A REFERENCE DOCUMENT

Neurological Registry Best Practice Guidelines

A Peer-Reviewed Practical Guide to Patient Registry Development and Operations in Canada

Acknowledgements

Sincerely,

Lawrence Korngut, Nathalie Jette, Tamara Pringsheim, Megan Johnston

Correspondence to:
Lawrence Korngut
Department of Clinical Neurosciences
University of Calgary
480060, 4th Floor Administration
South Health Campus
4448 Front Street S.E.
Calgary, AB, T3M 1M4
Phone 403.956.2462 • Fax 403.956-2992
Email: lawrence.korngut@albertahealthservices.ca

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The Case for Neurological Registry Best Practice Guidelines in Canada

Nathalie Jette[1,2], Megan Johnston[1], Tamara Pringsheim[1], Lawrence Korngut[1]

RATIONALE

Why are neurological conditions so important to Canadians?

In 2005, The World Health Organization (WHO) reported that neurological conditions account for over 6% of the global burden of disease.[1] The relative contribution of neurological conditions is greater in high income countries such as Canada.[1] The burden of neurological conditions is substantial because many: (1) are chronic and lack curative therapies; (2) occur or manifest throughout the lifespan (e.g. epilepsy, traumatic brain injury); (3) follow a progressive course; (4) lead to functional limitations; and (5) require significant healthcare resources and caregiver investment. The WHO predicts that the healthcare burden from neurological conditions will increase over the next 20 years. Estimated total deaths attributed to neurological conditions are predicted to rise by approximately 0.6% by 2030 while estimated total disability is predicted to rise by about 0.5%.[1]

A recent report from the Canadian Institute for Health Information (CIHI) focusing on 11 neurological conditions reported that in Canada: (1) the total cost of these conditions ($8.8 billion) represented 7% of the total attributable cost of all illness while nine of the 11 conditions accounted for 8.3% of the total indirect cost of illness ($6.5 billion per year) in 2000-2001; (2) six of the 11 conditions accounted for 10.6% of the total disability adjusted life years in Canada; (3) in 2004-2005, nearly 20% of patient days in Canadian acute care hospitals were for persons affected by one of the 11 conditions and (4) in 2005-2006, 50% of complex continuing care stays were for patients with Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), cerebral palsy (CP), epilepsy, traumatic brain injury (TBI), multiple sclerosis (MS), Parkinson's disease (PD) or stroke.[2]

National Population Health Study of Neurological Conditions

On June 5, 2009 the federal Minister of Health announced the four year National Population Health Study of Neurological Conditions.[3] This study was led by the Public Health Agency of Canada in collaboration with Neurological Health Charities Canada; the Canadian Institutes of Health Research and Health Canada. The objectives of the study were to improve knowledge of the scope of 14 neurological conditions in Canada (incidence, prevalence, and co-morbidities); use of health services; gaps in services and recommended improvements; and impacts of neurological conditions now and projected over the next 20 years (including economic cost). A comprehensive report of the study findings will be published in 2014.

Information on the burden of neurological conditions is limited or unavailable

The WHO's Global Burden of Disease report (2006) and CIHI's report on the Burden of Neurological Diseases, Disorders, and Injuries in Canada (2007) both found that while the burden of neurological disorders in Canada is high (over 10% of total disability), complete information on the burden of these conditions is unavailable.[1,2] Indeed, for CIHI's report, only 6 out of 11 neurological conditions examined had estimates of disability burden.

Patient registries are a key source of data to assess the burden of neurological conditions

A patient registry can be defined as an observational cohort study of real-world clinical practice related to a disease condition or procedure/therapy, without a study-mandated treatment. With the ability to securely catalogue and track many patients across large geographical areas, registries can provide epidemiological data and fill gaps in medical evidence.[4] In addition to tracking disease burden and therapeutic effectiveness, registries may be useful for tracking the use of medical therapies, performance measurement for the purpose of quality improvement, evaluating the "real world" effectiveness of medical therapies in practice outside the highly controlled conditions of clinical trials, identifying relationships between risk factors and disease outcomes, and evaluating access to care. Despite the utility of registries little guidance is available for investigators and stakeholders on the quality of information derived from these data sources.[4]

The WHO's World Health Report identified five core competencies for long term patient care.[1] One of these five core competencies was the development of information and communication technologies including registries to ensure continuity of care.

As Canada's healthcare system faces multiple stressors over the next 20 years including increasing costs, mismatches between human resource supply and demand, and an aging population, solutions to address the increasing burden of neurological disease must be identified urgently. The first step towards this goal is to improve the available information on neurological disease burden in Canada.

The key to successful national neurological registries is to develop consensus guidelines and a toolkit that will guide registry leaders in their development to ensure comprehensive, systematic, and meaningful collection of data.

Patient registries present an important opportunity to improve the information available in Canada on neurological disease burden. However, statistics collected from patient registries will only be meaningful if the registries are implemented consistently so the data collected can be compiled and compared.

A significant need exists for comprehensive guidelines for registry development (including online registries) and implementation within neurological disease in Canada. Varying provincial privacy regulations and research ethics review board (REB) perceptions result in logistical and financial obstacles to multi-regional and national registry implementation and operation within Canada. The development of consensus guidelines targeting best practices and identified obstacles will facilitate current registry operations and the design and implementation of new registries.

METHODS

To inform the guideline development process we performed a comprehensive exploratory literature review. Patient and caregiver focus groups were concomitantly performed to ensure the relevance of the guidelines to the target population.

Literature Review

A literature review aiming to identify all patient registry-related literature was performed using search terms such as register, registry and registries. The search strategy (see Appendix A) was developed in consultation with a research librarian and included the following databases: Medline, EMBASE, Pubmed, Cochrane Central, Cochrane SR, PsycINFO, ABI Inform, BIOSIS Previews, and PAIS (Public Affairs Information Service). Figure 1 outlines the flow of article identification and screening. We identified 19,002 abstracts with 6,435 remaining after duplicates and non-English articles were removed. The first reviewer excluded 2, 238 abstracts. Included abstracts were then reviewed by a second reviewer and a further 3,787 abstracts were excluded. In total 410 full-text articles were reviewed. Relevant aspects of this literature review are outlined in this document and served to inform the guideline development process.

Guideline Development

This guideline document was developed through an iterative process involving multiple stakeholders. In April of 2012, three patient and caregiver focus groups were held at the University of Calgary. The methods and results of the focus groups are published elsewhere.

Second, the results of the literature review and the focus groups were presented at a preliminary meeting of registry and disease experts held in Calgary in May 2012. At this meeting, the overall climate for registry development in Canada was discussed and work teams were formed to brainstorm and develop the sections of this document. Finally, a second meeting was held in Calgary in September 2012 with work team members, and additional registry, disease experts, and other stakeholders (e.g. ethics, legal, privacy) to finalize the content of this guidelines document.

Toolkit Development

Accompanying this guideline document is a toolkit of resources conceived to assist in the design and implementation of new neurological registries in Canada. This toolkit was assembled from a variety of existing resources across the entire registry spectrum. The toolkit and the guideline document are intended to be used in concert and it is our sincere hope that it will be a helpful resource. The complete toolkit is available at http://www.canadianregistrynetwork.org.

Overview

This guideline document is organized into three parts consecutively addressing registry design, quality and impact. Each part begins with an executive summary that summarizes key points. More in-depth and supporting information is presented thereafter.

It is our hope that this guideline document and accompanying toolkit will be useful to registry leaders, staff, investigators, patient organizations, governmental agencies, the pharmaceutical and biotechnology industries, and other institutions, groups and individuals with respect to the following:

1. Determining whether a registry is appropriate to address a specific question or series of questions
2. Providing resources to assist in developing the case for a registry
3. Providing a comprehensive framework for registry design (i.e. protocol development, ethics board submission, data collection infrastructure development)
4. Understanding and addressing the importance of quality control and assurance
5. Techniques in validation and interpretation of registry data
6. The importance of the impact of a registry and its measurement
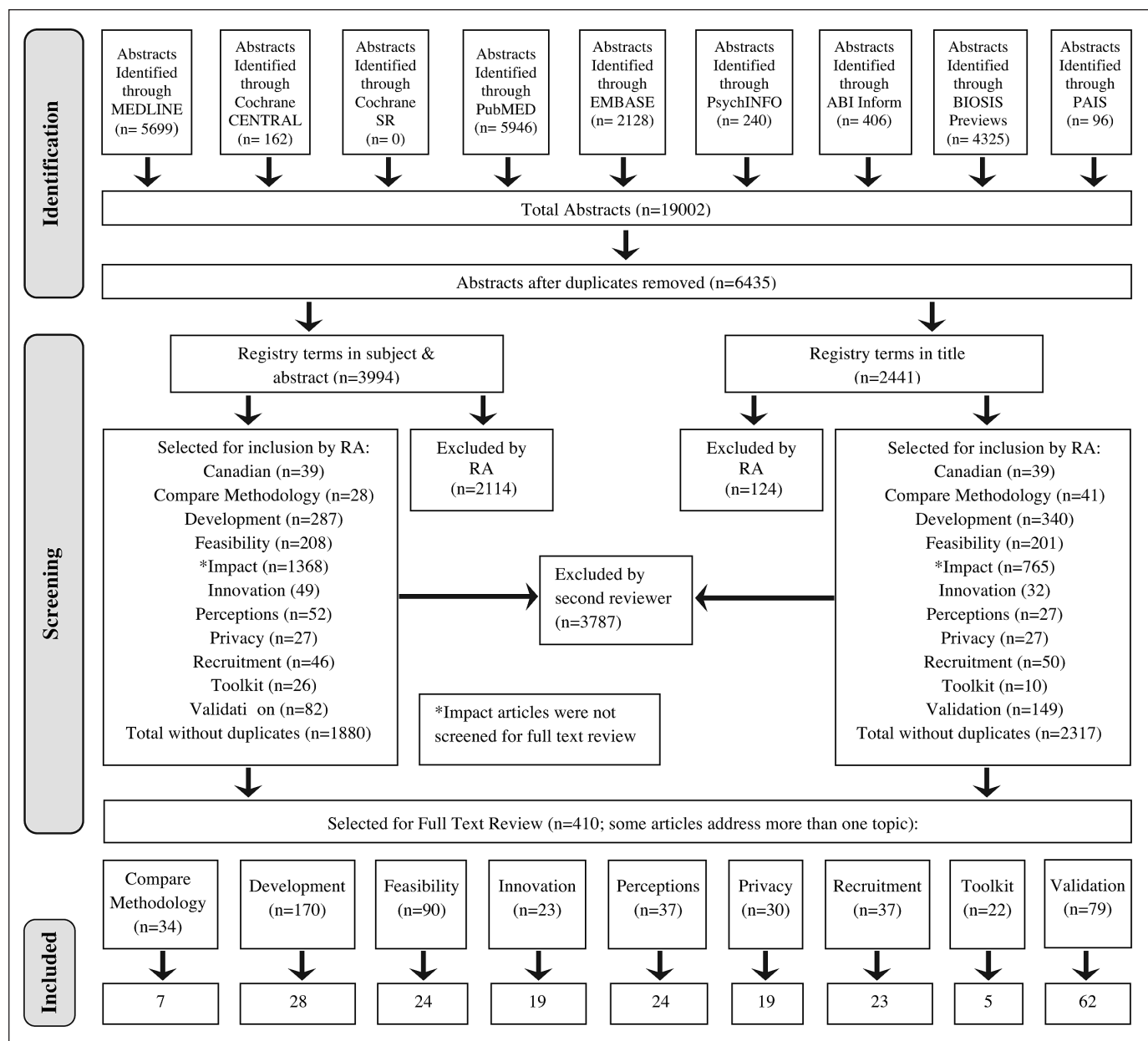
Figure 1: Registry Literature Review Flowchart. Outline of the flow of article identification and selection.

This guideline document and accompanying toolkit can also be used to:

1. Identify appropriate references from the literature to support funding application and manuscript preparation
2. Support registry standards and best practices in Canada in funding applications and ethics board submissions.
3. Provide published benchmarks for data quality
4. Provide examples of registry impact

A key additional resource to which all users of this document may wish to refer is the Agency for Healthcare Research and Quality "Registries for Evaluating Patient Outcomes: A User's Guide" document (AHRQ manual).[5] Throughout this guideline document we have highlighted specific areas where the AHRQ manual is relevant and useful in the Canadian context. During the preparation of this guideline we utilized the Second Edition of the AHRQ manual (http://www.innovations.ahrq.gov/content.aspx?id=3012). A new edition is forthcoming in 2013.

Part I - Registry Design

The design of registries is a complex task. Across Canada, relevant and applicable legislation varies by province; ethical policies and procedures vary by province and institution; and the logistical implementation of a registry faces many technical and physical challenges due to the vast distances and separations between research teams in Canada. Neurological diseases affect adults and children across all racial groups and jurisdictions, therefore neurological registries must consider multi-jurisdictional implementation and the needs of varied populations including Aboriginal groups.

In summary, good registry design will employ the following:

- Participant Informed Consent – this will likely be required in Canada as mandatory registries are not consistent with Canadian law.
- Transparency – publicizing the protocol and other relevant documents add to registry credibility; newsletters and other patient/public interactions tools should be employed; open disclosure of the use; storage; and destruction of data should be made.
- Advisory Council – registries should establish an oversight body consisting of relevant expertise based on the purpose and discipline of the registry.
- Data Ownership – needs to be considered and articulated in the planning of a registry. Consideration should also be given to long-term plans for the data beyond registry operation as this should be disclosed to participants.
- Data Security – at a minimum password authorized user access must be employed; but registries should also consider accessibility of data from the Internet and demarcation of identifiable data from de-identified data.
- Data Release – data release procedures should be documented and disclosed.
- Patient Recruitment – multi-modal strategies for patient recruitment should be used.
- Patient Follow-Up – follow-up methods should be designed and implemented to minimize participant attrition.
- Data Linkage – during the planning stages of a registry consider other registries with overlap or additional target population and the necessary aspects required to link data between the registries. Depending on data points collected it may also be necessary to consider administrative data linkage. In either case, linkage considerations must be addressed early so that appropriate consent can be obtained and logistical considerations can be included in the registry timeline.
- Documentation – all registries should have thorough standard operating procedures (SOPs) and policies in written form in addition to the registry protocol.
- Data Management – ensure a comprehensive data management plan has been created including specifications for data curation; data storage; and data access/security.
- Data Collection – consider your data collection methods and how they may impact access and participant selection; ensure the methodologies employed are appropriate to the target population.

Registry design considerations should be thoroughly discussed during the planning phases of a registry. Early discussion in a comprehensive fashion will help to reduce obstacles as the registry is implemented.

Ethical and Legal Considerations for Canadian Registries

David B. Hogan[1] , Janet Warner[2], Scott Patten[2], Glenys Godlovitch[2], Essie Mehina[2], Lynn Dagenais[3], Guillermo Fiebelkorn[2], Paula de Robles[2], Gail MacKean[2], Lisa Casselman[2], Nathalie Jette[1,4], Tamara Pringsheim[2], Lawrence Korngut[1], Megan Johnston[2]

This section summarizes the ethical and legal considerations that will impact the creation and operation of neurological disease registries in Canada. This document is not meant to provide legal or ethical advice. In order to ensure that applicable laws and organizational policies are adhered to in an appropriate manner, it is recommended that legal advisors and relevant organizational representatives be consulted. For registries to succeed, it is critical to proactively consider legal and ethical issues such as consent and privacy. Additional ethical and legal considerations include: the involvement of Aboriginal people and their communities, languages and communication; setting up of biobanks; data management; data ownership; and conducting transparent registry operations.

The Belmont Report - Ethical Principles and Guidelines for the protection of human subjects of research[6] and the Government of Canada *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS-2)[7] should be referred to for the ethical principles that need to be considered during the creation of disease registries. In addition, *Registries for Evaluating Patient Outcomes: A User's Guide*[5] produced by The Agency for Healthcare Research and Quality provides useful information. However, this document presents perspectives and reviews legislation particularly relevant to the United States which differ in some respects from Canadian law and research policies and practice.

In preparation of this guideline, we examined relevant Canadian and international literature as well as Canadian policy and legislation. We also consulted with Canadian privacy officers and specialists in research ethics. Finally, topic themes and issues were discussed with patients and families in project focus groups.

BACKGROUND

In Canada, Research Ethics Boards (REBs) are the equivalent of what is more commonly known as Institutional Review Boards (IRBs) in other jurisdictions. The TCPS-2 describes the authority, mandate and accountability of REBs. In some cases, provincial and federal legislation also applies. While investigators should consult with their local REB for information that is specific to their institution and province/territory, general overview of REBs is provided here.

1) REBs are established by the highest body governing an institution, to review the ethical acceptability of research conducted within their jurisdiction. Provincial legislation often discusses an institution's jurisdiction. REBs may be internal or external to an institution depending on arrangements made with external agencies.

2) The composition of an REB and the number of REBs will depend on the range and scope of research carried out within the jurisdiction.

3) REBs must operate independently and must be free from real or perceived conflicts of interest. They must also be provided sufficient financial and administrative resources by the host institution.

4) REBS have the authority to approve, reject, or request modification of incoming research proposals and also have the authority to terminate ongoing research.

5) REBs must consist of at least five members with a minimum of: two members with expertise in the relevant research discipline; one member who is knowledgeable in the area of ethics; one member who is knowledgeable in relevant law; and at least one community member who has no affiliation with the institution.

6) Institutional senior administrative members may not serve on the REB.

7) REBs shall use a proportionate approach to ethical review determined by the level of foreseeable risk to study participants. Two levels of review are permitted: full board review and delegated review for research with minimal risk.

8) REB review should be continuous throughout the research duration with at a minimum annual status reports. Researchers must also report unanticipated events with impact on participants in a timely fashion.

9) REBs must maintain appropriate documentation

including records of all submissions to the REB as well as attendance and minutes for REB meetings.

10) REBs must have a mechanism for reconsideration or appeal of REB decisions.

In general, most registry projects will require REB review as they involve living human participants or human biological materials (tissues, organs, blood, plasma, serum, skin, hair, nails, DNA, RNA, proteins, urine, saliva or other body fluid) and the extension of knowledge through disciplined inquiry or systematic investigation which is the TCPS-2 definition of "research". Registry projects in a single jurisdiction will require only their local REB approval; however, projects being conducted in multiple jurisdictions may encounter additional challenges. In general operating a registry in multiple jurisdictions involves the need to apply to multiple REBs (one or more per jurisdiction) depending on institutional arrangements or agency agreements governing the operation of REBs for each institution and jurisdiction that will be involved in the registry. In some jurisdictions, efforts to reciprocate individual institutional REB review across a broader jurisdiction have been undertaken both formally and informally. TCPS-2 does contain an alternative review model for multi-jurisdictional projects that consisting of review by a single specialized or multi-jurisdictional ethics board. However, the discretion to form such a multi-jurisdictional ethics board lies with individual institutions and therefore is unlikely to be created solely for project specific purposes. An example of multi-jurisdictional REBs widely seen in Canada is in the area of cancer specific REBs. The province of Ontario, for example, has an "Ontario Cancer Research Ethics Board (OCREB)" which was introduced to help expedite multi-centre cancer research studies. More information on the OCREB and how it works can be found at: http://oicr.on.ca/oicr-programs-and-platforms/ontario-cancer-research-ethics-board/terms-reference.[8]

Relevant Literature

Consent

The Canadian Standards Association (CSA) *Model Code for the Protection of Personal Information* (CAN/CSA-Q830) states that consent is required for the collection of personal information and its subsequent use or disclosure.[9] CAN/CSA-Q830 was prepared by the CSA Technical Committee on Privacy, under the jurisdiction of the CSA Steering Committee on Business Management Systems, and was formally approved by these Committees. It has been approved as a National Standard of Canada by the Standards Council of Canada, and the key elements from the Standard were incorporated into the *Personal Information Protection and Electronic Documents Act* (PIPEDA) which is one part of Canada's national privacy legislation. CAN/CSA-Q830 lists ten topics that require special consideration (referred to as "Principles"): Accountability; Identifying Purposes; Consent; Limiting Collection; Limiting Use, Disclosure, and Retention; Accuracy, Safeguards, Openness, Individual Access, and Challenging Compliance. The Quebec Myotonic Dystrophy Registry compared registry privacy needs with CAN/CSA-Q830 and found them to be compatible. The authors recommended that the principles of the standard be considered during registry design and implementation.[10]

Considerable discussion has arisen around the issue of obtaining consent for registries and its potential impact on registry viability, comprehensiveness and data quality. The CAN/CSA-Q830 unequivocally states that consent is required for the collection of personal information and its subsequent use or disclosure. Additionally for the purpose of registries, consent is also likely to be required for projects where there will be direct patient contact or where genetic information will be collected and/or linked.[11] CAN/CSA-Q830 does indicate that in some medical circumstances it may be inappropriate to obtain consent (individual is a minor; individual is seriously ill or mentally incapacitated; or, when seeking consent is otherwise impractical).[9] However, CAN/CSA-Q830 states that in such circumstances while it is possible to collect information without consent, consent must be obtained in the event that the information is disclosed. According to CAN/CSA-Q830 consent must only be obtained from an individual after they have been informed of the purposes for which the collected information will be used and that organizations must not collect, use or disclose information beyond what is needed to fulfill the clearly outlined and legitimate purpose for which the information was collected.[9] It holds that express consent should be sought when information is likely considered sensitive and cautions that many types of information can be sensitive within a given context.[9] The standard is clear that consent can be given by an authorized representative including legal guardians and parents for minors. CAN/CSA-Q830 does not require that consent be given in writing.[9] Methods of consent that are considered acceptable under the standard include:[9]

a) An application form that collects information and informs the individual of the potential use and/or disclosure of the information if it features a signature from the individual. By completing and signing the form an individual is considered to have provided consent.

b) A check-box may be used to allow individuals to request that their names and addresses not be given to other organizations. Individuals who do not check the box are assumed to have consented to the transmission of their information to third parties.

c) Consent may be given orally when information is collected over the telephone.

d) Consent may be given at the time that individuals use a product or service.

