focusing the enrollment and ongoing follow-up of subjects on a potentially more severely affected group of patients. As enrollment and follow-up occur, epidemiologists should be actively involved to assess if selection bias has been introduced. Comparisons of demographic and baseline clinical features of subjects before and after the transition may be sufficient to assess the degree of bias introduced and to understand which factors or variables can be considered for stratification or covariate adjustment. Advanced methodologies such as comorbidity indices or propensity score analyses may be necessary to adequately adjust for the changes in the cohort over time.

Introducing New Data Elements

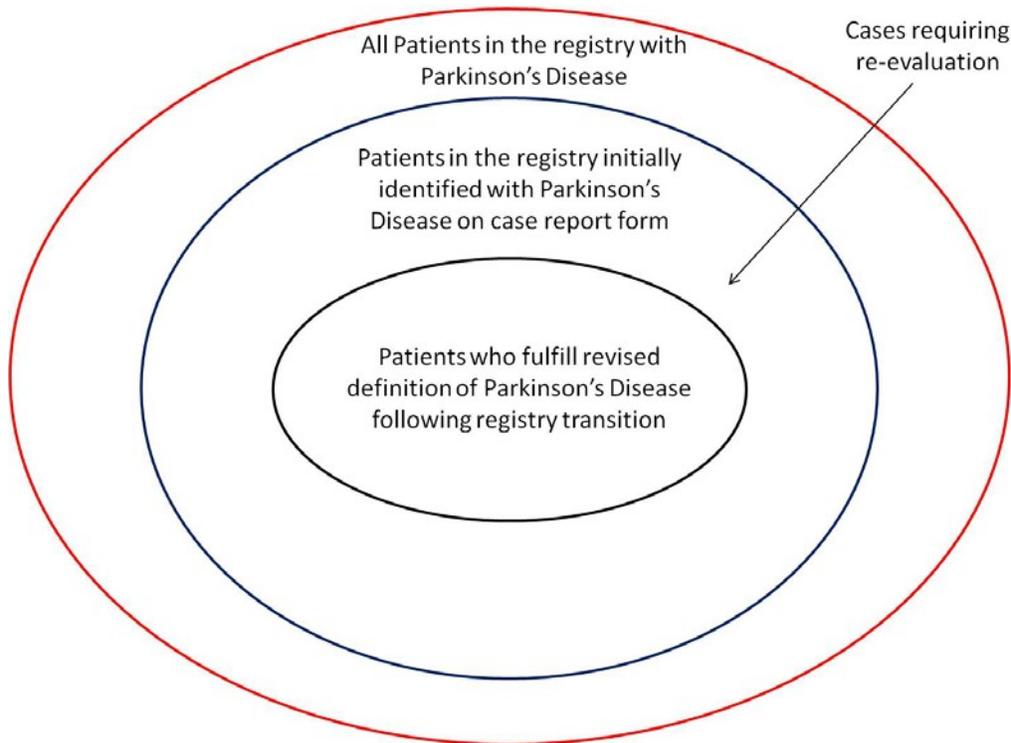
As scientific advances further the understanding of a particular disease or new treatments become available, new hypotheses will likely be formed. In order to test new hypotheses, adding data elements and/or refining the definition of existing data elements may be necessary. Validating new data elements, through source document verification of the original medical records, laboratory tests, or diagnostic

reports, may be required. Results of source document verification may show there are discrepancies in the accuracy of new data elements being captured. For example, investigators interested in collecting data on heart failure as an outcome may find variation in how the definition of heart failure is applied across contributing centers. While the refinement of definitions for data elements occurs, analyses on the outcome variables may still take place. However, methods of quantitative sensitivity analysis may be necessary to understand the degree to which misclassification of variables may introduce bias into the analytic results. Results of source document verification efforts can be used as inputs into quantitative sensitivity analysis to directly estimate the sensitivity and specificity of the outcome variable.

Impact on Existing Cases of an Outcome

A registry transition may lead to redefining an outcome in order to increase sensitivity and specificity. For example, a registry that has been collecting data about the onset of Parkinson's disease as an outcome measure may transition to more stringent inclusion and exclusion criteria. Although this may result in increased validity of the outcome, the statistical power of the analyses from the registry may be compromised, as there will likely be fewer patients meeting the case definition going forward. Patients who have already been identified in the registry as cases may require re-evaluation (and possibly re-adjudication) to determine if their clinical scenario fulfills the revised selection criteria.