CAN/CSA-Q830 makes it clear that an individual may withdraw consent at any time subject to legal or contractual restrictions and reasonable notice.[9] The individual must also be informed by the organization of the implications of the withdrawal.[9]

With respect to obtaining consent, consideration of who will approach the patient must be made. In one study, approach rates to obtain informed consent were lower when lists of eligible patients could not be obtained from hospital records or if coordinators could not approach patients without a physician first approaching them; however, none of the differences found in consent rates were statistically significant.[11]

A clear majority of REBs in Canada feel that patient consent should be required for registries and indeed support for patient

consent is almost unanimous if the registry involves banking of biological samples or biomarkers (biobanking).[12] While consent is required, a little over 50% of the REBs felt that the consent could run for the duration of the registry provided that significant change did not occur and a clear majority of the REBs agreed with this if the option to withdraw was also present.[12]

In addition to the Canadian literature examined above, a total of 15 American, 6 United Kingdom, and 5 other country full text documents were reviewed. One paper commented that the World Health Organization standard for clinical trial registries does not include the need for informed consent.[13] However, it was felt that the inclusion of informed consent would significantly increase public confidence in clinical research and the manner in which clinical trials are conducted.[13] In some cases consent was required by legislation.[14-16] In one study an opt-out method for obtaining consent was utilized after a change in relevant legislation required consent and only 4% of patients opted out of the registry after receiving notice of the inclusion of their information in it.[14] Another study found that requiring consent reduced participation and suggested an opt-out method was preferred to reduce bias introduced by the consent requirement.[16] One registry used an electronic consent form that had to be completed before enrolling in an internet-based database.[17]

Privacy

Registries may raise concerns on the part of participants and healthcare practitioners with respect to the security and privacy of registry data. In 2008, a Canadian Internet Use Survey by Statistics Canada found that 74% of Canadians were concerned or very concerned about privacy on the internet.[18] This finding could be of particular concern to registries collecting data over the internet. It is important, though, not to overstate the extent of privacy concerns. One study found that concerns about internet privacy did not affect participant willingness to register in a database over the internet after 88% of registrants used this method.[17] One study found that individuals registering over the internet were significantly younger than those registering through a call centre.[17] As such, privacy concerns in solely electronic registries may introduce an age-selection bias.

Privacy can be viewed as both an objective inherent value desired by registry participants as well as a qualitative condition that describes access to or knowledge of thoughts, opinions, behaviors, and personal property.[19] Research participants freely making their decision to participate in a research registry do so notwithstanding the risk arising from stigma associated with being identified as having a disease, discrimination by insurance companies or employers, and causing fear or distress to family members.[19] Clear communication of the benefits that registries afford and the safeguards being employed may help to alleviate participant privacy concerns.[19] Establishing trust by putting in place robust methods to prevent confidentiality breaches is fundamental to ensuring long-term participation.[20]

Privacy may be of particular concern for patients with a stigmatizing health condition.[5] Inappropriate access to registry data could lead to the misuse of the information the registry contains and ultimately harm the registry participants.[5] It is important to discuss administrative, physical and technical data safeguards with participants as a part of the informed consent process.[5]

Privacy legislation and ethics committee guidelines that require consent for patients to join registries may hinder the ability of rare disease registries to collect unbiased data.[21] This risk can be ameliorated by procedures that ensure security and of the data, which may improve consent rates by reassuring participants that their data will be safe. Data confidentiality should be reconsidered each time data is used.[10]

In considering recruitment strategies, the involvement of patient organizations in advertising the registry may assist the protection of patient privacy during recruitment[21] by enabling the notification of all patients involved with the patient organization about the registry including those patients could not otherwise be contacted by the registry team or may be unknown to the registry team. All research recruitment strategies should ensure that the trust of the participant is not abused, and protect them against over-solicitation.[10]

Registry Design

There was agreement in the international literature that policies and procedures around data collection, data access, and maintaining privacy should be developed and approved by local ethics review boards.[5,22-24] In one jurisdiction it was suggested that generic policies might not be sufficient to protect data from being disclosed for legal purposes (e.g. subpoena) leading to a recommendation that specific access policies be created to ensure that registry data cannot be subpoenaed.[24] It was also suggested that registry data on participating physicians should be protected from disclosure.[24] Another report recommended privacy auditing by independent privacy consultants, training of registry staff about privacy and confidentiality, and obtaining signed confidentiality agreements from staff and contractors.[22] In this registry, background checks were conducted on staff.[22]

Registries should clearly identify in their management policies who is accountable from an organizational standpoint for data. This individual should be accessible for those who wish to request information or submit complaints[10].

Both the amount and type of personal information collected by an organization should be limited to what is necessary to fulfill the purposes of the registry.[10] CAN/CSA-Q830 indicates that any information collected should be obtained with informed consent and that information handling policies and practices should be publicly available in accordance with the principle of "Openness" outlined in the standard.

Security safeguards protecting information contained within registries are to prevent loss, theft and unauthorized access, disclosure, copying, use or modification.[10] CAN/CSA-Q830 states that the safeguards used should be appropriate for the sensitivity and amount of information being collected, how it will be distributed, and the format and method of storage. The greater the sensitivity of the information, the higher the level of protection required.

CAN/CSA-Q830 holds that guidelines and procedures should be developed regarding the retention of personal information for any given purpose. These guidelines should include minimum and maximum retention periods. Information that is no longer required to fulfill the purposes outlined by the organization collecting the data should be destroyed, erased or made anonymous. Procedures and policies for the destruction of personal information must be developed. Personal information

contained within registries that have fulfilled their purpose, lack funding, are ineffective for research purposes, or otherwise are not operational should be destroyed.[10] Anonymization or pseudo-anonymization through coding should be used to ensure confidentiality. This coding approach should be explained to participants.[21]

The use of custom-designed software applications with encrypted data exchange and firewall protection was advocated.[23] Anonymizing data whenever possible was recommended.[25]

Researchers should receive data with encrypted patient identification (ID) numbers in order to ensure that ID numbers cannot be used to link data within the registry for unauthorized purposes.[22] Registry data, when used for research, should be released only to investigators who have obtained ethics approval for their research.[25] Documentation of registry data release procedures and the process for reviewing requests should be developed.[26] Subgroups of less than six individuals may be considered identifiable and excluded from data release procedures and processes for this reason.[5]

Data servers should be housed in a physically secure location inaccessible by the Internet.[22,26] Utilization of a two-server model where one server stores patient identifiers and a second server stores health information has been recommended.[22,27] Electronic data access should be controlled by confidential passwords.[22,23,25,26] Additionally, since electronic filing is more secure than hard copy filing, files should be backed up electronically and hard copies destroyed.[22] The use of a data-viewing tracking system within registry software can enhance the protection of privacy.[5,23,26]

It is important to consider data linkage during the inception of a registry and to incorporate potential or actual data linkage plans into the informed consent process.[5] Privacy and confidentiality are especially important to consider as when linking datasets one may be able to infer the identity of a patient in a linked database even after de-identification of the patients in the database.[5] Data de-identification could involve coding data using a unique identifier; removing certain data elements and/or a statistical assessment of low probability of patient identification using the dataset.[5] More information on data security practices and mitigation of risks associated with data linkage will be provided in the Data Storage and Curation and Linkage sections of this guideline document.

OTHER CONSIDERATIONS

Informed Consent Process

In general, mandatory participation or inclusion in registries is not consistent with Canadian law. In most circumstances, a registry must obtain participant consent in a free and voluntary manner. Care must be paid to the potential influence of family members or the person obtaining consent within the consent process. Additionally, during the consent process participants must be given an appropriate amount of time to reflect. In some cases, it may be possible to apply for a waiver of consent especially where the neurological condition carries significant risk of death and/or population-based statistics are required; however, such waivers must be applied for in each applicable jurisdiction in which the registry operates.

With respect to registries, there are three important considerations with respect to informed consent: consent to creation of the registry using patient data, consent to the initial research purpose and use of registry data, and consent to subsequent use of data by the developers or others.[5] It is important to note that additional consents may be needed for each unique research purpose.[5,7]

In most cases, registries should confirm participant consent on an ongoing basis.

Capacity to Consent

For certain neurological conditions, the issue of capacity to consent not infrequently arises. A number of the diseases that could be considered for a registry may affect children who are minors and unable to provide informed consent under Canadian law. Among adults with progressive neurological diseases, the ability to provide informed consent may have been lost when the person is initially approached or could be lost during the course of the illness after recruitment. Assessment of capacity to consent to participate in a research study always requires careful consideration. Legal competence is a necessary aspect of free and informed consent.[5] Due to the progressive nature of many neurological conditions it may be important to designate a substitute decision maker depending on project duration. The substitute decision maker could be an authorized representative such as a legal guardian, parent, or an individual named as the person's agent in an advanced (or personal) directive.[7,9] This ensures that registry data could still be collected even if the patient loses the capacity to provide consent either permanently or on an intermittent basis as long as their substitute decision maker concurs. It is essential to address issues related to capacity to consent during initial registry design.

According to the TCPS-2,[7] those who lack capacity to consent should neither be excluded from participation nor have their lack of capacity used to unfairly influence their participation. Typically, decisions regarding consent are authorized by a substitute decision maker, who is a person with legal authority to make decisions on an individual's behalf. It is, nevertheless, important for those who lack capacity to consent to remain as involved as possible in the decision about whether or not to participate.[7]

The participation of minors in long-term registries also presents ethical concerns. While parents may consent for their children to participate for altruistic reasons, it is possible that a minor's participation in a registry could lead to adverse outcomes such as exclusion from educational opportunities and social programs.[5] Over the course of the project, children may reach the age of majority and/ or otherwise develop the capacity to consent. Thus, procedures must be in place to ensure the renewed consent of registry participants who were recruited as minors and reach the age of majority.

Although non-competent individuals by definition lack the capacity to consent, every effort must be made to ascertain and respect their wishes.[7] Hence, in addition to seeking consent from a substitute decision maker, a best practice would be to also seek assent from the non-competent individual. This assent could by sought by means of an assent form appropriate to the level of comprehension possessed by the individual. If the assent cannot be obtained in writing, oral assent should be sought and

documented.[7] It is important to emphasize that assent by the non-competent individual should occur in addition to the informed consent process.[7]

Withdrawal

While participants have the right to withdraw their consent to participate in the registry overall at any time, registry design may prevent them from withdrawing data or biological materials they have already contributed. For example, if the registry anonymizes participant's biological samples, it may be impossible to destroy them once a withdrawal is received. If the registry is designed in a way that does not permit a participant to withdraw all of their data or biological materials, this limitation to their ability to withdraw and the nature of what will happen to such retained data should be clearly communicated during the informed consent process.[5,7] It is also important that the procedure for withdrawal be clearly communicated to participants during the informed consent process.[5,7]

Research Involving Aboriginal People and Communities

This document uses the term "Aboriginal" to refer to all Canadian people of First Nations, Métis or Inuit descent.

Most of the research conducted in Aboriginal populations has historically been conducted by non-Aboriginal groups with external interests.[7,28] As a result, the content of research and the approach to research design and methodology has not generally reflected Aboriginal views.[7,28] Not only have Aboriginal people tended not to benefit from these research activities,[7] but in some cases the outcomes of research have been harmful to Aboriginal people and communities.[28] Given this history, Aboriginal communities tend to be wary of external research and researchers.[28] Therefore, it is particularly important for those developing registries to be aware of the unique considerations that arise if an Aboriginal community is to become involved in a registry project and to work with the community in an ethical and respectful manner.[7,29,30] It is strongly recommended that Aboriginal community members be involved in the design and implementation of the registry if at all possible.[7,28,31,32]

Chapter 9 of theTCPS-2 is dedicated to research involving First Nations, Inuit and Métis peoples of Canada.[7] The Canadian Institutes of Health Research (CIHR) use this chapter as its policy with respect to research involving Aboriginal communities.[29] The same principles of Respect for Persons, Concern for Welfare and Justice apply when conducting research on Aboriginal people or in Aboriginal communities.[7] The TCPS-2 acknowledges the unique status, cultural values and traditions of Aboriginal people and has established additional guidelines for how to conduct research in an ethical manner.[7]

Community engagement at all stages is essential for research conducted in Aboriginal communities.[7,28,30] Additionally, formal research agreements should be established; research should be conducted, interpreted and disseminated in collaboration with communities and their representatives; and, research should be relevant to community priorities and generally be of benefit to the communities.[7,28,30,31,33] Elders and other knowledge holders play important roles in Aboriginal communities and must be acknowledged and respected by researchers.[7,28,30] Of particular relevance to registries is the requirement that an institutional

REB review take place for linkage of anonymous data sets or data associated with biological materials.[7]

During the initial planning stages, it may be necessary for researchers to obtain permission from territorial/regional licensing agencies in some jurisdictions, in addition to obtaining permission from community authorities/representatives.[34] In Nunavut and the Northwest Territories, researchers must have a license to do research: both territories have research institutes that can assist with licensing.[31,32,35] The licensing process involves submitting a proposal that describes, in plain language, the research question and methodology.[31,34] Conditions of the license include notifying the appropriate authority of any changes to the information about the study, and the production of a report six months after the license expires.[34] For a long term project, it may be necessary to have a license extended or renewed.[34] It is important to note that research being conducting in multiple Aboriginal communities may require licenses from each of the communities and/or jurisdictions.[31,34] Additionally, multidisciplinary research projects may require permits from several different agencies.[31]

Cultural and language barriers may impede the informed consent process.[36] It is important to consider local languages during all stages of research.[28,30-32] This might involve translating materials such as informed consent forms and interview questions.[32] Producing research summaries in local languages is recommended.[30] The Nunavut Interpreter/Translator Society is one organization that may be able to assist with translation.[35] Literacy may also be an issue with respect to written consent because not all languages are written and not all people can read written languages.[32,33] To address this, researchers may want to consider a verbal consent option and keep a written record of the verbal consent process.[32,33]

When recruiting participants into a registry, it is important to consider differences in the age of majority in different Aboriginal communities. Those who have not reached the age of majority lack the capacity to give informed consent.[7] In Nunavut, the Northwest Territories and the Yukon the age of majority is 19 while in other areas of Canada the age may be 18 or 19 depending on the province.

One important issue with respect to consent is the misconception held by some Aboriginal people that refusing to participate in government funded research will result in a loss of government funding and resources to the region.[28] Hence, it is especially important to insure that consent is given freely and with appropriate knowledge of the research project.[7,28] *Ethical Principles for the Conduct of Research in the North* published by the Association of Canadian Universities for Northern Studies describes the importance of free, informed and ongoing consent and establishes a model consent process which aligns with TCPS-2 guidelines for research involving Aboriginal people.[7,30] Additionally, as a part of ongoing consent, it is recommended that researchers provide explanations of research objectives, methods, and results to the communities in which they do research.[28,30]

Languages

It may be necessary to ensure that consent forms and other relevant materials are available in languages other than English and French in order to ensure a representative sample is gathered

Table 1: Intellectual Property and Ownership Considerations by Province [1]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Alberta Health Information Act http://www.qp.alberta.ca/574.cfm?page=H05.cfm&leg_type=Acts&isbncln=9780779752607	Custodians, as defined by the Health Information Act, have custody and control of health information. Custodians may be individual health professionals; health facilities or the provincial health board. Health information includes diagnostic information; information about treatment or care; information about health service providers and registration information.	According to the Health Information Act, custodians, information managers, and researchers who enter into agreements with custodians can store health information data.	This is not specified in the Health Information Act, but the researcher is obligated to adhere to conditions set out by the custodian and any relevant ethics committee relating to the use, protection, disclosure or disposal of health information (Health Information Act: Section 54(1)(a)(ii)) When custodians, disclose health information, they must make a record as per section 41 and retain that record of disclosure for 10 years following the date of disclosure.	This is not specified in the Health Information Act, but the researcher is obligated to adhere to conditions set out by the custodian and any relevant ethics committee relating to the use, protection, disclosure or disposal of health information (Health Information Act: Section 54(1)(a)(ii))	According to the Health Information Act, "record" means a record of health information in any form and includes notes, images, audiovisual recordings, x-rays, books, documents, maps, drawings, photographs, letters, vouchers and papers and any other information that is written, photographed, recorded or stored in any manner, but does not include software or any mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required. (Health Information Act)	This is not specified in the Health Information Act, but the researcher is obligated to adhere to conditions set out by the custodian and any relevant ethics committee relating to the use, protection, disclosure or disposal of health information (Health Information Act: Section 54(1)(a)(ii)) When custodians, disclose health information, they must make a record as per section 41 and retain that record of disclosure for 10 years following the date of disclosure.
British Columbia Freedom of Information and Protection of Privacy Act (FIPPA) http://www.oipc.bc.ca/legislation/FIPPA/Freedom_of_Information_and_Protection_of_Privacy_Act%28April%202010%29.htm Personal Health Information Access and Protection of Privacy Act (e-Health Act) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_08038_01 Personal Information and Protection Act (PIPA) http://www.oipc.bc.ca/legislation/PIPA/PIPA%282006%29.pdf	Ministry of Health, health authorities and Population Data BC per the provisions of the Freedom of Information and Protection of Privacy Act (FIPPA) and the Personal Health Information Access and Protection of Privacy Act (e-Health Act). Health professionals in private practice are subject to the Personal Information and Protection Act (PIPA).	Ministry of Health health authorities, and Population Data BC under FIPPA. Health professionals in private practice are subject to PIPA.	According to the FIPPA Act and the Personal Health Information Access and Protection of Privacy Act, data can be stored as long as it is needed for the purpose for which it was collected. When the information is no longer needed for the purposes for which it was collected it should be destroyed or at a minimum de-identified and in accordance with institutional policies and legislation, the stipulations of the data sharing agreement; data stewardship committee, or other appropriate institutional policies or safeguards.	FIPPA and the e-Health Act prohibit the disclosure of personal identifiable information outside of Canada as well as access to such records from outside Canada except in the presence of explicit consent. An amendment to FIPPA in 2006 relaxed these constraints somewhat with respect to out of country data system management and data recovery but with the following strict conditions: access must be necessary; should be granted only for the minimum period required; and must be controlled and secure. According to the e-Health Act, when data are disclosed for research, researchers must enter into an information sharing agreement and adhere to its terms.	According to the FIPPA act, a "record" includes books, documents, maps, drawings, photographs, letters, vouchers, papers and any other thing on which information is recorded or stored by graphic, electronic, mechanical or other means, but does not include a computer program or any other mechanism that produces records. BC legislation (FIPPA and the e-Health Act) also define "Health Information Banks" which are electronic repositories of health information. Under both FIPPA and PIPA regardless of the format of the record, the establishment of safeguards to prevent unauthorized use, disclosure, disposal, and access including copying and modification is required.	According to the *FIPPA Act and PIPA*, information collectors must retain personal information for one year if it is used to make a decision directly affecting the individual. PIPA further stipulates that collected personal information must be destroyed when the purpose for the collection of the information is no longer being served, and/or the information is no longer required for business or legal purposes. Researchers must also adhere to retention periods that are established by tax legislation and institutional records retention and disposition schedules.

from multi-ethnic populations.[5,11] When translating materials, it is important to ensure that the translation is not only accurate, but linguistically and culturally appropriate.[5] A best practice would be to use a certified translation service to translate materials and/or to have a qualified interpreter attend the informed consent process.[5] An alternative might be to engage community translators in a reverse translation activity for the purposes of verifying the accuracy of the translation. Overall, consent documents must be written in plain language, and the literacy level of the target population should be considered.[7] Individual ethics boards may also have specific requirements about the reading comprehension level of informed consent documents.

Biobanks

In order to establish a biobank (a large collection of tissue samples brought together for use in research), REB review is necessary.[7] The different nature of a biobank and a genetic research database should be noted.[37] While the terms are often used synonymously, a genetic research database contains information on the genetic characteristics of registered individuals while a biobank will contain samples of tissue or blood from registered individuals which may or may not give rise to genetic information stored within the biobank. Biobanks are commonly linked with other health record information

Table 1: Intellectual Property and Ownership Considerations by Province [continued 2]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Manitoba The Personal Health Information Act http://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=p33.5	Trustees collect and maintain personal health information. Trustees may include health professionals; health care institutions; and government organizations involved in healthcare.	Trustees, information managers, researchers who enter into agreement with trustees. Information must be stored in a secure physical location in an electronically secure manner with appropriate access safeguards. Electronic or manual logging of access to data must be kept. Written security policies and procedures must be in place. Security safeguards must be audited at least every two years.	As long as is permitted under the institution's written records retention and destruction policy which is required under the Act. Compliance with other rules regarding retention and destruction of records may be required if the trustee is a public body.	Not specified in the Personal Health Information Act, however, trustees must enter into written agreement when information is shared with information managers and researchers. Information managers and researchers would be subject to the terms specified in the agreement.	The Personal Health Information Act defines "record" or "recorded information" as a record of information in any form, and includes information that is written, photographed, recorded or stored in any manner, on any storage medium or by any means, including by graphic, electronic or mechanical means, but does not include electronic software or any mechanism that produces records; Removable media must be physically secured.	Records of user activity with respect to the data must be retained for a minimum of 3 years. User activity records must also be audited at least once prior to destruction. A written policy regarding storage and destruction of health information must be in place and must be complied with. This policy must not violate rules around retention and destruction of records of public bodies if the trustee is a public body. Trustees must enter into written agreement when information is shared with information managers and researchers. Information managers and researchers would be subject to the terms specified in the agreement.
New Brunswick The Personal Health Information Privacy and Access Act http://www.gnb.ca/0062/PDF-acts/p-07-05.pdf	Custodians collect and maintain personal health information. Custodians could include health professionals; health institutions; health service organizations; public bodies; researchers or other designated parties.	Custodians, agents, information managers, researchers who enter into agreements with custodians. Custodians and their agents must have written documentation outlining safeguards in place to protect data and activities undertaken in the event of a breach. Breaches must be logged and follow-up mitigation of future risk must be documented. Agreements with information managers must outline safeguards employed by the information manager with respect to the information.	Information that is more than 100 years old is not subject to the Act. Additionally, if 50 years or more have elapsed since the death of the individual that the information pertains to, it is not subject to the Act. However, custodians must set and adhere to written policy regarding archival storage, access and secure destruction of personal health information as per Section 55(1). .	If the transfer will involve disclosure of the information to a party outside of New Brunswick or for the purposes of research, express consent from the relevant individual is required. Written or physical disclosures without consent must be noted. Access to information systems as the means of disclosure need not be noted, provided that electronic logging of access is in place. Disclosure outside of the Province is only permitted for the purposes of securing health care; health programs or is limited to registration information only. Information managers from outside the province or outside Canada are permitted provided an appropriate agreement is in place.	The Personal Health Information Privacy and Access Act defines "record" as a record containing information in any form, including information that is oral, written, photographed, recorded or stored in any manner, on any storage medium or by graphic, electronic, mechanical or any other means, but does not include electronic software or any mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required.	Records provided for the purposes of research must be destroyed or de-identified at the earliest opportunity consistent with the purposes of the project.

including disease characteristics, treatment options and patient personal data. Such linkage may give rise to unique privacy concerns where traditional methods of data de-identification may not be adequate given the unique characteristics provided by some genetic information alone or in combination with other medical or personal data. Genetic data should be treated as personal data and coded accordingly.[37] There is also concern that biological information will be used not only to gather knowledge on the individual from whom the information was collected, but that the biological information will be used to infer knowledge about that individuals biological relatives.[5] In addition, there is concern that biological information gathered by registries will be used against participants and their biological relatives in decisions about employment and life insurance.[5] This is particularly a concern for conditions that can be predicted or diagnosed using genetic information.[5] Given these concerns, it is

Table 1: Intellectual Property and Ownership Considerations by Province [continued 3]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Newfoundland Personal Health Information Act http://assembly.nl.ca/Legislation/sr/statutes/p07-01.htm Health Research Ethics Authority http://www.assembly.nl.ca/legislation/sr/statutes/h01-2.htm	According to the Personal Health Information Act, custodians have custody and control of health information. Custodians may include healthcare professionals or providers; administrators or boards/committees of health institutions; and various faculties and schools of Memorial University of Newfoundland.	Custodians, information managers, and researchers whose project has been approved by the Health Research Ethics Authority. Written policies outlining data safeguards appropriate to the type of storage, location of storage and sensitivity of the information must be in place. Information managers designated to store or handle health information must have a written agreement with the custodian in place.	Not specified in An Act to Provide for the Protection of Personal Health Information, but agreements between custodians and information managers must be established. Additionally, the Health Research Ethics Authority may impose conditions for approval for researchers.	Disclosure outside of the province is permitted provided that consent has been obtained or that the disclosure is for a purpose permitted under the Act. Written or physical disclosures must be noted. Access to information systems as the means of disclosure need not be noted, provided that electronic logging of access is in place.	According to the Personal Health Information Act, a "record" is a record of personal health information in any form, and includes personal health information that is written, photographed, recorded or stored in any manner, but does not include a computer program or a mechanism that produces records on a storage medium. Regardless of the format of the record, the establishment of safeguards is required.	Not specified in An Act to Provide for the Protection of Personal Health Information, but agreements between custodians and information managers must be established. Additionally, the Health Research Ethics Authority may impose conditions for approval for researchers
Northwest Territories Access to Information and Protection of Privacy Act http://www.justice.gov.nt.ca/pdf/ACTS/Access%20to%20Information%20and%20Protection%20of%20Privacy.pdf	Public bodies that collect and maintain health information are subject to the Access to Information and Protection of Privacy Act.	Public bodies, researchers who enter into agreements with public bodies.	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions. Conditions regarding data safeguards, destruction and de-identification of data, and further or subsequent disclosure may be imposed by the public body disclosing the information.	Disclosure to the Northwest Territories Archives for the purposes of archiving is permitted. According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.	According to the Access to Information and Protection of Privacy Act, a "record" is a record of information in any form and includes information that is written, photographed, recorded or stored in any manner, but does not include a computer program or other mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required.	The Exceptions to disclosures do not apply to information that has been in a record for more than 15 years. According to According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions. Conditions regarding data safeguards, destruction and de-identification of data, and further or subsequent disclosure may be imposed by the public body disclosing the information.

essential to store biological materials in appropriate facilities and in compliance with applicable standards and appropriate safeguards must be established to protect participants biological materials and, in turn, information about participants that can be obtained by their biological materials.[7] Additionally, biobanks must institute sound and robust policies and procedures that are actively monitored.[38]

Mandatory Reporting

It is possible that information obtained during participation in a registry study may warrant further action on the part of the researchers/medical professionals. For example, the information

collected may indicate that a patient diagnosed with Alzheimer's disease or another form of dementia is still driving a motor vehicle. Some Canadian provinces have mandatory reporting obligations on the part of physicians with respect to certain types of information. There are differences in applicable laws across provinces. If mandatory reporting of certain types of information may be required for public safety reasons, this should be disclosed to participants at the time of recruitment.

Family Members

Registries obtaining information on family members should consider privacy implications carefully and wherever possible obtain this information with consent or in a manner that does not

Table 1: Intellectual Property and Ownership Considerations by Province [continued 4]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Nova Scotia Personal Health Information Act https://www.gov.ns.ca/dhw/phia/	Custodians as defined by the Personal Health Information Act. This includes health professionals or a person operating a group practice of health professionals; health authorities, pharmacies and continuing care facilities.	Custodians and researchers who enter into agreements with custodians. Written policies governing data infrastructure and associated security safeguards must be in place. A record of user activity and security breaches must be kept.	Information that is more than 120 years old is not subject to the Act. Information on persons that is accessed more than 50 years after the person's death is not subject to the Act. According to the Personal Health Information Act, researchers and custodians must enter into a formal agreement and researchers must adhere to the conditions set by research ethics boards and custodians. Additionally, a written records retention schedule must be established by data purpose and adhered to. Information that is used to update a health information record and its user activity log must be kept for 1 year from the date of the update.	Disclosure without consent must be documented including what was disclosed and to whom. Consent is required for disclosure to non-custodians and persons outside of the Province. De-identified information may be stored beyond the period permitted for the original data collection purpose. According to the Personal Health Information Act, researchers and custodians must enter into a formal agreement and researchers must adhere to the conditions set by research ethics boards and custodians.	According to the Personal Health Information Act, a "record" means a record of information in any form or in any medium, whether in written, printed, photographic or electronic form or otherwise, but does not include a computer program or other mechanism that can produce a record. Regardless of the format of the record, the establishment of safeguards is required.	According to the Personal Health Information Act, researchers and custodians must enter into a formal agreement and researchers must adhere to the conditions set by research ethics boards and custodians. Researchers must disclose a records retention and destruction plan and schedule within the research plan given to the custodian.
Nunavut Access to Information and Protection of Privacy Act http://www.atipp.gov.nu.ca/en/Act.aspx	Public bodies that collect and maintain health information.	Public bodies, researchers who enter into agreements with public bodies	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions. The removal of identifiers must be conducted at the earliest possible time.	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.	According to the Access to Information and Protection of Privacy Act, "record" means a record of information in any form and includes information that is written, photographed, recorded or stored in any manner, but does not include a computer program or other mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required.	The Exceptions to disclosures do not apply to information that has been in a record for more than 15 years. According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.

inadvertently personally identify the individual described in the obtained information.

Online Registries

Special considerations regarding privacy and confidentiality with respect to online registries are addressed in the Online Registries section of this document.

Administration

Support - In order for a registry to be successful it is necessary to have support on a political, administrative and clinical level.[39] Collaboration between researchers, policy makers, patient advocates and healthcare providers is important in the design of a sustainable registry.[40] Support for a registry can be influenced by establishing a steering committee, or expert panel.[39] Steering committees are important to help insure timelines are met, objectives are clear, and that the interests of the general community are met.[39] Both ethical and scientific oversight committees can be established to address key issues and make recommendations.[41] While a steering committee may be functional in terms of operations oversight, many provincial laws require a single data owner (acting as a custodian, trustee, and other equivalent terminology) and therefore it may still be necessary to have a single person who is responsible for the registry data and its custodianship.

Table 1: Intellectual Property and Ownership Considerations by Province [continued 5]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Ontario Personal Health Information Protection Act http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm Long-Term Care Homes Act, Public Hospitals Act http://www.e-laws.gov.on.ca/html/source/regs/english/2010/elaws_src_regs_r10079_e.htm Medicine Act, 1991 http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_940114_e.htm	Custodians are responsible for health data as defined in the Personal Health Information Protection Act. Custodians may include health professionals or an individual operating a group of health professionals; and those that operate home care, long-term care; communicate care or hospitals facilities as defined by their respective Acts.	Custodians, researchers, information managers or other custodian appointed agents. Researchers are permitted to store and access health information provided they have an ethically approved research plan and have signed an agreement with the data custodian.	There is no retention period set out in the Personal Health Information Protection Act. The retention periods are set out in sector specific legislation such as the Long-Term Care Homes Act, Public Hospitals Act and Medicine Act, 1991. However, it is a fundamental fair information practice that identifying information should not be retained any longer than is necessary for the purpose. A retention and disposition schedule must be outlined in the research plan.	Records may be kept in a subject's home or another location other than the custodian's premises provided consent has been obtained. Disclosures must be documented on the health record and disclosed as soon as reasonably possible to the individual whom the information is about. Transfer of records to the Ontario Archives or other persons permitted to store historical records is permitted. Identifying information should not be retained any longer than is necessary for the purpose regardless of the location where it is being retained or stored.	Records of identifying information may be stored in paper or electronic format. Regardless of format, the Personal Health Information Protection Act requires identifying information to be retained in a secure manner. "record" means a record of information in any form or in any medium, whether in written, printed, photographic or electronic form or otherwise, but does not include a computer program or other mechanism that can produce a record .	There is no retention period set out in the Personal Health Information Protection Act. The research plan however is required to specify how long the information will be retained in identifying format.
Prince Edward Island *Freedom of Information and Protection of Privacy Act* http://www.gov.pe.ca/law/statutes/pdf/f-15_01.pdf	Public bodies that collect and maintain health information.	Public bodies, researchers who enter into agreements with public bodies	The *Freedom of Information and Protection of Privacy Act* states that researchers must sign a written agreement to comply with imposed conditions, policies and procedures. Conditions imposed by the public body include conditions around data security and confidentiality and the removal/destruction of identifiers at the earliest possible opportunity.	The *Freedom of Information and Protection of Privacy Act* states that researchers must sign a written agreement to comply with imposed conditions, policies and procedures. Information may be disclosed to the Public Records and Archives Office. Such information may be available to researchers if the information is older than 25 years and disclosure will not result in an invasion of privacy; or the individual has been dead for 25 years; or the information is 75 or more years old. Consent for disclosure may be required.	The *Freedom of Information and Protection of Privacy Act* states that a "record" means a record of information in any form and includes notes, images, audiovisual recordings, x-rays, books, documents, maps, drawings, photographs, letters, vouchers and papers and any other information that is written, photographed, recorded or stored in any manner, but does not include software or any mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required.	The Exceptions to disclosures do not apply to information that has been in a record for more than 20 years. The *Freedom of Information and Protection of Privacy Act* states that researchers must sign a written agreement to comply with imposed conditions, policies and procedures

Advisory Council - An external review committee or advisory board can be useful for providing independent oversight and periodic reviews.[5] Having such a committee may enhance both the feasibility and the credibility of a registry by giving scientific and technical guidance to ensure the smooth operation of the registry, providing recommendations for resolving any issues that may arise during the course of the registry project, and helping to establish the independence of the registry from perceived or actual conflicts of interest.[5] These committees should include a variety of perspectives (e.g., people who have the disease, caregivers, practitioners, non-governmental organizations, statisticians, lawyers, ethicists, members of the general public, IT experts, knowledge translation specialists, and communication expertise). It is important, however, to keep the size of this council reasonable and to balance conflicting viewpoints regarding the purpose(s) of registries among the different perspectives on the council.

Human Resources - A registry requires consistent human resources. Registries need trained and skilled researchers and clinicians to coordinate, collect and analyze data.[39,42] A full-time individual should be hired and trained to improve data quality.[36] In order to maintain long-term interest from collaborators, the Victorian State Trauma Registry aimed to train postdoctoral fellows and newly graduated specialists.[39]

Standard Operating Procedures (SOPs) - are documents that outline the standard methodology applied to a given process. SOPs are an essential best practice in any area desiring high quality, repeatable results. In the case of disease registries, SOPs are particularly important where multiple sites are involved (to ensure all sites follow the same methodology for each task);

Table 1: Intellectual Property and Ownership Considerations by Province [continued 6]

PROVINCE	Who is responsible for health information data	Who can store health information data	How long can identified health information be stored?	Can identified health information be transferred to another location for additional storage duration	What formats are used to store health information?	How long must researchers store data once a study is closed?
Quebec An Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information English: http://www2.publicationsdu quebec.gouv.qc.ca/dynamicS earch/telecharge.php?type=2 &file=/A_2_1/A2_1_A.html Français http://www2.publicationsdu quebec.gouv.qc.ca/dynamicS earch/telecharge.php?type=2 &file=/A_2_1/A2_1.html	Such data are "held" by Public bodies (Health and social services institutions).	Public bodies (Health and social services institutions), researchers as per Section 125. Personal information may not be used for a purpose other than for which it was collected except where consent has been obtained.	Information can be stored as long as it is required to fulfill the intended purpose. Once the purpose has been obtained, the information must be destroyed in compliance with the Archives Act or Professional Code. Information collected for scientific research is not subject to these constraints provided the information is never disclosed.	All releases of personal information must be documented in a register.	According to An Act Respecting Access to Documents Held by Public Bodies and the Protection of Personal Information, information can be "recorded in writing or print, on sound tape or film, in computerized form, or otherwise". Regardless of the format of the record, the establishment of safeguards is required.	Information collected for scientific research purposes is permitted to be stored beyond the restrictions around purpose placed on other personal information repositories, however, such information may not be disclosed.
Saskatchewan Health Information Protection Act (HIPA) http://www.qp.gov.sk.ca/do cuments/english/Statutes/St atutes/H0-021.pdf	Trustees such as government institutions; health authorities; community clinics; and licensed health professionals own records of personal information.	A trustee, an Information Management Services Provider (IMSP), an employee of a trustee, an approved archive all subject to compliance with HIPA, regulations particularly sections 16, 17 and 18. Researchers may receive data with subject consent and ethics approval. All researchers obtaining health information data must have an agreement with the trustee. A waiver of consent is permitted in certain circumstances.		Yes, designated archives are outlined in the regulation. These archives may refuse to accept data from a trustee.	According to HIPA, a "record" means a record of information in any form and includes information that is written, photographed, recorded, digitized or stored in any manner, but does not include computer programs or other mechanisms that produce records. Regardless of the format of the record, the establishment of safeguards is required.	Researchers receiving health information data must sign an agreement with the trustee indicating when records must be destroyed.
Yukon Territory Access to Information and Protection of Privacy Act http://www.gov.yk.ca/legisla tion/acts/atipp.pdf	Public bodies that collect and maintain health information. Health information legislation is pending in the Yukon Territory.	Public bodies, researchers who enter into agreements with public bodies	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.	According to the Access to Information and Protection of Privacy Act, a "record" includes books, documents, maps, drawings, photographs, letters, vouchers, papers and any other thing on which information is recorded or stored by graphic, electronic, mechanical or other means, but does not include a computer program or any other process or mechanism that produces records. Regardless of the format of the record, the establishment of safeguards is required.	According to the Access to Information and Protection of Privacy Act, the person to whom the information is disclosed must sign a formal agreement and comply with its conditions.

where multiple data collectors are involved (to ensure uniform data collection) and where multiple jurisdictions may necessitate the need to find a process that fits all appropriate regulations/policies. Well written SOPs can help to ensure Good Clinical Practice principles are followed and can help to minimize errors and their associated rework.[43] A well written SOP uses plain language in a clear and concise format and is best written by someone familiar with the process.[43] SOPs should have an authorization process and be reviewed and updated on a regular basis.[43] A useful guideline for constructing SOPs can be found here: http://hub.ucsf.edu/sop-guidelines.[44] A good example of what an SOP manual can look like can be found at http://www.frsq.gouv.qc.ca/en/financement/SOP.shtml.[45]

Intellectual Property

Data ownership is an important topic to consider with respect to registry design and implementation. Registries involve many people and agencies that could potentially assert claim over ownership of the data.[5] Specifically, the principal and co-investigator(s), the involved institutions, funding agencies, and the patients themselves are all, to some degree, stakeholders in the registry.[5] It is essential to clarify who owns and possesses the registry data a priori. Ownership of health information should be conceptualized with two considerations in mind. The health information contained within the health record is fundamentally owned by the patient, however, the health record itself is owned by the healthcare provider/institution/facility that produced the record.[46] Under Canadian rights legislation as well as human rights principles and many aspects of provincial legislation, patients fundamentally have a right to access their health information contained within various health records. Registries have a duty to provide this right of access. However, the registry records themselves, like health records are owned by the registry and registry governance documents should clearly stipulate who in the registry operations owns the registry data.