Figure 3 shows the potential impact of a change in an outcome (e.g., case definition of Parkinson's disease) following a registry transition. Note that the smaller cohort size following the registry transition may reduce statistical power and cases that met original case definition may require re-evaluation.

Figure 3: Potential Impact of a Change in Outcome

Impact of Patient Reported Outcomes

Registries frequently include patient reported outcomes, such as the SF-36® health survey or activities of daily living. It is important to note and characterize whether the type of patients and their disease severity or outcome status who are reporting self-assessments to the registry is changing over time because of the transition. If such instruments are introduced during a registry transition, patients may begin to preferentially recall events, which can lead to a bias in the outcomes. In addition, if the registry transitions from a purely disease-based registry to a therapy- or product-based registry, patients who become aware of this change may begin to report their health status more or less favorably.

The example below illustrates the possible consequences of transitioning from a disease-based registry to a focus on patients with the disease exposed to a particular therapy. Prior to the transition, the risk of the outcome among exposed and unexposed patients was similar. Following the transition, there are more exposed patients, and, for the purposes of illustrating the impact of bias, assume awareness of the registry transition results in exposed patients preferentially reporting onset of a particular outcome. Because of

this preferential report, the risk is approximately 25% greater among the exposed as compared to prior to the transition. The apparent risk ratio is now 1.46 comparing exposed to unexposed.

	Exposed	Unexposed
Before Transition		
Cases with specific patient- reported outcome	70	50
Total Patients	450	375
Cumulative Incidence per 100	15.6	13.3
Risk Ratio	1.17	
Following the Transition*		
Cases with specific patient- reported outcome	175	50
Total Patients	900	375
Cumulative Incidence per 100	19.4	13.3
Apparent Risk Ratio	1.46	

**The emphasis on enrolling patients who have been exposed to the therapy leads to an apparent 25% increase in the incidence of cases among the exposed.*

Comparative Effectiveness Analysis

A registry may transition from a disease-based cohort to one that is focused on specific treatment(s) in order to establish comparative effectiveness studies between multiple treatments. A greater emphasis on baseline covariate data may be required in this situation, and epidemiologists should be involved to identify the key variables that would account for differences in disease severity between the treatment groups in order to mitigate bias such as confounding by indication. Epidemiologists must also be involved in planning the statistical analysis, which may require matching techniques or other multivariate statistical techniques.

Biostatistics and Statistical Power

Statistical power must be considered in registry transitions that lead to changes in the size of the cohort and/or the extent of follow-up. For example, a transition that focuses the registry on a smaller number of participating centers may diminish the number of new enrollees, but have the benefit of providing an extended length of follow-up. The transition may eventually provide a greater number of exposed patients who develop the outcome(s) of interest. Biostatisticians should be involved in assessing the impact of changes in cohort accrual on statistical precision of the analyses. Previously specified hypotheses of interest may no longer be testable from the standpoint of statistical power. Alternatively,

consideration of statistical power for newly specified hypotheses following the transition may provide an assessment for the extent of enrollment and follow-up required for robust future analyses.

Conclusions

Many registries will undergo a major transition at some point in their lifecycle, most often related to a change in purpose, sponsor, and/or technology platform. A major registry transition is a complex and resource-intensive process with associated risks. Careful and comprehensive planning will maximize the probability of success. However, unexpected challenges may still occur during the implementation phase. The transition team should be prepared to react to circumstances as they arise and modify the project plan accordingly. This paper has reviewed the steps involved in the execution of a registry transition, including the planning and design, implementation, subsequent impact on data management and analysis issues. Figure 4 presents a checklist of key issues that may be helpful to readers who are considering a major registry transition.

Figure 4: Checklist of Key Considerations for a Registry Transition

Planning and Design Phase

- 1) Determine if a registry transition is appropriate and feasible.**
 - a. Has the purpose of the transition been clearly articulated?
 - b. Is a transition an appropriate means of achieving the purpose?
 - c. Is the transition feasible from a resource perspective?
- 2) Organize a transition team.**
 - a. Has a transition team been assembled with all necessary areas of expertise?
 - b. Is the team in agreement on the rationale for and goals of the transition?
- 3) Develop a transition project plan.**
 - a. Does the project plan cover timeline, budget, and staffing?
 - b. Have ‘lessons learned’ from operating the current registry been considered and addressed in the transition plan, as necessary?
 - c. Have major risks been identified and risk mitigation strategies considered?
- 4) Engage advisory boards and other stakeholders.**
 - a. Is the scientific advisory board in agreement with the rationale for and goals of the transition?
 - b. Are any changes to the scientific advisory board needed to ensure that appropriate areas

of expertise for the transition are represented?