Table 1 addresses intellectual property across relevant national and provincial legislation.

Additionally, as biobanks and registry data are commodities that can be bought and sold, there may be a need to inform participants that it is possible that the biobank with their samples may be sold.[7] It should be disclosed during the informed consent process and made clear in consent forms that the patient does not have a claim on the discoveries arising from their biological specimens.[7] Additionally, samples can be used for a variety of purposes and it should be disclosed to participants which ones are being pursued.[7]

Transparency

It is important to be as transparent as possible about the operation of a registry.[5] Publicizing such information as the research protocol, data security procedures and other relevant information will help to increase the credibility of the registry.[5] Producing a website, newsletter and/or articles in various forms of media are also ways to increase registry transparency.[5]

There is a need to be transparent about what may happen at the end of a registry with respect to the data. At a minimum information on how data will be secured or destroyed should be disclosed as well as who will maintain responsibility for the data

if they are not destroyed. Additionally, this information must include disclosure of plans with respect to potentially selling data to a third party, especially to a private entity such as a pharmaceutical company.

Foreign Registries

In addition to having to meet international standards, international registries operating in Canada must meet Canadian standards because in order to operate in a Canadian facility, appropriate institutional research ethics board approval is required.[7] Ideally a registry should have the capacity to evolve to incorporate data from different nations. Contacting the appropriate international institutions during the registry design stage can help to facilitate the design of a registry that has the potential to be multi-national.[7]

Registry Purpose

Some activities which may involve the development of a registry may not be subject to ethics review. These activities would fall under the umbrella of quality improvement. They are essential to the improvement of healthcare delivery and are specific and local in nature.[47] All other activities conducted by registries where generalizable knowledge is produced will fall under the review of research ethics committees in Canada.

Registry Taxonomy

In "Registries for Evaluating Patient Outcomes: A User's Guide"[5] the Agency for Healthcare Research and Quality (AHRQ) has derived a taxonomy for registries that may be useful in helping to characterize your registry.

Table 2 is an adapted version of this reference.

Policy & Legislation

Tables 3 and 4 feature links and information regarding relevant policy and legislation by province. Those considering the design of registries in Canada should review the relevant links for their desired jurisdictions.

RECOMMENDATIONS

✓ All registries operating in Canada (domestic or foreign) should adhere to Canadian ethical, legal and privacy standards and applicable legislation.

✓ Registries should pro-actively consider legal and ethical issues within their operating jurisdictions. Careful consideration of issues such as capacity to consent and data confidentiality must be undertaken.

✓ Registries should be transparent in their operation. Transparency includes at a minimum clear articulation of the registry purpose; data ownership; data security measures; data usage; and operating term. If a limited operating term is expected, information on how data will be destroyed at the end of the term should be disclosed. It is also recommended that registries make protocols, policies and procedures; and other appropriate documentation available publicly to increase credibility.

✓ Registry operation should include an Advisory Council with broad expertise and perspectives.

✓ Participant consent should be considered ongoing and the informed consent process must include adequate time for reflection. Consent may also consist of three components: 1) consent to collection of data; 2) consent to the initial registry research purpose; 3) consent to subsequent research uses of the data (i.e. additional research projects). Additionally participants must always have the right to withdraw.

✓ Registries including a biobank component must be reviewed by an REB and the purpose of the biobank must be clear and fully disclosed.

✓ Registries with plans to sell data to a third party, especially a private entity, must disclose this.

✓ The ownership of registry data must be clarified in the initial design and communicated to all stakeholders which may include investigators, researchers, participants, host institutions, and funding agencies.

✓ Registry data servers should be housed in a physically secure location inaccessible to the Internet. Ideally, registries will also employ a minimum two-server model where one server stores patient identifiers and the other server stores health information. Anonymization or pseudo-anonymization (coding) should be utilized wherever possible.

✓ Registry data access should be controlled by user type and secured through the use of passwords. Electronic backup files should be kept as hard copies present a security risk.

✓ Registry data requests should be reviewed using a standardized process and data release procedures should be documented. Subgroups of less than six individuals should be considered identifiable.

✓ Registry informed consent forms should include information on the purpose of the registry; how the registry is managed to ensure patient privacy and data security; and why the data being collected is relevant to improving knowledge about the condition and the potential development of treatments.

✓ Registries obtaining information regarding someone other than the direct participant (e.g. family member) should avoid collecting this information if it potentially identifies the individual or obtain consent to collect the information. Registries collecting information that may have sensitive implications or required physician reporting must disclose this possibility to participants.

It is recommended that those planning registries:

✓ Address participant concerns about data access and the type of data stored by the registry.

✓ Consider graduated levels of consent.[48]

✓ Address participant, provider, and stakeholder concerns about data security by establishing a committee to monitor data safety and the release of data rather than having an individual with this responsibility.[48]

✓ Encourage recruitment and utilization in a clinical environment, through efficient and effective registry design. An example could be a software platform with clear procedures supporting the registry infrastructure.[49]

✓ Consider centralized data collection and curation.[50,51]

✓ Select one of two models for patient consent:

a) Written informed consent for the duration of the registry with the option for participant withdrawal and ethical review of research studies utilizing data.[12]

b) Waiver of consent when information is de-identified, not shared, and the option to opt-out is offered.[52]

✓ Employ a two-phase review approach to help in obtaining ethics approval for multi-site registries. Phase one involves review of the registry data collection, curation and storage methods as well as operational policies and procedures. This review would focus on confidentiality and privacy. Phase two involves review of specific research projects utilizing registry data.[47]

✓ Develop a research network infrastructure that will support the registry and help with policy adherence by providing consistent guidance and technical support.[52]

Table 2: Registry Taxonomy by Type

Registry Type	Definition	Examples
Product Registries	Participants are exposed to a healthcare product such as a drug or device. Exposure can be brief or can occur over an extended interval. The registry may feature all individuals exposed to the product or only a subset of individuals exposed to the product.	Registry of patients using subcutaneous IVIG pump. Registry of patients receiving Riluzole. Pregnancy registry examining safety of epilepsy medication.
Health Services Registry	Participants are exposed to a particular healthcare service such as a procedure. These registries may be used to evaluate the quality of the service provided; or to monitor patient outcomes.	Registry of patients accessing home care services following a diagnosis of ALS. Registry of patients undergoing invasive ventilation with a neurological condition.
Disease or Condition Registries	Participants have been diagnosed with a permanent or temporary medical condition or disease. Enrollment may be at any time during disease progression or in some cases may coincide with a particular event.	Registry of patients who have a neuromuscular disease and have developed cardiomyopathy. Registry of patients who have suffered a stroke. Registry of children with atypical seizures.

Table 3: Summary of Relevant Policy and Legislation [1]

	Privacy	Research Ethics	Health	Licensing
NATIONAL	Personal Information Protection and Electronic Documents Act (PIPEDA) English: **http://laws-lois.justice.gc.ca/PDF/P-8.6.pdf** Français: **http://laws-lois.justice.gc.ca/PDF/P-8.6.pdf** Access to Information Act English: **http://laws-lois.justice.gc.ca/eng/acts/A-1/** Français: **http://laws-lois.justice.gc.ca/fra/lois/A-1/** Privacy Act **English: http://laws-lois.justice.gc.ca/eng/acts/P-21/index.html**	TCPS 2—2nd edition of *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* English: **http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/** Français: **http://www.ger.ethique.gc.ca/fra/policy-politique/initiatives/tcps2-eptc2/Default/** Canadian Association of Research Ethics Boards: Resources English: **http://www.careb-accer.org/resource** Français: **http://www.careb-accer.org/fr/resource**		
NATIONAL	Français: **http://laws-lois.justice.gc.ca/fra/lois/P-21/index.html** CSA Standard CAN/CSA-Q830, *Model Code for the Protection of Personal Information* English: **http://www.csa.ca/cm/ca/en/privacy-code/publications/view-privacy-code** Français: **http://www.csa.ca/cm/ca/fr/privacy-code/publications/view-privacy-code/article/preface** CIHR Best Practices for Protecting Privacy in Health Research (September 2005) **English: http://www.cihr-irsc.gc.ca/e/29072.html** Français: **http://www.cihr-irsc.gc.ca/f/29072.html**	The Belmont Report **http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html**		
Alberta	Freedom of Information and Protection of Privacy Act (FOIPP) **http://www.qp.alberta.ca/574.cfm?page=F25.cfm&leg_type=Acts&isbncln=9780779762071** Personal Information Protection Act (PIPA) **http://www.qp.alberta.ca/574.cfm?page=P06P5.cfm&leg_type=Acts&isbncln=9780779762507**	**Health Quality Council of Alberta** **http://www.hqca.ca/** Alberta Provincial Ethics Network (Part of HQCA) **http://www.phen.ab.ca/** Research Ethics Committees **http://www.phen.ab.ca/ecommittees/research.asp** Information/Resources **http://www.phen.ab.ca/articlepackages/index.asp**	Health Information Act **http://www.qp.alberta.ca/574.cfm?page=H05.cfm&leg_type=Acts&isbncln=9780779752607**	
British Columbia	Freedom of Information and Protection of Privacy Act (FIPPA) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/96165_00 Personal Information Protection Act (PIPA) **http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_03063_01**	Healthcare Consent Regulation from the Healthcare Consent and Care Facility Administration Act. http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/20_2000#section2	E-Health (Personal Health Information Access and Protection of Privacy) Act **http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_08038_01**	
Manitoba	Freedom of Information and Protection of Privacy Act (FIPPA) **http://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=f175**	Manitoba Provincial Health Ethics Network **http://www.mb-phen.ca/index.html** MB-PHEN Implementation Council **http://www.mb-phen.ca/aboutCouncil.html** Health Ethics Resources **http://www.mb-phen.ca/aboutHealthEthics.html**	The Personal Health Information Act **http://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=p33.5**	
New Brunswick	Right to Information and Protection of Privacy Act **http://www.gnb.ca/legis/bill/FILE/56/3/Bill-89-e.htm**		Personal Health Information Privacy and Access Act **http://www.gnb.ca/0062/PDF-acts/p-07-05.pdf**	

Table 3: Summary of Relevant Policy and Legislation [continued 2]

	Privacy	Research Ethics	Health	Licensing
Newfoundland and Labrador	Access to Information and Protection of Privacy Act (ATIPPA) http://assembly.nl.ca/Legislation/sr/statutes/a01-1.htm	Health Research Ethics Authority Act http://www.assembly.nl.ca/legislation/sr/statutes/h01-2.htm Health Research Ethics Authority Regulations under the Health Research Ethics Authority Act http://www.assembly.nl.ca/legislation/sr/regulations/rc110057.htm Does your study require ethics review? http://www.hrea.ca/Ethics-Review-Required.aspx Health Research Ethics Board http://www.hrea.ca/HREB.aspx	Personal Health Information Act (PHIA) http://assembly.nl.ca/Legislation/sr/statutes/p07-01.htm	
Nova Scotia	Freedom of Information and Protection of Privacy Act (FOIPOP) http://nslegislature.ca/legc/statutes/freedom.htm Privacy Review Officer Act http://nslegislature.ca/legc/bills/60th_2nd/3rd_read/b234.htm Personal Information International Disclosure Protection Act (PIIDPA) http://nslegislature.ca/legc/statutes/persinfo.htm	Nova Scotia Health Ethics Network: http://www.nshen.ca/ Ethics Resources: http://www.nshen.ca/ethicsresources.html Nova Scotia Health Ethics Network FAQ/Contact Information http://www.nshen.ca/faqs.html	Personal Health Information Act https://www.gov.ns.ca/dhw/phia/	
Ontario	Freedom of Information and Protection of Privacy Act (FIPPA) http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90f31_e.htm Municipal Freedom of Information and Protection of Privacy Act (MFIPPA) http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_90m56_e.htm Manual for the Review of Prescribed Persons and Prescribed Entities http://www.ipc.on.ca/images/Findings/process.pdf		The Personal Health Information Protection Act (PHIPA) http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm	
Prince Edward Island	Freedom of Information and Protection of Privacy Act (FOIPP) http://www.gov.pe.ca/law/statutes/pdf/f-15_01.pdf	Prince Edward Island Research Ethics Board http://www.healthpei.ca/reb Submission Requirements - PEI Research Ethics General Guidelines http://www.gov.pe.ca/photos/original/doh_reb_guideli.pdf Prince Edward Island RESEARCH ETHICS BOARD: Mandate http://www.gov.pe.ca/photos/original/doh_reb_mandate.pdf	Health PEI: Privacy and Access http://www.healthpei.ca/index.php3?number=1020297&lang=E No separate legislation.	
Quebec	An Act respecting Access to documents held by public bodies and the Protection of personal informationEnglish: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/A_2_1/A2_1_A.html Français: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/A_2_1/A2_1.html An Act respecting the protection of personal information in the private sector English: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/P_39_1/P39_1_A.html Français: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/P_39_1/P39_1.html	Fonds de recherche Santé Québec English: http://www.frsq.gouv.qc.ca/en/ethique/ethique.shtml#02 Français: http://www.frsq.gouv.qc.ca/fr/ethique/ethique.shtml#02 Also refer to: (Governance Framework for Data Banks and Biobanks used for Health Research (FRSQ, 2006)) English: http://www.frsq.gouv.qc.ca/en/ethique/pdfs_ethique/Sommaire_groupe_conseil_anglais.pdf Français: http://www.frsq.gouv.qc.ca/fr/ethique/pdfs_ethique/Rapport_groupe_conseil_francais.pdf (Code of ethics and professional conduct (FRSQ, 2003)) English: http://www.frsq.gouv.qc.ca/en/ethique/pdfs_ethique/code_ethique_ang.pdf Français: http://www.frsq.gouv.qc.ca/fr/ethique/ethique.shtml	Commission d'accès à l'information du Québec English: http://www.cai.gouv.qc.ca/english/ Français: http://cai.gouv.qc.ca/	
Saskatchewan	Freedom of Information and Protection of Privacy Act (FOIP) http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/F22-01.pdf The Local Authority Freedom of Information and Protection of Privacy Act (LA FOIP) http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/L27-1.pdf The Privacy Act http://www.qp.gov.sk.ca/documents/English/Statutes/Statutes/P24.pdf OIPC Investigation Report 2005-002: http://www.oipc.sk.ca/Reports/H-2005-002.pdf	HIPA Approved Ethics Committees http://www.health.gov.sk.ca/approved-research-ethics-committee	Health Information Protection Act (HIPA) http://www.qp.gov.sk.ca/documents/english/Statutes/Statutes/H0-021.pdf HIPA Checklist http://www.health.gov.sk.ca/hipa-checklist	
Northwest Territories	Access to Information and Protection of Privacy Act http://www.justice.gov.nt.ca/pdf/ACTS/Access%20to%20Information%20and%20Protection%20of%20Privacy.pdf			Northwest Territories Licensing http://www.nwtresearch.com/licensing (Scientists Act http://www.nwtresearch.com/licensing/nwt-scientists-act)
Nunavut	Access to Information and Protection of Privacy Act (ATIPP) http://www.atipp.gov.nu.ca/en/Act.aspx			Nunavut Research Institute: Licensing Process http://www.nri.nu.ca/apps/authoring/dspPage.aspx?page=process
Yukon	Access to Information and Protection of Privacy Act http://www.gov.yk.ca/legislation/acts/atipp.pdf			Guidebook on Scientific Research in the Yukon http://www.tc.gov.yk.ca/pdf/science_research_guidelines.pdf Scientists and Explorers Act http://www.tc.gov.yk.ca/pdf/scientists_and_explorers_act.pdf Scientists and Explorers License http://www.tc.gov.yk.ca/scientists_explorers.html

Table 4: Registry Requirements & Considerations by Province [1]

Province or Territory (Corresponding Legislation)	Is a Privacy Impact Assessment required? (yes/no)	Is Research Ethics Board Approval required? (yes/no)	Permission from the health authority or other health administration body	Patient Consent	Data Matching or Data Linkage
Alberta (Health Information Act) http://www.qp.alberta.ca/574.cfm?page=H05.cfm&leg_type=Acts&isbncln=9780779752607	Yes. This is to be completed by custodians in accordance with 64(1) of the Health Information Act. According to sections 70(2) and 71(2) of the Health Information Act, privacy impact assessments are required for data matching. Consult **http://www.oipc.ab.ca/Content_Files/Files/PIAs/PIA_Requirements_2010.pdf** for more information	Yes according to 27(1), 49 and 50 of the Health Information Act According to the Health Information Act ,(v) "research" means academic, applied or scientific research that necessitates the use of individually identifying health information	Permission from custodian needed according to sections 51-56 of the Health Information Act	Not required for non-identifying information according to section 32 of the Health Information Act. Required for individually identifying information according to section 34 and subject to sections 35-40 of the Health Information Act. Requirement of consent for disclosure of health information for research to be determined by ethics committee according to 50(1)(a) of the Health Information Act	According to the Health Information Act , (g) "data matching" means the creation of individually identifying health information by combining individually identifying or non-identifying health information or other information from 2 or more electronic databases, without the consent of the individuals who are the subjects of the information. To be conducted in accordance with sections 70-72. Data matching for research (Section 72) must be done in accordance with sections 48-56 of the Health Information Act (disclosure for research purposes).
British Columbia (FIPPA) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/96165_00 Health Care Consent Regulation http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/20_2000 E-Health (Personal Health Information Access and Protection of Privacy) Act http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_08038_01 Health Care Consent Act http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_96181_01	Yes. In order to be compliant with FIPPA, a PIA is required for all initiatives that deal with personal information. Consult **http://www.cio.gov.bc.ca/cio/priv_leg/foippa/pia/pia_index.page** and **http://www.oipc.bc.ca/index.php?option=com_content&view=article&id=80%3Apublic-sector-g-privacy-impact-assessment-pia&catid=16%3Aresources-for-public-bodies&Itemid=1** for more information	Yes and boards with authority are defined in the Health Care Consent Regulation.	Permission needed from data stewardship committee in accordance with section 14 of the E-Health (Personal Health Information Access and Protection of Privacy) Act	Patient consent is always required when information is being disclosed outside of Canada in accordance with section 14(2b) of the E-Health (Personal Health Information Access and Protection of Privacy) Act Consent is also always required where treatment or intervention will be provided (Health Care Consent Act). Otherwise not specified in legislation but may be a condition of disclosure set by data stewardship committee according to section 14(3) of the E-Health (Personal Health Information Access and Protection of Privacy) Act	According to section 3(5) of the E-Health (Personal Health Information Access and Protection of Privacy) Act: If a health information bank is established or designated by a designation order, personal health information may be collected, used and, subject to sections 14 [disclosure for planning or research purposes] and 19 [information-sharing agreements required for disclosure], disclosed through the health information bank by a person who is authorized to do so by the designation order, according to the terms of the designation order.
Manitoba FIPPA http://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=f175 The Personal Health Information Act http://web2.gov.mb.ca/laws/statutes/ccsm/_pdf.php?cap=p33.5	No reference to this found in legislation Consult **http://www.gov.mb.ca/chc/fippa/public_bodies/privacy_impact_assessment.html** for more information	In Manitoba, the legislation refers to REBs as "Institutional Research Review Committees" Approval from institutional research review committees is necessary according to section 24 of the The Personal Health Information Act.	Approval may be given by those specified in section 24(2) in accordance with section 24 of the The Personal Health Information Act.	Sometimes required (sections 21 and 22). However, sometimes not required according to section 24(3) of the The Personal Health Information Act. When consent is required, follow it must be collected/retained according to Section 19 of the The Personal Health Information Act.	According to Section 28(e) of the The Personal Health Information Act, the Ombudsman may comment of the implication of disclosing personal health information for linkage and using technology to collect, store and transfer personal health information.
New Brunswick (Personal Health Information Privacy Access Act.) http://www.gnb.ca/0062/PDF-acts/p-07-05.pdf	Yes, according to section 56 of the Personal Health Information Privacy Access Act. With respect to data matching, a privacy impact assessment is required when one custodian uses data held by another custodian (section 56) but not when using data in its own custody for authorized purposes (Section 57)	According to 43(2) of the Personal Health Information Privacy Access Act "An approval may be given by a research review body that meets the requirements prescribed by regulation." "research" means a systematic investigation designed to develop or establish principles, facts or general knowledge, or any combination of them, and includes the development, testing and evaluation of research.	Approval from custodian needed in accordance with section (43) of the Personal Health Information Privacy Access Act.	Consent is required unless obtaining consent is deemed by a research review body to be unreasonable or impractical (according to section 43(3) of the Personal Health Information Privacy Access Act)	According to section 37(6)(d) of the Personal Health Information Privacy Access Act, a custodian shall disclose personal health information without individual consent to a custodian who compiles or maintains a registry for facilitating or improving health care or that involves the storage or donation of body parts and substances. "data matching" means the creation of identifying information by combining identifying information or deidentified personal health information or other information from 2 or more electronic data bases or 2 or more electronic records. Must be done in accordance with section 57 of the Personal Health Information Privacy Access Act.
Newfoundland and Labrador Personal Health Information Act (PHIA) http://assembly.nl.ca/Legislation/sr/statutes/p07-01.htm Health Research Ethics Authority Act http://www.assembly.nl.ca/legislation/sr/statutes/h01-2.htm	Privacy Impact Assessments are done as a self-monitoring tool to ensure compliance with the Personal Health Information Act. A toolkit including PIA forms is available at: http://www.health.gov.nl.ca/health/PHIA/	Yes according to section 44 of PHIA as well as the Health Research Ethics Authority Act According to PHIA, "research" means a systematic investigation designed to develop or establish principles or facts or to generate knowledge, or any combination of principles, facts and knowledge, and includes the development, testing and evaluation of research.	Approval from custodian is needed in accordance with section 44 and the Health Research Ethics Authority Act. Custodians must also adhere to sections 48 and 49 when disclosing information.	Consent is required according to section 36. However, according to section 44, disclosure without consent is permitted in accordance with Health Research Ethics Authority Act.	According to section 39(4)(d), a custodian shall disclose personal health information without individual consent to a custodian who compiles or maintains a registry for facilitating or improving health care or that involves the storage or donation of body parts and function. According to Section 79(e), the Commissioner may comment of the implications of using and disclosing personal health information for linkage and using technology to collect, store and transfer personal health information.

Table 4: Registry Requirements & Considerations by Province [continued 2]

Province or Territory (Corresponding Legislation)	Is a Privacy Impact Assessment required? (yes/no)	Is Research Ethics Board Approval required? (yes/no)	Permission from the health authority or other health administration body	Patient Consent	Data Matching or Data Linkage
Nova Scotia (Personal Health Information Act) https://www.gov.ns.ca/dhw/phia/	Yes may be required by some institutions. Not required in legislation. Consult the following for more information: **http://www.gov.ns.ca/just/IAP/_docs/Appendix%20B%20PIA%20Template.pdf**	Yes, according to sections 55 and 57 of the Personal Health Information Act. Note that a research plan must be submitted in accordance with section 59 of the Personal Health Information Act. Note that according to section 53 of the Personal Health Information Act planning and management of the health system does not constitute research.	Approval from custodian needed in accordance with sections 54 and 56-60 of the Personal Health Information Act	Sometimes Required. According to section 57 of the Personal Health Information Act the research ethics board and custodian determine whether consent is required. When consent is required, sections 13-23 of the Personal Health Information Act must be followed.	According to the Personal Health Information Act , (a) "data matching" means the creation of individual identifying health information by combining individual identifying or non-identifying health information or other information from two or more databases without the consent of the individuals who are the subjects of the information According to sections 59(3)(e) and 59(3)(j) of the Personal Health Information Act, a research plan must explain how linkage of personal health information to other information will be conducted and why data matching is required. Data matching must be done in accordance with sections 53-60 of the Personal Health Information Act.
Ontario (Personal Health Information Protection Act) http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm	Not required under legislation but viewed as a best practice by most health organizations. Consult the following for more information: **http://www.ipc.on.ca/images/Resources/up-phipa_pia_e.pdf**	Yes, according to section 44(3) and 44(4) of the Personal Health Information Protection Act According to the Personal Health Information Protection Act "research" means a systematic investigation designed to develop or establish principles, facts or generalizable knowledge, or any combination of them, and includes the development, testing and evaluation of research	Approval from custodian needed in accordance with section 44 of the Personal Health Information Protection Act. Note section 30 of the Personal Health Information Protection Act.	Consent required according to section 29 of the Personal Health Information Protection Act and must be in accordance with sections 18-28 of the Personal Health Information Protection Act. However, a research ethics board may need that it is impractical to obtain consent according to section 44(3)(d) of the Personal Health Information Protection Act	According to section 39(1)(c) of the Personal Health Information Protection Act, a custodian may disclose personal health information to a prescribed person who compiles or maintains a registry for facilitating or improving health care or that involves the storage or donation of body parts and substances.
Prince Edward Island (Freedom of Information and Protection of Privacy Act) http://www.gov.pe.ca/law/statutes/pdf/f-15_01.pdf	No legislative requirement Some institutions may require this internally. **http://www.gov.pe.ca/photos/original/oipc_pia.pdf**	No reference to this found in legislation. There is reference in the Pharmaceutical Information Act which names only the Prince Edward Island Research Ethics Board and the University of Prince Edward Island Research Ethics Board. A Health Research Ethics Board was formed but is currently without an arm's length sponsor (Feb 2012).	Approval from public body needed in accordance with section 39 and 40 of the Freedom of Information and Protection of Privacy Act.	According to section 15(4)(a) of the Freedom of Information and Protection of Privacy Act, disclosure of medical, psychiatric or psychological history, diagnosis, condition, treatment or evaluation is an unreasonable invasion of a third party's personal privacy. However, according to section 15(2)(a) of the Freedom of Information and Protection of Privacy Act, disclosure of such information is not an invasion of a third party's personal privacy if the third party has given written consent.	According to section 39(b) of the Freedom of Information and Protection of Privacy Act, a public body may disclose information for research if the record linkage is not harmful and benefits are in public interest. According to Section (50)(1)(e) of the Freedom of Information and Protection of Privacy Act, the Commissioner may comment of the implications of using and disclosing personal information for record linkage According to section (77(1)(k) of the Freedom of Information and Protection of Privacy Act, the Lieutenant Governor in Council may make regulations regarding standards and procedures for data sharing, data matching and data linkage.
Quebec (An Act respecting Access to documents held by public bodies and the Protection of personal information) English: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/A_2_1/A2_1_A.html Français http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/A_2_1/A2_1.html Commission d'accès à l'information du Québec English: http://www.cai.gouv.qc.ca/english/ Français http://cai.gouv.qc.ca/ FRSQ English: http://www.frsq.gouv.qc.ca/en/ethique/ethique.shtml Français http://www.frsq.gouv.qc.ca/fr/ethique/ethique.shtml	No reference to this found in legislation	By ministerial decree the FRSQ (Fonds de recherche Santé) is charged with administering policy and procedure around research ethics.	Approval needed by the Commission in accordance with section 125 of An Act respecting Access to documents held by public bodies and the Protection of personal information.	Not required if approved by the Commission in accordance with section 125 of An Act respecting Access to documents held by public bodies and the Protection of personal information.	May require an application to the Commission d'accès à l'information du Québec

Table 4: Registry Requirements & Considerations by Province [continued 3]

Province or Territory (Corresponding Legislation)	Is a Privacy Impact Assessment required? (yes/no)	Is Research Ethics Board Approval required? (yes/no)	Permission from the health authority or other health administration body	Patient Consent	Data Matching or Data Linkage
Saskatchewan (Health Information Protection Act) http://www.qp.gov.sk.ca/documents/english/Statutes/Statutes/H0-021.pdf	No legislative requirement, however, considered a best practice. Consult the following for more information: **http://www.oipc.sk.ca/resources.htm** **http://www.oipc.sk.ca/Resources/PIA_HIPA.pdf**	Yes according to section 29 of the Health Information Protection Act (HIPA).	Approval from trustee or designated archive needed in accordance with section 29 of the Health Information Protection Act (HIPA).	According to section 29(2) of the Health Information Protection Act (HIPA), consent is not required if it is deemed to be "not reasonably practical" for consent to be obtained.	Will require an agreement between the researcher and data trustee. May require an application to Ministry of Health (public admin data).
Northwest Territories (Access to Information and Protection of Privacy Act and the Scientists Act) http://www.justice.gov.nt.ca/pdf/ACTS/Access%20to%20Information%20and%20Protection%20of%20Privacy.pdf Scientists Act http://www.nwtresearch.com/licensing/nwt-scientists-act	No legislative requirement. No privacy office requirement.	According to the Scientists Act, those who want to conduct research or collect specimens must hold a license issued under the act. These licenses are issued by the Commissioner	Approval from public body needed in accordance with section 49 of the Access to Information and Protection of Privacy Act	Yes, according to sections 4(a), (24)(2)(a), 43, 48 of the Access to Information and Protection of Privacy Act	Section 49(b) of the Access to Information and Protection of Privacy Act, a public body may disclose information for research if the record linkage is not harmful and benefits are in public interest
Nunavut (Access to Information and Protection of Privacy Act) http://www.atipp.gov.nu.ca/en/Act.aspx *Nunavut Research Institute: Licensing Process http://www.nri.nu.ca/apps/authoring/dspPage.aspx?page=process	No legislative requirement. No privacy office requirement.	Those who want to conduct research in Nunavut must hold a license issued by the Nunavut Research Institute.	Approval from public body needed in accordance with section 49 of the Access to Information and Protection of Privacy Act.	Yes, according to sections 23, 24, 43, 48 of the Access to Information and Protection of Privacy Act	Section 49(b) of the Access to Information and Protection of Privacy Act, a public body may disclose information for research if the record linkage is not harmful and benefits are in public interest
Yukon (Access to Information and Protection of Privacy Act and the Scientists and Explorers Act) http://www.gov.yk.ca/legislation/acts/atipp.pdf Scientists and Explorers Act http://www.tc.gov.yk.ca/pdf/scientists_and_explorers_act.pdf	Office of the Information and Privacy Commissioner of the Yukon recommends completion and submission of an ATIPP Compliance Assessment. http://www.ombudsman.yk.ca/uploads/general/ACA_ATIPP_Compliance_Assessment_August_2011.pdf A PIA worksheet is also available: http://www.ombudsman.yk.ca/uploads/general/PRIVACY%20IMPACT%20ASSESSMENT.pdf	According to the Scientists and Explorers Act, research must be conducted with a license issued by the Minister.	Approval from public body needed in accordance with section 38 of the Access to Information and Protection of Privacy Act.	Yes, according to sections 25, 35 and 36 of the Access to Information and Protection of Privacy Act.	According to Section 38(b) Access to Information and Protection of Privacy Act, a public body may disclose information for research if the record linkage is not harmful and benefits are in public interest

Patient Recruitment by Neurological Registries

*Mark Hamilton[1], Angela Genge[2], Megan Johnston[1], Darren Lam[1],
Theo Mobach[1], James Marriott[3], Thomas Steeves[4], Elizabeth Donner[4,5],
Julie Wysocki[6], Karen Barlow[1], Michael Shevell[2], Ruth Ann Marrie[3],
Steve Casha[1], Gail MacKean[1], Lisa Casselman[1], Lawrence Korngut[1],
Tamara Pringsheim[1], Nathalie Jette[1,7,8]*

This section summarizes the considerations surrounding patient recruitment that Canadian neurological registries should address during planning and design. In preparation of this guideline, we examined relevant Canadian and international literature; Canadian policy and legislation. We also consulted with Canadian privacy officers and specialists in research ethics.

BACKGROUND

Clinical registries capture patient information contingent upon successful recruitment and retention of patients who will consent to participation. To accomplish this requires the elements that affect patient recruitment. For example, failure to adequately engage physicians or other healthcare professionals can have as much impact on recruitment success as failure to adequately identify the patients relevant to the purposes of the registry. A strategy for recruitment that is not properly targeted to relevant patients will fail to provide desired information.

RELEVANT LITERATURE

A literature review identified 96 abstracts describing registry recruitment. Full text reviews were performed on 37 articles and identified 23 articles for summarization.

General Overview

Recruitment in a comprehensive manner can result in population-based registries that are highly generalizable and can be used for the identification of eligible participants for future research studies.[53-56] Those involved in the creation of population-based registries should be aware that recruitment and participant biases occur when individuals that consent or refuse to participate are inherently different from the population as a whole.[53,55,57,58] Such biases in registries may result in unrepresentative or non-generalizable data thus it is important to ensure that recruitment strategies are effective and that the resulting sample is representative of the target population.

Although recruitment of clinic-based populations may prove to be more successful with respect to retention, using a population-based sampling frame offers the methodological advantage of recruiting a representative sample.[59] Recruitment and enrollment into a registry may be mandatory for certain conditions such as Creutzfeld-Jacob Disease,[17,53-56,60] yet many other diseases require patient consent to enroll into the registry. Barriers to development of population-based registries exist but specific strategies have been shown to be effective in both recruitment and retention.

The Agency for Healthcare Research and Quality (ARHQ) Manual "Registries for Evaluating Patient Outcomes A Users Guide"[5] is a valuable resource that critiques strategies for retention and recruitment. The validity of registry data may be profoundly compromised if common problems associated with clinical studies are not addressed (e.g. difficulties with patient enrollment, losses to follow-up, and certain sites contributing most patients). Generally, the burden of participation should be minimized, while the relative rewards, particularly non-monetary rewards, should be maximized. One must be aware of the use of confusing terminology (i.e. it is critical that the language and terminology are clear and concise) as a potential further source of recruitment bias.

Ethnic Diversity & Other Barriers toward Recruitment

Mitigation of factors that may result in selection bias requires consideration of ethnic diversity. Fear of foreign medical institutions and skepticism related to research might prevent certain groups from enrolling in registries.[21,61] Bachman et al[61] postulated a number of reasons that may contribute to the difficulties in recruiting certain ethnic groups for research purposes: Information about research not reaching the community, the perception that research is biased to benefit the white population, insufficient community involvement by the research team to allow trust to develop, concerns that the research is not relevant to their community, the lack of use of

From the [1]Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta; [2]McGill University, Montreal, Quebec; [3]University of Manitoba, Winnipeg, Manitoba; [4]University of Toronto, Toronto, Ontario; [5]Hospital for Sick Children, Toronto, Ontario; [6]Parkinson Society of Canada, Toronto, Ontario; [7]Institute for Public Health, University of Calgary, Calgary, Alberta.

existing networks and failure to advertise in appropriate locations, the lack emphasis to the community regarding the importance of research, inadequate compensation for participation, the possibility that the research does not address a personal or family medical problem, inadequate representation of minorities on the research team, and limited time for healthcare-related activities for potential participants and family members. Other documented reasons for recruitment refusal include not wanting to travel to participate, feeling unable to commit, and lack of interest.[53] Physicians are often involved in the recruitment process[53,54,60-62] and some have noted that involving their patients in a registry involves time commitment and intrusion of the study on the physician-patient relationship[53] – a potential barrier to recruitment. Other limitations include geographical remoteness and related transportation costs.[21]

Vulnerable Populations

Within neurological conditions it is not uncommon to seek enrollment of patients who may be members of a vulnerable population. Such vulnerable populations may include minors; individuals with mental or cognitive difficulties; and individuals with low socioeconomic status. With respect to issues of capacity (minors and individuals with cognitive impairment) more information can be found in the Ethical and Legal considerations section of this document. Addressing recruitment strategies toward individuals with low socioeconomic status may be more challenging. Assessment of the relative or expected socioeconomic status in the registry's target population is a critical step toward ensuring recruitment strategies can be inclusive of participants with low socioeconomic status. Additionally, it may be helpful to obtain statistics on the socioeconomic profile of patients attending clinics where recruitment will occur to ensure a representative sample can be obtained. Finally, utilizing multiple recruitment modalities may help to reach vulnerable populations.

Sources and Methods of Patient Recruitment

A critical aspect of any successful registry involves the correct identification of the relevant patient population. This process begins by defining the diagnostic characteristics and how the population will be accurately identified. The patient population may, for example, be predominately diagnosis-based (e.g. Multiple Sclerosis) vs. treatment-based (e.g. anti-epileptic medications) or hospital-based vs. community physician-based. Once the location and characteristics of the population are established, recruitment methodologies can be addressed. As examples, patients may potentially be approached after reviewing diagnostic codes associated with medical records or other administrative data sources, or in association with visits to family practice or specialty care clinics.

Recruitment of individuals meeting eligibility criteria has been accomplished through a myriad of strategies – both active and passive. Active strategies include recruitment through medical staff and clinical sites[11,56,58-61,63], searching through health records,[16,55,57,60] seeking participants in specific community locations (e.g. senior housing venues, senior co-op housing, city senior services),[64] or reaching out to the community by providing educational learning series[63,64]. Passive strategies include attracting patients through the Internet and websites,[17,23,57,62] media and awareness campaigns,[17,55,57,63,65,66] and information brochures, flyers, or both[17,23,57,63-65] In several prior studies, a toll-free information contact number on brochures/flyers and media and awareness campaigns were provided to interested individuals.[57,63]

Additional Points Regarding Physician and Patient Recruitment and Retention

The overall success of a patient registry is largely dependent on the successful recruitment of patients. However, this requires the engagement of patients and physicians or other healthcare professionals. The importance of this element should not be underestimated. Strategies to involve physicians and other healthcare professionals include providing a clear representation of the registry structure, methods and standard operating procedures (SOPs) so as to avoid any process confusion; and the development of strategies to keep the process of patient recruitment and data collection as simple as possible. It is equally important to keep health professionals engaged in the process by providing regular updates. The success of a registry is enhanced by providing adequate resources to support the recruitment of patients, and the collection, verification and entry of data. While it is often challenging to obtain funds for registries, this should be a goal.

A lack of physician experience with research may also impact successful patient recruitment into registries. To provide for long-term registry viability it may be wise to try to team a senior member (physician) to act as a mentor with a junior member. The establishment of a clear business plan with a detailing of any financial resources available and financial obligations for physician participants is also critical to avoid surprises that may discourage physician recruitment or retention in a registry.

During the process of establishing a registry, it could be useful to hold multiple focus groups inviting both healthcare professionals and patients to participate. This would allow for assistance in identifying key registry issues before methodology and SOPs are established. During this process, stakeholder organizations should be engaged to obtain their input regarding how to improve patient recruitment and retention strategies.

Ethical Recruitment

It is vital to ensure that recruitment is accomplished with clear regard to all ethical considerations. Strategies for recruitment and retention should be vetted for practical and ethical concerns, developed into SOPs and implemented with monitoring to ensure compliance. These strategies should deal with (but not be limited to) such issues as where and how patients can be approached (e.g. clinic vs. letter), who can approach patients (e.g. clinician vs. research team member), whether it is suitable to pay transportation costs for patients who participate in a registry, and how to manage the recruitment of vulnerable populations such as the cognitively impaired.

Also, as part of the development of SOPs, clear guidelines must be established which define who has access to data entry, data review and data analysis for a registry. This information (i.e. the clearly developed and vetted SOPs) can be communicated with patients so that they have a clear understanding of their responsibilities and trust regarding the safety and security of their personal information.

More detail on ethical recruitment considerations can be found in the Ethical and Legal considerations section of this document.