- c. Will changes to the data access policies and procedures be necessary?

5) Consider legal and ethical issues.

- a. Will the changes require review/approval by an IRB/EC?
- b. Do the changes require informed consent, or does the existing informed consent form need to be updated?
- c. Is the registry expanding to collect data in new countries? If so, what additional ethical and legal considerations must be addressed?
- d. Are any changes needed to existing contracts or agreements?

6) Assess the potential impact of technology changes.

- a. Does the transition involve changing to a new technology? If so, have the hardware, software, and browser configurations been assessed at participating sites to ensure that the new technology will perform well?
- b. Is there a plan for transferring personnel (usernames/passwords) from the previous system to the new system?
- c. Will a new registry vendor be selected? If so, have potential vendors been thoroughly assessed (see Figure 1)?

Implementation

1) Share information on the transition with registry participants and stakeholders.

- a. Is there a communication plan that clearly defines who should communicate what information to whom and at what time?
- b. Who will answer questions about the transition?

2) Train registry participants and support them through the launch.

- a. Have training plans been developed for registry staff and participants?
- b. Is there sufficient registry staff to carry out training for participants?
- c. Have registry materials (e.g., user guides, data definitions) been updated?
- d. Has a plan been developed to support participants after launch of the revised registry?

Data Management and Data Analysis

1) Develop a plan for data migration.

- a. Is data mapping or migration necessary?
- b. Are the timeline and budget sufficient for data migration, which is often an iterative, complex process?

- c. Is there a clear rationale for adding, modifying, or deleting each data field?
- d. Have the implications of changes to the data structure been carefully considered?

2) Determine how the transition may affect data analyses.

- a. Did the transition change the definition of the study cohort? If so, has the potential for selection bias or recall bias been assessed?
- b. Have new or modified data elements been reviewed to determine if participants are reporting this information correctly?
- c. Have outcome measures been redefined? Will existing cases of the outcome require re-adjudication?
- d. If comparative effectiveness research is planned, will additional baseline covariates be needed for the analyses?
- e. Will the transition affect the statistical precision of the analyses?

References

-
- ¹ Nosowsky R, Giordano TJ. The health insurance portability and accountability act of 1996 (HIPAA) Privacy Rule: implications for clinical research. *Ann Rev Med* 2006; 57: 575-90.
- ² Littenberg B, MacLean CD. Passive consent for clinical research in the age of HIPAA. *JGIM* 2006; 21: 207-211.
- ³ al Shahi R, Warlow JC. Using patient-identifiable data for observational research and audit. *BMJ* 2000; 321: 1031-2.
- ⁴ Tu JV, Willison DJ, Silver FL, et al. Impracticability of Informed consent in the registry of the Canadian stroke network. *NEJM* 2004; 350: 1414-21.
- ⁵ Truyers C, Kellen E, Arbyn M, et al. The use of human tissue in epidemiological research; ethical and legal considerations in two biobanks in Belgium. *Med Health Care and Philos* 2010; 13: 169-175.
- ⁶ Hauser RM, Weinstein M, Pool R, Cohen B, eds. (2010) *Conducting Biosocial Surveys: Collecting, Storing, Accessing, and Protecting Biospecimens and Biodata*. Washington (DC): National Academies Press (US).
- ⁷ Hofmann B. Broadening consent--and diluting ethics? *J Med Ethics*. 2009 Feb;35(2):125-9.
- ⁸ Ries NM. Growing up as a research subject: Ethical and legal issues in birth cohort studies involving genetic research. *Health Law J* 2007; 15:1-41.
- ⁹ Ries NM. Growing up as a research subject: Ethical and legal issues in birth cohort studies involving genetic research. *Health Law J* 2007; 15:1-41.
- ¹⁰ Ries NM, LeGrandeur J, Caulfield T. Handling ethical, legal and social issues in birth cohort studies involving genetic research: responses from studies in six countries. *BMC Medical Ethics* 2010; 11:4-9.
- ¹¹ Knowles, M. (1996). *Adult Learning*. In Robert L. Craig (Ed.), *The ASTD Training and Development Handbook* (pp. 253-264). NY: McGraw-Hill.