Maximizing Enrollment

Several proposed strategies may help achieve a high registry participation rate. First, using a variety[17,65] of recruitment strategies can improve the participation rate. Wei et al's Internet-Based Clinical Trials Database for colorectal cancer showed that 88% of patients registered through the Internet as opposed to 12% through the call center, supporting the efficacy and usefulness of the Internet for recruitment.[17] Gupta et al further supports the idea of Internet-based patient recruitment because it represents an opportunity for efficient recruitment of patients for rare lung disease studies.[21] However, internet registration may not be effective at reaching all age groups or demographics, therefore there is utility to using multiple approaches to ensure a representative sample can be obtained. The adoption of technology may aid recruitment process for patients – this can involve the use of online questionnaires[18,27] or using touch-screen computers.[27] More detail can be found in the Online Registries section of this document. Involving treating physicians that have established a good physician-patient relationship can also be effective for recruiting participants.[16,20,54] Providing clear information in advance so patients have time to raise questions about the study, explaining the benefits of participation, clarifying how the costs to the participants will be covered, ensuring that the patient is aware of the confidential nature of the study, ensuring that the patient understands that they have the ability to withdraw at any time, and supplying local media with stories that will raise the profile of the study are all strategies that can help achieve a high enrolment rate.[20] To improve recruitment, Gupta et al[21] suggested providing benefits with registry membership (such as access to disease forums and information resources), and using clinical research networks and organizations. Newberry et al[58] concluded that several specific recruiter and interviewer training techniques were associated with higher recruitment and retention: increased communication, becoming familiar with the community and recruitment sites, being flexible with recruitment approaches, being aware of cultural differences in participation, and the timing of the approach in relation to the initial diagnosis (higher chance of refusal if approached too soon after diagnosis) may impact willingness to participate in neurology research. Sending a post-card and a phone call following initial contact resulted in the best patient response rates in the Ontario Familial Breast Cancer Registry.[60]

Reducing Attrition

Following successful recruitment, patients may be lost to follow-up over time. It is necessary to implement strategies that limit attrition. Loss of follow-up tends to be highest in those registries relying on voluntary reporting through healthcare providers where incentives for complete reporting are not provided.[67] Golding et al[20] recommend obtaining contact information of one or two individuals who would be likely to know the new location of the study participant/family in the situation that they relocate or are lost to clinical follow-up. Reminders such as fridge magnets[66] or phone calls[58] can also help limit attrition.

A critical factor in retention is delivery on promises made during recruitment (i.e. that the burden of patient participation is low). Provider participation retention tools include: Web sites, newsletters, telephone helplines, instruction manuals, training meetings, site audit/retraining visits, satisfaction/opinion surveys, regular data reports to stakeholders, presentations at conferences, regular reports to registry participants on registry growth and publications, and the ability of participating physicians to publish based on registry data. Retaining patients require the development of a retention plan. For patients who transfer to non-enrolled practices, enlisting site staff to reach out to patients beyond their standard interactions, following patients directly through a central patient management center, and linking to other data sources to obtain key long-term outcomes data on patients who are lost to follow-up is essential.[5]

Special Considerations in Canada

There is literature regarding recruitment strategies for hospitals that does not have any significant practical context in Canada.

Registries may be centered in one jurisdiction or span multiple jurisdictions which requires that careful attention be paid to the legislative requirements and privacy considerations for each jurisdiction (e.g. province) that is involved. This may become more complex if data-linkage with health system administrative data is planned.

Potential Canadian-specific sources for patient recruitment include provincial home-care networks (which may capture people not identified in clinics), public health clinics, and in Quebec, the CLSCs (centre local de services communautaires or local community service centres) where patients may not directly interact with a physician. Non-physician sources of recruitment such as rehabilitation centres or allied healthcare practitioners (e.g. occupational therapists, physical therapists; dietitians etc) should also be considered.

Specific Canadian cultural considerations must be addressed while developing a registry to ensure that all population characteristics are represented. One specific aspect relates to the benefits of bilingual recruitment, which allows researchers to reach out to a more diverse population. This may involve increased cost and challenges with regard to providing seamless access to interpreters and professionally translated materials.

When determining the registry population to be targeted, it also is important to consider Aboriginal groups which otherwise might be underrepresented or missed with conventional recruitment strategies. This will require a clear understanding of Aboriginal policies and legalities so that appropriate representative bodies are involved. More information on considerations for registries working with Aboriginal populations can be found in the Ethical and Legal considerations section of this document.

RECOMMENDATIONS

✓ Ensure that physicians and other healthcare professionals are involved as needed, engaged and regularly updated. Consider engaging participants and healthcare professionals during the design phase to assess needs and gather resources.

✓ Recruit patients from various sources to ensure that the study population is representative of the total disease population of interest. Address challenges associated with physician/healthcare professional participation and utilize strategies to engage non-academic physicians/healthcare professionals when appropriate.

✓ Establish a registry website that can be used as a resource by patients. The registry website may also be used as a recruitment tool.

✓ Consider utilization of a patient consent to be contacted about research within routine clinical practice. This can increase the ability to recruit registry patients through phone or letter contact.

✓ Engage advocacy groups and other stakeholders to encourage participation or reach potential participants that are otherwise inaccessible.

✓ Minimize participant and clinician burdens of participation, especially time.

✓ Ensure every registry site / jurisdiction has its own representative and champion as well as adequate resources (e.g. nursing staff support; financial etc.).

✓ Develop and test SOPs outlining recruitment strategies and procedures. Ensure that these are reviewed by a research ethics board.

✓ Ensure that registry participants and healthcare professionals feel as though they belong to a group.

✓ Where bilingual or multi-lingual recruitment is desired, ensure that recruitment documents and procedures address the appropriate language needs.

✓ Ensure that recruitment strategies address the needs of special populations (e.g. pediatric assent strategies; considerations for Aboriginal populations etc.).

Neurological Registry Data Collection Methods and Configuration

Eric E. Smith[1], Janet Warner[2], Megan Johnston[2], Kristin Atwood[3], Ruth Hall[4], Jean K. Mah[2], Colleen Maxwell[5], Claire Marie Fortin[6], Mark Lowerison[2], Moira K. Kapral[4], Vanessa K. Noonan[7], Ted Pfister[2], Gail MacKean[2], Lisa Casselman[2], Tamara Pringsheim[2], Nathalie Jette[1,8], Lawrence Korngut[1]

The purpose of this section of the document is to identify issues related to data collection and registry configuration. When designing a disease registry, it is important to consider the registry's purpose and target population as this will influence the type of data, source(s) of data, and the manner in which it is collected. A data dictionary defining the specific data elements to be collected is key to ensuring registry data quality. Compliance of physicians and patients who provide registry data is instrumental to data collection and should be addressed early. Additionally, it is important to consider if the registry will be linked to other databases. Finally, it is important to address procedures for making changes in the registry and to establish what types of documentation are necessary.

In preparation of this section, we reviewed the literature, scholarly sources, and consulted with medical experts and registry/database specialists on the topics mentioned above.

RELEVANT LITERATURE

In preparing the information below 139 full text articles were reviewed.

Conventional and Innovative Roles for Registries

Most registries aimed to serve conventional registry roles. As examples, Byrne et al used a registry to examine the natural history of Pompe disease[68]; three registries pursued quality improvement (stroke care, cardiac catheterization and management of childhood diabetes[69-71]); disease subgroup characterization was facilitated for pituitary and lung tumors,[72,73] post-market device monitoring for cardiovascular stents,[74,75] as well as monitoring of treatment outcomes and safety follow up for cardiac transplant patients receiving everolimus, general cardiac care, biological agents for arthritis, giant intracranial aneurysms, and TPA for ischemic stroke.[76-80] Other registries aimed to serve innovative roles:

- examining the impact of a diagnostic test on patient management (i.e. PET scanning on management of cancer patients),[81]
- clinical instrument development (i.e. management of hospitalized patients with heart failure),[82]
- linkage of clinical data to a DNA bank for patients with congenital heart disease,[83]
- imaging information capturing MRI data from stroke patients,[84]
- curation of data for genetic linkage analysis in systemic lupus erythematosus,[85]
- monitoring of adverse events and medical errors in surgical patients,[86,87]
- adherence to clinical best practice guidelines (i.e. lack of lymph node dissection for penile cancer),[88]
- serving as a ureteral stent removal reminder system to Urologists,[89] and
- identification of management not consistent with best available evidence (i.e. not targeting evidence-based INR for prevention of venous thromboembolism.[90]

Registry Configuration

The Agency for Healthcare Research and Quality (AHRQ) users' guide[5] was the most comprehensive document identified to guide the process of registry development. The authors illustrate current uses for patient registries and how they may play critical roles in providing high quality evidence in circumstances where randomized trials cannot be conducted or may not generate generalizable results. In particular, the guide focused on patient outcomes including studies of natural history, effectiveness determination, measuring or monitoring safety and harm, and measuring quality. Registries can be designed as product, health services, or disease registries, or combinations thereof.

The AHRQ guide[5] provides suggested steps in planning a registry. These begin with articulation of the purpose, determination that registry design is the appropriate methodology for the purpose, identification of key stakeholders, feasibility assessment, building of the team, establishment of governance and oversight, scope of data, as well as defining of

From the [1]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta; [2]University of Calgary, Calgary, Alberta; [3]BC Ministry of Health, Victoria, British Columbia; [4]University of Toronto, Toronto, Ontario; [5]University of Waterloo, Waterloo, Ontario; [6]Canadian Institutes of Health Information, Toronto, Ontario; [7]Rick Hansen Institute, Vancouver, British Columbia; [8]Institute for Public Health, University of Calgary, Calgary, Alberta.
Correspondence to: Lawrence Korngut, Clinical Neurosciences, 480060, 4th Floor Administration, South Health Campus, 4448 Front Street SE, Calgary, Alberta, T3M 1M4, Canada. Email: Lawrence.korngut@albertahealthservices.ca.

the core dataset, patient outcomes and the target population. The guide also suggests that a clear protocol and project plan be developed and planning for study completion.

Is a Registry Appropriate?

The first step in designing a registry for obtaining information on neurological diseases is to determine whether a registry is the best means of obtaining the desired information.[91] Registries are useful tools for facilitating research, performing audits, facilitating policy decisions, and managing health care services and associated resources.[5,92] However, sometimes registries are not an appropriate means of obtaining information; for instance if the data necessary to answer a research question have already been collected, the data are of the quality needed to properly address the question and the data are accessible to the researchers.

Selecting a Registry Design

Once it has been determined that a registry is the best method of collecting data, there are a number of decisions regarding its configuration that must be made. First, it is important to consider what kind of registry is most desirable. There are several types of registry designs including clinic-based, community-based, online, patient self-registration that have a variety of purposes such as disease surveillance, quality improvement, natural history studies and longitudinal research.[5,36] It is important to clearly describe the registry's purpose[36] as well as the specific research questions the registry will purport to answer and specific, measurable objectives the registry will seek to accomplish[5] before defining data collection methods and forms. This will ensure that registry data collection is relevant in terms of the study objectives, that the data that gets collected can be used to its full potential, and that data collection is proportional to the resources that are available.[5,36,69,90,91,93]

Target Population

It is important to determine the registry's population. A population-based registry is one that represents all incidences of a given condition in a given population.[39] A province-wide registry accessing all potential participants is an example of a population-based registry.[39] Beghi et al emphasize the importance of strict adherence to population-based registry design when examining for disease risk factors, the importance of appropriate control selection when using registry participants in a case-control study, and validation of the quality of data registration.[94] Establishing a population-based registry will provide more complete and comprehensive information about those afflicted with the condition of focus in that population.[39] Although a population-based registry is the most desirable, the challenge is the reliance on voluntary consent. It is therefore possible that targeting a subset of a population for a registry may be more practical and sustainable.[39]

Regardless of whether or not the registry is population-based, it is essential to define the population to which the registry findings are intended to be applied, i.e. the target population.[5,91] For example, registries may choose to focus on patients with particular diseases, those with an exposure to a particular product or procedure or those who participated in a quality improvement project or other program.[5] The target population of the registry will influence many aspects of registry planning and design, such as which sampling practices are most appropriate.[5]

Patient Recruitment

It is important to consider various challenges faced by patients (such as cognitive issues, mobility issues, etc.) and physicians/centres (such as limited time, limited staff, limited resources) when planning a recruitment model because addressing the needs of the people who will be providing data is instrumental to successful data collection. Using only a single mode of data collection may lead to biased sampling because patients with cognitive and/or mobility issues may find particular modes of data collection more challenging than others. Hence, using diverse recruitment practices - such as telephone, mail, in-person discussions during clinic visits, online recruitment and mobile applications - will decrease the likelihood of biased sampling.

One challenge with respect to rare disease research is that one must sample from centres in multiple jurisdictions in order to get an appropriate sample size. However, under-representation is likely to occur in those centres which lack the resources to participate in registry recruitment. Diverse recruitment practices are one way to resolve this issue. Additionally, in Canada, different jurisdictions have different regulations with respect to privacy and research ethics: these are discussed in more detail in the Ethical and Legal Considerations section of this document.

Incentives which conform to the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2)[7] may also increase compliance with data collection requirements. For example, providing patients and physicians with regular correspondence in the form of individualized reports may serve as an incentive for participation because those involved in registries tend to want to have access to the data they are providing and tend to want to know what is being done with the data that they are providing.[95] Additionally, it is recommended that clinicians be guaranteed open access to their own registry data as it can be used for clinical studies[95] and may facilitate clinic note dictation. In addition to providing useful information, this will likely increase transparency about how the registry is using the data it collects.

With respect to using registries to facilitate study recruitment, it is recommended that passive recruitment such as notifying patients of existing research be used as opposed to active recruitment such as marketing for and promoting other studies.

Concerns about privacy may influence patients' willingness to participate in registries.[48,96] In order to address these concerns, it is important to consider how data will be stored, who will have access and what security measures will be taken. Furthermore, it is important to address how patients' privacy will be protected during the informed consent process.[5] More specific information about data storage and privacy considerations can be found in the Data Storage and Curation section of this document as well as the Ethical and Legal Considerations section of this document.

For more information about patient recruitment, consult the Patient Recruitment section of this document.

Data Collection Sources and Methodology

Registry data can be obtained from such sources as patients, clinicians, paper medical records, electronic medical records,

administrative sources, other registries, national disease organizations, laboratory data and physician billing data.[5]

Full text review of 34 documents was conducted and revealed that there are a number of potential sources of data and methods of data collection for registries.

Types of Registries

Physician Driven Registries

Physician driven registries have great potential to gather large amounts of clinical and demographic information,[93] but time constraints on physicians make it challenging for them to be able to gather large amounts of patient data for registries[93] Recruitment of patients for a registry by a physician is one of the most successful recruitment strategies because the direct involvement of a patient's physician in a registry is a key factor influencing participation.[5] However, to avoid data collection fatigue physician driven registries must have unambiguous datasets which are not a tax on physician time.[93] Clearly defining and documenting expectations of clinical professionals involved in recruitment and making use of technology to automate data entry and reminders are measures that can be taken in order to reduce the physician's burden. Efficient workflows that align with clinical process will maximize data quality.[97]

Patient Driven Registries

Patient driven registries can provide access to large patient populations in a cost-effective manner,[93] and readily cross geographic boundaries. However, these registries may not gather uniformly high quality data due to the high potential of errors in diagnosis and other key data points when physician review of collected data does not occur.[93] While it is possible to create successful patient driven registries with accurate diagnoses,[93] in general physician driven registries are more likely to produce datasets with limited bias and registries that retain patient interest and commitment. One concern with any registry methodology is the potential for patient populations to be biased through recruitment methods (selection bias). This concern can be partially addressed by stratifying registry data to represent geographic distribution, and then sub-sampling across the registry for study purposes.[98]

Periodic reassessment of registry participants in either physician or patient driven registries has the potential to provide rich longitudinal data which would also be beneficial for examining outcomes and facilitating research.[83,85]

Approaches to Data Collection

Data can be abstracted from patient records by a person other than the clinician who interacts with the patient.[5] Sometimes the person who abstracts the data from the record will "code" the data onto the case report form (the form that contains the data elements the registry intends to collect from its patients). Coding consists of replacing a text diagnosis in a chart with a standardized code: these codes are usually defined in a data dictionary.[5] If data linkage is being considered, it is important to ensure that data elements allowing linkage are compatible with the linkage data source.

Web-based Registries

Web-based registries collect retrospective data over the internet from patients or clinics and transmit the data to a central repository. The data are manually entered by the patient healthcare provider or delegated research assistant.[99] While there is a general perception that web-based registries improve the speed of data entry, one study found only a ten second difference between paper-based data collection and web-based data collection per patient over a total of one initial entry and one follow-up visit and initial data entry collection was actually longer by eight second versus paper-based data collection.[100] Additionally one study compared online registry data collection to a previous paper-based methodology in the same discipline and found that it increased participation by 42%.[101]

Electronic Chart – Based Registries

As a new concept,[99] electronic chart based registries can enroll patients in real time based on chart data such as International Classification of Diseases (ICD) codes and populate registry fields through automatic download of relevant chart data.

When comparing the two data collection methods above, a key benefit of the electronic chart-based registries is the elimination of manual data entry errors.[99] However, electronic chart-based registries rely on compatibility with electronic charting systems (e.g. versioning etc.) and may require periodic updates or reconfiguration. Clinical follow-up may also be problematic if patients do not return to the primary hospital although this issue also exists with other types of registries.[99]

When selecting a modality with respect to registry type, consideration should be based on the availability of patient data through a given modality and the likelihood of registry success considering comprehensive factors from data collection efficiency to overall cost efficiency. What may be appropriate and successful with one patient population in any particular country may be starkly inappropriate in another patient population or country and evidence to support or refute any particular choice is likely to be found in the literature. Evidence in the literature is clear that registry usefulness is far more impacted by the overall quality of the data present in the registry, not the method of data collection.[101]

Data Elements and Data Dictionary

It is essential for registries to clearly define which data elements are to be collected, how they are to be collected and ultimately to collect these data elements in a uniform way.[5] It is also essential to clearly describe and document guidelines for data abstraction and coding[5,102] and for those in charge of abstraction and coding to be properly trained in order to minimize the probability of errors.[36] Using a paper or electronic case report form or formatted list of elements as well as producing a manual which clearly defines the data elements, how the data elements are interpreted, acceptable parameters and logical rules for data elements are recommended practices for encouraging uniform data collection.[5] Finally, it is important for the data entry process to be standardized and user-friendly.[36,39,40,103,104]

Linkage of data among registries can be facilitated by using common data elements.[5] More information about common data elements suggested for Canadian neurological registries can be found in Part 3 of this document.

Data Linkage

Registries can be linked to one another or to various data sources. Planning of new registries must consider existing registries and possible linkages or overlap in patient recruitment. New registries may also expand the target population of existing registries through linkage. Since one disease registry is typically not representative of the entire population with that disease, linking registries to one another can provide more representative information across a disease population. It is best to consider data linkage from the outset rather than attempting to link data after registries have been developed, because data definitions and formats developed separately are often not standardized across databases; translation between systems would be required and transferring data from one database to another could potentially lead to errors.[5] Hence, the process of linking registries is facilitated if registries are consistent in the data elements they collect and the manner in which they are collected. It is for this reason that the use of common data elements is recommended[5,93]. Increasingly, networks of registries are emerging to facilitate collaboration and planning of large studies such as the Orphanet rare disease database and meta-registry.[105]

Furthermore, appropriate permissions for data linkage should be sought a priori.[5] Additionally, it is important to be transparent about the sources from which data are being obtained and to consider establishing reciprocal data sharing agreements. With respect to data linkage, it is essential to consider who owns the data and who is responsible to maintain privacy during the inception stage.[5] More information can be found in the Data Linkage section of this document; more information about privacy considerations can be found in the Ethical and Legal Considerations section of this document.

Data Quality and Management

Given the potential usages of registry data, the data should be complete and accurate.[36,40] In the planning and design stages of a registry, it is important to consider issues related to data quality. For example, in a multi-disease registry, using and clearly stating standardized disease definitions, familiarizing participants with these disease definitions as well as using standardized sampling techniques are all recommended practices in order to promote optimal data quality.[7,90] More specifically, it is essential to work to maximize internal and external validity as well as generalizability.[5] Additionally, it is important to consider possible forms of biases and work to minimize bias within the registry.[5] Although bias cannot be eliminated, having a documented understanding of what biases exist and how such effects can be managed will be helpful, particularly in reporting outcomes.

Additional issues which can have a deleterious impact on registry data quality include: missing data, invalid entries, erroneous entries and inconsistent data.[5] It is recommended that registries have a manual which addresses how to assess and ameliorate these issues.[5] Possible ways to resolve these issues with data include re-checking the case report form, interviewing the patient and examining an alternate source of patient information.[5] It is important to perform database queries or reviews designed to screen for problems in the database.[5] The date, time and results of all reviews of the database should be documented. Additionally, for good registry management, it is essential to track all data received, all information entered into the database, and all data cleaning practices that are implemented.[5] It is recommended that a member of the registry's staff should have the role of quality assurance[36] i.e. someone who regularly assesses data items for accuracy, completeness and relevance.[36,39,40]

It is recommended that epidemiologists, statisticians and other database specialists be consulted throughout all stages of the registry in order to ensure that it is designed in a manner that maximizes the potential for gathering high quality data.[92] Registry data should be as comprehensive as possible while also being simple enough to reduce data collection burden.[10,36,69,91,104,106] It is hence recommended that the registry balances the need for parsimony (for instance, collecting the minimum amount of variables that it needs in order to answer its study questions and accomplish its objectives) with a reasonable anticipation of future needs that may require additional data not immediately necessary for the study's initial objectives.[36,94] In some instances, it may not be feasible to assess all aspects of the data initially, but future plans could include more detailed analyses that warrant the collection of additional information. However, these plans should be fully articulated at the onset of the registry design so that all data elements can be rationalized. Inclusion and exclusion criteria must also be clearly defined and the rationale for these criteria should also be clearly documented.[5,94] Five additional characteristics of a high quality registry database are as follows:[92,99]

1. The registry must be representative of its target population
2. Data must be complete and accurate
3. Data validation procedures should be used to assess data accuracy
4. Variables must be explicitly defined
5. There must be independence of observation of outcomes

Given that the quality of a registry's data is related to the abilities of the registry's staff, proper training of data collection staff is essential.[5,91] This training could take the form of an initial training session during on-boarding followed by regular continuing education sessions.[99] Database training environments, videos, and webinars are all useful training tools which are especially beneficial for registries with multiple centres as they can be used in a remote training situation. Additionally registries should have a manual of operations in which data collection staff members are well versed. When multiple sites are involved, it can also be beneficial to have regular meetings (teleconferences with abstractors/sites) or site visits to discuss progress, review procedures and resolve any issues that may arise.[83]

Prior to the launch of the registry, it is recommended that pilot tests be conducted. Pilot tests will allow registries to detect and resolve data collection issues which will detrimentally impact the successful implementation of the registry.[5,107] It is

helpful to directly involve staff who will be responsible for collecting data in the piloting process in order to receive feedback on considerations such as how user-friendly data collection methods are.

More specific information about how to address these issues of data quality can be found in the Quality Control/Quality Assurance section of this document while more information about how to evaluate data quality post hoc can be found in the Registry Evaluation section of this document.

Data Analysis

Factors to consider when developing observational cohorts with respect to subsequent data analysis include participant (database) bias, missing data, and subject misclassification.[108] The frequency and manner in which registry data are analyzed also need to be considered in the design stages of the registry because the way in which data is collected will influence whether or not planned analyses are feasible. The anticipated size of the registry, and the duration of the registry will also influence the way in which data are collected and analyzed and are hence important to define in the early stages of a registry.[94]

RECOMMENDATIONS

✓ Establish clear objectives for the registry based on its purpose.

✓ Define your target population, and what will constitute an appropriate sample.

✓ Employ diverse recruitment methods in order to reduce selection bias. Consider your target patient population and your chosen recruitment strategy to identify potential challenges that may be present

✓ Present clinical staff with clear expectations and use technology to reduce their recruitment burden.

✓ Utilize regular reporting to increase registry transparency and participation by physicians/healthcare professionals and participants.

✓ Develop a training program for data collection staff. Provide them with aids and resources to maintain training on an ongoing basis. Consider using technology to facilitate remote training and reduce costs.

✓ Consider including healthy age/sex match controls in the registry to facilitate research.

✓ Thorough documentation is essential for registry success. To that end, it is important to clearly document the following aspects of the registry in the registry protocol and additional documentation[5]:

1. Purpose of Registry
2. Research Questions/Specific, Measurable Objectives
3. Inclusion/Exclusion criteria and rationale for these criteria
4. Target population and sampling methodology
5. Anticipated size and duration of the registry
6. Manner and Frequency of data collection and analysis
7. Data dictionaries and coding manuals as appropriate.
8. Sources of registry data
9. How to use the paper and/or electronic case report form, whether or not the case report form is to be retained/copied/archived.
10. Roles of registry personnel and corresponding job descriptions and necessary qualifications for each position
11. Recruitment/withdrawal procedures including copies of appropriate consent/withdrawal forms and how they should be retained/copied/archived.
12. Procedures for promoting and subsequently evaluating data quality.
13. How patient identification codes are assigned, how duplicate records are prevented
14. Procedures for access to data for research purposes (internal and external).
15. Data security measures and procedures in the event of a security breach.
16. Registry governance structure and roles.
17. Legal and ethical documentation such as: confidentiality agreements; data-sharing agreements and ethics certificates and submissions.
18. Data management policies and agreements governing data management (e.g. contractor agreements; database administrator position description etc).

✓ Define anticipated registry size and duration to assist with selection of data collection strategies.

✓ Conduct pilot data collection to evaluate training protocols and database function.

✓ Determine data linkage needs in advance and seek appropriate permissions.

✓ Utilize passive recruitment methods for research study recruitment within a registry population.

Linkage Between Neurological Registry Data and Administrative Data

Nathalie Jette[1,2], Kristin Atwood[3], Mark Hamilton[4], Rachel Hayward[4,5], Lundy Day[4], Theo Mobach[4], Colleen Maxwell[6], Claire Marie Fortin[7], Guillermo Fiebelkorn[4], Karen Barlow[4], Michael Shevell[8], Moira K. Kapral[9], Steve Casha[2,4], Megan Johnston[4], Samuel Wiebe[2], Lawrence Korngut[2], Tamara Pringsheim[4]

This section of the guideline discusses considerations when planning and designing a registry that will require linkage to administrative data. Administrative data may include hospitalization and surgical or other procedure data; physician billing data; vital statistics data (e.g. births, deaths); prescription and other pharmacy data; long-term care services and admissions; and other data collected by provincial and territorial governments, health authorities and hospitals or care sites for administrative purposes.

Linkage of registry data to administrative data may create unique challenges and considerations during registry design. For example, linking to administrative data may require patient identifiers such as a personal health number that might not otherwise be collected. Linkage may present schedule challenges or constraints with respect to registry launch, operation, and data analysis. And finally, linkage of administrative data to registry data may impact the data fields collected and research ethics board (REB) approval required for the registry.

Clinical registries often capture a wealth of clinical information, and as a result help address and answer key health related questions. However linkage of registry data to other data sources is sometimes necessary to achieve a particular registry's pre-determined objectives. For example, a large number of patients with a particular neurological condition may self-register to a particular registry, and agree for their data to be linked to administrative data. Linkage to administrative data may allow for confirmation of a diagnosis that may not have been possible solely by self-report, enhancing the validity and quality of the registry data.

Although administrative health data were originally used solely for "administrative purposes", they have become a rich source of health data for research and surveillance purposes. They are many advantages to administrative data, in that they are often population-based capturing nearly every contact with the health care system, they are often cost effective, they can allow investigators to follow people over time, they are not affected by selection or recall biases and they can be used to study rare outcomes. However, the amount of data can at times be overwhelming and lack some of the rich clinical information which is often captured in clinical registries. Data quality, as with any other data sources can also be an issue. Regardless, administrative health data are used widely in health care for quality improvement, surveillance, and to study health services, morbidity and to study a variety of outcomes, including mortality.[109]

In preparing this section of the guideline we reviewed available literature and consulted with registry, disease, administrative data, legal, ethics and privacy experts to derive consensus recommendations.

RELEVANT LITERATURE

Unfortunately there was a paucity of literature addressing the issues surrounding linkage between registry data and administrative data. Furthermore, many of the identified articles from the literature review pertaining to this topic were not relevant in the Canadian context. Although the Agency for Healthcare Research and Quality (AHRQ) manual provided rich information on how to develop and implement registries, the information regarding data linkage was not Canadian specific.[5]

Policy & Legislation

There is an ethical and legal obligation to protect patient privacy when collecting health data, whether from a single source of from multiple linked sources. There is a need for methods and formal approaches to ensure that individual identifiable information is protected. There were no peer reviewed articles discussing ethics regulations and privacy legislation requirements in each of the Canadian provinces and territories. It is well known that these differ from one province

to another. In some provinces, ethics approval is only required for research questions and privacy impact assessments are only required for clinical care or quality assurance purposes. Details of the relevant policy and legislation by province can be found in the Ethical and Legal considerations section of this document.

OTHER CONSIDERATIONS

Linkable Data Sources

Although the focus of this section of the guideline is on linkage of registry data to administrative data, it is important to consider all possible linkable data when developing a registry, as similar issues arise whether or not these linkable data are administrative in nature or not. Sources of data beyond administrative data include clinical databases, survey and census data (e.g. national health surveys), imaging data, electronic medical records, laboratory data, and biological specimens.

Significant gaps in the literature review were identified in this area.

Technical Considerations

Although there was a lot of information in the published literature regarding how to enhance data quality and data collection for registry, there was a paucity of articles discussing the technical aspects of data linkage in a Canadian context. There was a good chapter in the AHRQ manual discussing linking registry data, but much of the information provided was only relevant to American researchers,[5] with a major emphasis on the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule.

Linking patient data from multiple sources can increase the quality and completeness of data collection and assist in tracking patients who are lost to follow up. A group of researchers created and evaluated the feasibility of electronic linkage of the North Carolina Emergency Medical Services (EMS) Data System with the North Carolina Stroke Care Collaborative Registry.[110] This system matched de-identified data from a prospective registry to EMS data using hospital name, arrival date, time, age and sex. The system was validated in three registry hospitals manually using patient names. Results of the study generated 63% probable patient matches and 89% of these matches were verified as true matches. One limitation to data verification and linkage was the quality of EMS data. However, linking EMS records electronically to a stroke registry was feasible and led to a large number of valid matches. They concluded that data linkage was a useful tool for registries to collect patient information from various sources and enhance coordinated systems of care. However, linkage may not be possible when databases are coded differently or when data collection methods and privacy laws might place limitations on using identifiable data.

Obtaining Linkage Data

Computer-assisted record linkage dates back to the 1950s.[5] There are several data linking methods, most of which rely on the use of unique identifiers. The most commonly used method is the so-called "deterministic" method where unique identifiers are used in each of the databases of interest.[5] In Canada, ideal unique identifiers used for health data linkage include:

i. Personal health care number (PHN) that is a unique identifier given to all Canadian citizens with provincial health care coverage.
ii. Last name
iii. First name
iv. Date of birth
v. Postal code

The most unique challenges not only in Canada, but internationally relates to obtaining linkage data. In some Canadian provinces, administrative health data can take up to three years to be released to researchers, despite following all of the proper ethical and legislative processes.

Data Protection

One of the most important aspects of the data linkage process includes the processes in place to ensure ongoing data protection. Here, we do not discuss in details the methods used to mitigate the risk of re-identification. These are discussed in some detail in the AHRQ manual.[5] We however emphasize the need to involve data linkage, privacy and legislative experts who have familiarity with these processes early on in the registry inception to ensure risk mitigation is in place.

Cost

If data linkage is being considered, the cost for data linkage must be addressed during the planning stages of the registry. Cost considerations include: jurisdictions coverage; length of review and time to acquire data; and ongoing cost to maintain access to data. Costs for administrative data vary by data type and by province. Careful research into the required jurisdiction and type of data should be conducted during the planning phases. Jurisdictions also have substantially different lengths of time for review of administrative data requests and even following approval, acquisition of actual data files may involve further time delays. Consider the costs of these time implications against the registry plan. Finally, if the registry project plans ongoing linkage activities the sustainability costs must be addressed. For example, are there annual fees; ongoing security needs; or other aspects to this activity that will impact the project budget?

RECOMMENDATIONS

✓ Ensure data linkage is necessary, feasible, and ethically sound during the registry planning and design phase. For example, relevant data exists and can be obtained in a financially sound and time appropriate manner.
✓ Involve administrative data experts and data custodians early on if data linkage needs are identified.

✓ Carefully examine jurisdictions that will need to provide administrative data and examine costs; identify data custodians; research application requirements; and identify projected time to obtain data.

✓ Incorporate data linkage permission into participant informed consent at the outset.

✓ Determine the data fields needed to provide adequate linkage. Use a minimum dataset approach.

✓ Consider establishing reciprocal data sharing agreements and educating people about the benefits and value of data linkage in order to overcome challenges in obtaining linkable data.

✓ Registries containing linked data or data linkage references must have appropriate security protection in place which may include: password protection; levels of access by user; suppression and encryption. Additionally, database systems should be regularly backed up.

✓ Establish a desired timeline and linkage plan considering the time required to obtain data and how often it should be updated.

✓ Prepare policies and procedures around linked data including how data will be stored and when and how it will be destroyed. In some cases these aspects may be partially dictated by the data custodian.

Registry Data Storage and Curation

*Megan Johnston[1,7], Craig Campbell[2], Rachel Hayward[3], Mark Lowerison[1,7],
Vanessa K. Noonan[4], Ted Pfister[1,7], Colleen Maxwell[5], Claire Marie Fortin[6],
Eric E. Smith[1,7], Jean K. Mah[1,7], Moira K. Kapral[8], Nathalie Jette[1,7,9],
Tamara Pringsheim[1,7], Lawrence Korngut[1,7]*

The storage of patient and medical information in a disease registry is a critical concept for consideration during registry design and development. The choice of data storage methods may influence the ability to access data in the future; the ability to store data long-term; and the ability to exchange data with other registries or research projects as required. Additionally choosing a data storage method involves a certain degree of uncertainty in an era that has gone from the file cabinet to the five inch floppy to the cloud in a matter of 35 years. In preparing this section of the guideline we reviewed available scholarly and grey literature resources; consulted with disease, registry, legal, ethics, privacy, and information technology (IT) experts; and consulted appropriate legislation and policy documentation in Canada.

RELEVANT LITERATURE

Unfortunately our efforts to examine relevant literature in this topic area were unsuccessful. While there is a large body of IT literature on topics that may apply here, very little is specific to the Canadian context or the disease registry context. Where general principles applied we have reflected this as much as possible. Additionally, in some registry literature where mention to the issues of Data Storage and Curation were made we have noted this.

Policy and Legislation

Many Canadian provinces and territories have specific legislation components that address information technology applications and criteria that must be met by applications collecting health information. As a result, disease registry projects need to consider their relevant legislation within the jurisdiction in which the database itself will be housed, and any other additional needs that could be demanded of the registry based on the other jurisdictions in which it operates. Table 5 features a list of relevant documentation by province.

When examining software products to determine the best fit for a registry application; evaluate the product specifications to ensure that all legislative requirements can be met. Table 6

outlines some of the common requirements for neurological registries in Canada and some software products available in 2012 that meet some or all of the requirements.

OTHER CONSIDERATIONS

Storage Considerations

The type of database selected for a disease registry project will depend on a number of factors determined early in the registry development including: the expected number of records (database size); the expected number of users (database clients); the expected duration of the registry (length of data storage); the type of data being stored (data type); and the duration of the data storage after the registry project is complete. For example, in Canada, clinical trial data are required to be stored for 25 years under Part C Division 5 of the Food and Drug Regulations [C.05.012], however little consideration is typically given to the format of the storage of clinical trial data and whether or not this will remain accessible 25 years in the future. With electronic data storage, such considerations must not be underestimated. If registries are capturing both observational and clinical trial data, there may also be a need to store the observational data much longer than might normally be the case or to have the registry modules separated so that data from clinical trials can be stored for the longer time frame. These considerations should be made in advance of registry set up as they may impact the type of consent provided by patients in the area of data storage.

In addition to the above considerations disease registry projects may also want to consider Canadian legislation and privacy considerations with respect to data storage location. The following aspects should be considered:

A) Server Model (e.g. single server, dual server, or cloud server/storage?)
B) Physical Location of Servers (e.g. country, province, institution)
C) Physical Server Access (e.g. controlled, secure?)
D) Network location of Server (e.g. secured, visible, access controls)

From the [1]University of Calgary, Calgary, Alberta; [2]Western University – London Health Sciences Centre, London, Ontario; [3]Alberta Office of the Information and Privacy Commissioner, Edmonton, Alberta; [4]Rick Hansen Institute, Vancouver, British Columbia; [5]University of Waterloo, Waterloo, Ontario; [6]Canadian Institutes of Health Information, Toronto, Ontario; [7]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta; [8]University of Toronto, Toronto, Ontario; [9]Institute for Public Health, University of Calgary, Calgary, Alberta.

Correspondence to: Lawrence Korngut, Clinical Neurosciences, 480060, 4th Floor Administration, South Health Campus, 4448 Front Street SE, Calgary, Alberta, T3M 1M4, Canada. Email: Lawrence.korngut@albertahealthservices.ca.

E) Database user access (e.g. data access permission levels; authentication mechanisms)

F) Hardware and Software security controls (e.g. firewalls, encryption)

Database Genres

When selecting a database genre (database type) consider the complexity of the data processing that will be required during registry operation and the organizational resources available for the management of the database. Table 7, adapted from Brian Westrich, University of Minnesota[151] may be a useful tool during these considerations.

Following identification of the required database genre it will be necessary to select a specific software product with which to execute the database. Considerations during this process will include organizational assets (e.g. institutional licenses or IT services); budget (consider using open source software products if budget is small) and the development timeline. Additionally considerations must be made regarding the software product's ability to meet data storage requirements associated with legislation (See Table 5). Finally a key consideration during this stage involves the database size. The larger and more complex the database, the more important it becomes to select a software product that can create an efficient and readily accessible database while optimizing storage space. To this end, one must consider the structure of the database created by each database genre product. Additionally storage space will be impacted by the format of the data stored in the database.

Table 5: Relevant Legislation and Policy Relating to Software Considerations

Province/ Territory	Best Practice/Guidelines Document
Alberta	Personal Information Protection Act (PIPA) PIPA Advisory #8 Implementing Reasonable Safeguards (http://www.oipc.ab.ca/Content_Files/Files/Publications/PIPA_Advisory_8_Reasonable_Safeguards2007.pdf) [111]
	Alberta Electronic Health Record Regulation (http://www.qp.alberta.ca/documents/Regs/2010_118.pdf) [112]
	FOIP Guidelines and Practices Chapter 8. Records and Information Management (http://www.servicealberta.ca/foip/documents/chapter8.pdf) [113]
	Developing Records Retention and Disposition Schedules (http://www.rimp.gov.ab.ca/publications/pdf/SchedulingGuide.pdf) [114]
	Health Information Act Guidelines and Practices Manual (http://www.health.alberta.ca/documents/hia-guidelines-practices-manual.pdf) [115]
	FOIP Guidelines and Practices (http://www.servicealberta.ca/foip/resources/guidelines-and-practices.cfm) [116]
British Columbia	Physicians & Security of Personal Information (http://www.oipc.bc.ca/tools-guidance/guidance-documents.aspx) [117]
	Information Management and Information Technology Management (http://www.fin.gov.bc.ca/ocg/fmb/manuals/CPM/12_Info_Mgmt_and_Info_Tech.htm) [118]
	FOIPP Act Policy and Procedures Manual (http://www.cio.gov.bc.ca/cio/priv_leg/manual/sec30_39/sec30.page?) [119]
	Information Security Policy (http://www.cio.gov.bc.ca/local/cio/informationsecurity/policy/isp.pdf) [120]
Manitoba	University of Manitoba Safe Computing Topics (http://www.oit.umn.edu/safe-computing/topics/index.htm) [121]
	Respecting Privacy: A Compliance Review Tool for Manitoba's Information Privacy Laws: A Special Report http://www.ombudsman.mb.ca/pdf/Special%20Report%20English%20CRT%20-%20Oct%207.pdf [122]
New Brunswick	Guidelines for Custodians to assess compliance with the Personal Health Information Privacy and Access Act (PHIPPA) (http://www.gnb.ca/0051/acts/pdf/7133%20%E2%82%AC%20English%20long%20list%203s.pdf) [123]
Newfoundland	The Personal Health Information Act (Resources) (http://www.health.gov.nl.ca/health/PHIA/) [124]
Nova Scotia	Personal Health Information Legislation for Nova Scotia (http://novascotia.ca/dhw/phia/custodians.asp) [125]
	Privacy Impact Assessment Template (http://www.gov.ns.ca/just/IAP/_docs/Appendix%20B%20PIA%20Template.pdf) [126]
Nunavut	
Ontario	IPC Ontario Privacy and Confidentiality When Working Outside the Office (http://www.ipc.on.ca/images/Resources/up-num_20.pdf) [127]
	Manual for the Review and Approval of Prescribed Persons and Prescribed Entities (http://www.ipc.on.ca/images/Findings/process.pdf) [128]
Prince Edward Island	According to the Forms and Resource Materials section of the Information and Privacy Commissioner's website (http://www.assembly.pe.ca/index.php3?number=1013951),[129] PEI's FOIP Act is based on Alberta's FOIP Act and cites the Guidelines and Practices: 2009 Edition (http://www.servicealberta.ca/foip/resources/guidelines-and-practices.cfm)[116] as a useful reference. Chapter 9 lists technical safeguards.
Quebec	Minimum Requirements for the Security of Computerized Records of Health and Social Services Network Clients (http://www.cai.gouv.qc.ca/documents/CAI_G_securite_doss_info_rsss_eng.pdf) [130]
	Exigences minimales relatives à la sécurité des dossiers informatisés des usagers du réseau de la Santé et des Services sociaux http://www.cai.gouv.qc.ca/documents/CAI_G_securite_doss_info_rsss.pdf [131]
	CAI Quebec (http://www.cai.gouv.qc.ca/english/) (http://www.cai.gouv.qc.ca/)
Saskatchewan	Saskatchewan Archives Board Records Management Policies and Guidelines (http://www.saskarchives.com/services-government/record-management-policy-and-guidelines) [132]
	Security Controls for Protection of Personal Information (http://www.justice.gov.sk.ca/ITOSecurityControlsforProtectionofPersonalInformation.pdf) [133]
	Government of Saskatchewan Resources and Tools Security (http://www.justice.gov.sk.ca/AP-Security) [134]
Northwest Territories	GNWT INFORMATION TECHNOLOGY Electronic Information Security (http://www.fin.gov.nt.ca/documents/ocio/ppsg/6003.00.27%20-%20Standards%20-%20Electronic%20Information%20Security.pdf) [135]
Yukon	ATIPP Compliance Assessment (http://www.ombudsman.yk.ca/uploads/general/ACA_ATIPP_Compliance_Assessment_August_2011.pdf) [136]
	Yukon Information and Privacy Commissioner Privacy Breach Checklist (http://www.ombudsman.yk.ca/uploads/general/ATIPP_Privacy_Breach_Checklist_2011.pdf) [137]
	Yukon Information and Privacy Commissioner Best Practice: Responding to a Privacy Breach (http://www.ombudsman.yk.ca/uploads/general/ATIPP_Best_Practice_Privacy_Breach_Response.pdf) [138]
	Privacy Impact Assessment (http://www.ombudsman.yk.ca/uploads/general/PRIVACY%20IMPACT%20ASSESSMENT.pdf) [139]
Canada	Operational Security Standard: Management of Information Technology Security (MITS) (http://www.tbs-sct.gc.ca/pol/doc-eng.aspx?id=12328&section=text) [140]
	Guidance Document: Taking Privacy into Account Before Making Contracting Decisions (http://www.tbs-sct.gc.ca/atip-aiprp/tpa-pcp/tpa-pcp06-eng.asp)[141]
	Electronic Health Record (EHR)Privacy and Security Requirements Reviewed with Jurisdictions and Providers (https://knowledge.infoway-inforoute.ca/EHRSRA/doc/EHR-Privacy-Security-Requirements.pdf) [142]
	Health Canada Final Audit Report – Audit of Information Technology (IT) Security (http://www.hc-sc.gc.ca/ahc-asc/pubs/_audit-verif/2011-04/index-eng.php#_Toc2008) [143]
Other	ISO/IEC 27002:2005 Information technology — Security techniques — Code of practice for information security management (http://www.iso27001security.com/html/27002.html#) [144]

Table 6: Software features by product

FEATURE	Open-Source	Local Server Install	Authentication/ Platform	Password Controlled User Level- Authentication	User Action Log	Data encryption	Interacts with Third-Party Data Sources	Workflow Management	Patient Portal
PRODUCT									
REDCap (Produced by Vanderbilt University) www.project-redcap.org [146]	✔	✔ (if you are a participating site)	LDAP, Shibboleth or Table-Based (user selected)	✔	✔	Can be installed using additional software products	✔		
ClinicalPursuit www.patientregistrysoftware.com [147]		optional	Microsoft.NET	✔	✔		✔		
i2b2 – Informatics for Integrating Biology and the Bedside www.i2b2.org [148]	✔	✔	AJAX	✔	✔		✔	✔	
Patient Crossroads www.patientcrossroads.com [149]				✔					✔
Axiom Clarinet www.certus-tech.com [150]		✔	J2EE	✔				✔	

Database Structures

The type of database structure that is selected will influence many factors impacting the operation of the registry. These factors might include: computer hardware infrastructure; registry stability and performance; data entry and recall speed; and reporting capability.

Relational databases – This type of database (see Figure 2) is still a very common format created by many software products on the market however it can come with some significant limitations if data sizes are large.[152] These databases store data in a defined record where the common location of the data elements contained within the record is the sole logic between the data elements within the record. This limits the granularity of the database to the record level (i.e. data cannot be examined within a record except if the full record is recalled). As a result processing time to read and write records is high; total disk storage required for the database is high; and modifications to records require the whole record to be rewritten.
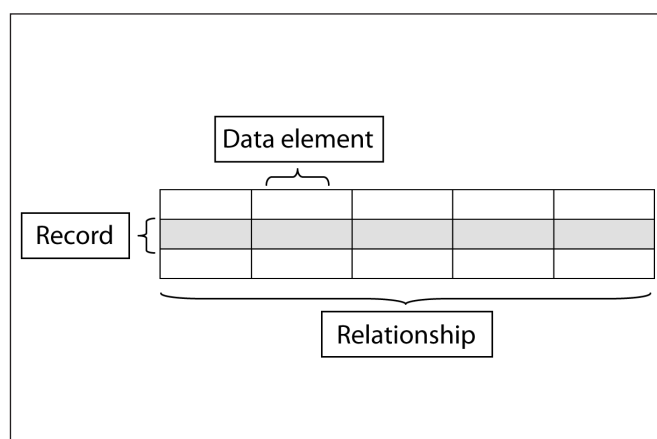
Figure 2: Relational Database Structure

Table 7: Database Genre Decision Support Tool

Complexity	Minimum required data resources	Database genre
Storage only	Paper case report forms	Non-automated file storage (paper based and/or electronic copies of paper forms).
Electronic storage	Computer	Word processor or basic file storage software. Basic file backup to external media (CD-ROM or DVD).
Structuring – Data that is stored needs to have different "fields" or "pieces".	Semi-skilled staff	Spreadsheet. Note that this is still a storage only task and no analysis is required.
Relating – Data is stored in fields and there is a need to define relationships or examine relationships between the fields.	Computer staff (part-time)	Personal database tools (e.g. Access). These tools feature simple data form and query design tools. Multiple data tables can be created and relationships between them can be defined. Analysis required is simplistic.
Complex, high volume – There will be large amounts of data between which complex relationships exist. This may also involve the need to have simultaneous access by multiple users.	Computer staff (full-time)	Industrial database tools (e.g. Oracle, mySQL). These tools allow for all of the features of Personal database tools but also allow for logging of user transactions; simultaneous access and updates by multiple users and complex query construction (for example, construction of data sub-sets). These software products may also allow database architecture to span over multiple servers for operation and storage.
Highly specific or specialized – The type of data being collected; the data collection process and/or the queries and analysis required of the data require customization beyond that available in standard tools.	Highly skilled computer programmers. High performance computing equipment. This type of solution may also require custom networking.	Programming languages (e.g. Java, C-plus). These tools may operate in conjunction with industrial database tools or other library structures to fully enable the required database architecture.

Columnar databases – This type of database (see Figure 3 below) is increasingly adopted due to the increase in analytical simplicity found through this method when compared to relational databases. These databases store information by column with all values within a column being stored as a single dataset (i.e. these datasets are made up of data from multiple "records").[152] A key advantage of this format is that "parts of records" from a relational database perspective can be analyzed and written or rewritten. This feature increases the speed with which data processing can be accomplished. However, the trade off here is that recalling records requires the assembly of data values across multiple columns into a pre-determined format which if the number of columns is large (complex dataset) or the number of requests is large (many users) may impact database performance.

Data Formats

There are three ways to physically store digital data available on the current market[153]:
1) Magnetic storage (e.g. magnetic tape or hard drive)
2) Solid state (e.g. flash memory)
3) Optical (e.g. Blu-Ray, DVD, CD-ROM)

Table 8 discusses some of the considerations for each method. Clearly demonstrated by the information in Table 8, the choice of backup infrastructure is best addressed by choosing multiple physical storage formats. It should be a regular practice to perform backups at pre-determined intervals to a hard drive space and then periodic backups to an optical format.

In addition to physical storage format, in registry development one must consider file format obsolescence. This is the state during which the digital format of the file is no longer readable due to changes in technology and file formatting practices. File format obsolescence is independent of physical storage format and is to do with the actual digital format of the files on the physical storage format. Both are important considerations when storing data long term.

As it is impossible to define the file formats of the future and indeed to define file formats that will not go obsolete this guideline instead recommends a risk assessment approach to addressing this concern. This risk assessment approach is derived from File Format Obsolescence Risk Decision Support System (Version 1.1 released November 2007).[155]

Figure 3: Columnar Database Structure

Correlation databases – This type of database (see Figure 4 below) stores each data value only once and then stores references allowing collocation of appropriate values for each "record" using descriptive metadata. Like a card catalogue, metadata stores information on what values are required for each "record" and where each value can be found allowing programming that reads the metadata to reassemble each "record" when required. These databases have similar advantages to columnar databases in terms of partial record access and writing actions. However due to the low storage volume of correlation databases, their performance often exceeds columnar databases.[152]

Once the database genre and database structure are selected, the final considerations are the database formatting and the configuration of adequate backup infrastructure.

Figure 4: Correlation Database Structure

Table 8: Data Format Considerations

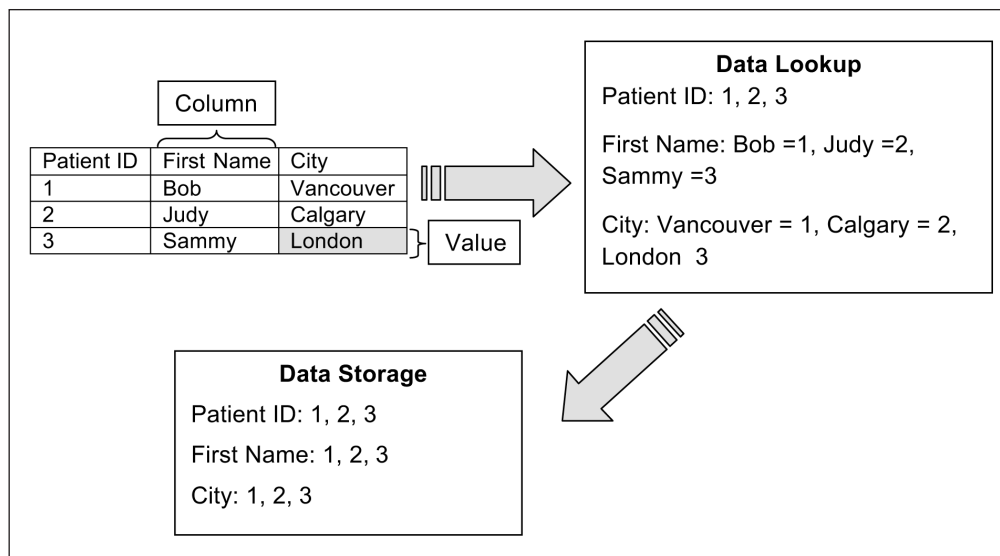| Data Format	Life Expectancy	Pros	Cons
Magnetic tape	0.7 – 1083 years depending on storage temperature, humidity, availability of error-correction coding[153]	• Readily available • Cheap • Convenient • Sizeable	• Oldest technology • Many known impacts on life expectancy • Reliability depends on manufacturing
Hard disk drives	Limited knowledge available but may range from as early as 3 months independent of utilization[154]	• Readily available • Convenient • Sizeable	• Limited capacity (currently in terabyte (TB) range) • Failure is typically catastrophic
Flash memory (solid state drives or memory sticks)	10 – 13 years without use. May extend up to 100 years with active management.[153]	• Readily available • Convenient • Small/Portable	• Current size limitation is 8 GB per unit. • Loss is inevitable without active management.
Optical media (ROM)	20 – 12,000 years.[153]	• Readily available • Requires little technical knowledge • Potentially lengthy life expectancy. • Permanent (once written it is only readable). • Multiple densities available	• Requires dedicated drive technology for reading and writing. • Drive technology may become obsolete. • Need for secure physical storage location in which to retain media. • Limited unit storage size.
Optical media (recordable)	Light and heat dependent but can be as low as a few hours in direct sunlight[154]	• Readily available • Requires little technical knowledge • Multiple formats available • Rewritable (non-permanent)	• Need for secure and dark physical storage location in which to retain media. • Requires dedicated drive technology for reading and writing. • Drive technology may become obsolete. • Limited unit storage size.

1) Is the file format a standard base coding format? (e.g. UNICODE, ASCII)
    a. Yes – This file format is low risk.
    b. No – Continue to Question 2.
2) Is the file format referenced in any searchable information resources?
3) Is there a known support end date for the file format?
    a. Yes – How many years until the support end date? (if within your long term storage needs, consider an alternate format).
4) How many years since this file format version was released?
    a. Are new versions available or on the horizon?
5) What is the primary rendering software needed for this file format? (i.e. what program is needed to read the files).
    a. Identified – is this software available to you?
6) Does the primary rendering software have critical hardware or software needs that might not be available in the future?
    a. Yes – what equipment/software is required and is it available to you?
7) Are there alternate rendering software solutions available? If so, what are they and what are their hardware/software requirements?
    a. Identified – how many of these are available to you with all their requirements?
8) Are there other means of providing safe and effective access? (e.g. custom coding, open source applications?)
9) What is the total number of access methods available for your chosen file format? Include all primary and alternate methods.
    a. 0 – Extremely high risk, consider your data as lost.
    b. 1 – High risk, consider alternate formats if possible
    c. 2 to 5 – Medium risk, ensure hardware/software requirements for access are documented and retained if possible.
    d. 5 or more – Low risk, you can proceed with implementation.

Data Migration

Data migration involves the process of moving data from one source to another where the structure of the data will change.[5] Data migration might be necessary if a registry platform becomes obsolete (either due to changes in software design or due to software discontinuation); if software cost becomes an issue (in the case of proprietary software platforms especially); or if additional functionality not planned in the initial registry design is required. Further data migration may be required if physical server characteristics or locations change; if data ownership requirements or personnel change; or to meet larger IT infrastructure expectations within the host organization. While it is possible to do data migration manually, the time investment will be considerable and efforts should be made to select software that can mediate an automated migration. For an automated migration to be successful and detailed data map correlating every data type from the old system into the new system must be created.[5] A plan for handling inconsistent data should be created at the outset and revised if any additional issues are raised during the migration process.[5] Following migration, quality assurance activities should be conducted to ensure that the data in the new system has been transferred as expected. Overall, a simple project management methodology made popular by W. Edwards Deming of "Plan-Do-Check-Act" (the Shewhart Cycle) can be a great approach for a data migration project. First, plan the data migration including required staffing and software/hardware resources; project timelines and any server down time that may occur. As previously mentioned, ensure that this plan features a detailed map of the data migration from the old system to the new system. Next perform a small test migration. Following the test, enact your quality assurance plan and evaluate if the desired results have been achieved. Once you have reviewed the test results, either revisit the plans and retest, or proceed with the full migration.

Data Curation

Data curation is defined by Lord and MacDonald as "the activity of managing and promoting the use of data from its point of creation, to ensure it is fit for contemporary purpose, and available for discovery and reuse".[156] This activity may include simple data management activities, enriching or adding value to data, the sharing of data, and the preservation of data for a later use. Data curation is a critical activity for the creation and maintenance of successful disease registries. While this guideline cannot define an individual registry's curation plan, below are some key points to ensure creation of a complete data management plan. These key points are taken from a Data Management Plan checklist produced by the Digital Curation Centre.[157]

1) Data types – understand what types of data will be collected in the registry. Ensure that data are defined using a data dictionary.
2) Data formats – consider the format of each type of data (e.g. text, alphanumeric, date etc). List all the possible formats that will be collected across the registry.
3) Standards – likely partly outlined in the data dictionary but ensure that there is clear definition of what data will be accepted and rejected. Additionally document if data will be compared to other sources and any associated standards dictated by this relationship.
4) Capture methods – document all methods of data capture and data flow into the data repository (database).
5) Data output – consider what content is being created by the project and document this. For example does the project simply produce raw data for further use or does the project produce derived data.[158]
6) Storage - what storage space is required for the data output? See Storage Considerations in this Guideline for more information.
7) File formats – what file formats will be used and why? Ensure that you document your analysis of file format considerations and risks in the data management plan. See Storage Considerations in this Guideline for more information.
8) Future uses – consider what the future uses or reuse of the data output and/or original data might be. What will be required to ensure these future uses/reuse can occur.
9) Sharing – ensure that consideration of whom might share the data and all associated ethical, legal and logistical issues are outlined and addressed.
10) Access – who will have access to the data and what are the access controls?
11) Existing data – are there existing data that are required or beneficial to the project. What constraints or considerations are present as a result? Is new data production actually needed? What is the value of the new data? What access is required to obtain existing datasets?
12) Data quality – what is your plan for data quality assurance and control?
13) Documentation – what documentation is required to ensure that data make sense in isolation? Consider that the context required may be stored with the data itself using metadata.
14) Metadata – if metadata will be included ensure you have considered how they will be created, maintained and stored.
15) Intellectual Property – ensure that the ethical and legal considerations associated with existing data and new data have been considered and addressed. See the Ethics & Privacy section of this guideline for more information.
16) Accountability – who is responsible for the data and who are the delegates of this authority if applicable? How is accountability assigned (e.g. legislation; institutional policy)? How will accountability be transitioned if required?

Data Management Plan

A data curation document will be part of a larger data management plan. The data management plan will include additional aspects such as:

- Who manages the data?
- Where, how and when will data be backed up?
- What mechanisms are in place for error tracking and change logging?
- Who is responsible for addressing changes, errors and trouble? What is the process for addressing changes, errors and trouble?
- What security systems are in place to protect the data?
- What is the process if there is a security breach?

For assistance creating a comprehensive data management plan, consider utilizing the DMPTool found at https://dmp.cdlib.org/.[159]

RECOMMENDATIONS

✓ In the context of applicable Canadian legislation consider the following items with respect to data storage:
  o Server Model
  o Physical Location of Servers and Access
  o Network Location of Servers
  o User Access levels and permissions
  o Hardware and software security controls

✓ Consider the complexity of your storage needs and the required personnel and software resources to maintain them.
  o Maximize organizational assets such as existing software licenses or discounts.
  o Wherever possible utilize open source software to minimize development and ongoing costs.
  o Document and plan your development timeline.
  o Ensure you have planned for adequate storage space and database size/functionality. Assess required computer hardware to facilitate desired access times; registry stability and needed reporting capabilities.

✓ Choose multiple data storage formats for short and long-term data backup. Ensure backup plans meet necessary legislation and policy expectations. Document data backup procedures and schedule in the data management plan.
✓ Assess file format storage risk.
✓ Create data curation and data management plans.

Online Neurological Registries

*Megan Johnston[1,8], Craig Campbell[2], Glenys Godlovitch[3], Lundy Day[1,8],
Julie Wysocki[4], Lynn Dagenais[5], Nathalie Jette[7,8], Lawrence Korngut[1,8],
Tamara Pringsheim[1,8], Ruth Ann Marrie[6]*

This section of the guideline focuses on the specific issues and special considerations that surround online registries. In developing this section of the guideline we reviewed available literature; consulted with disease, registry, ethics, privacy, legal and information technology (IT) experts, and derived expert consensus recommendations.

BACKGROUND

What is an online registry?

The term "online registry" is poorly defined in the literature. This may refer to a method of data collection or data dissemination, and may capture data directly from providers, patients or both. Data may be entered retrospectively or prospectively, as with other registries. Existing registries range from those where data are entered directly through an online interface into a local or central data repository, and where data are not accessible to local sites to those where aggregate data are available to all sites and to those that facilitate patient networking. A summary of possible features and some case examples of registries that employ these features are below in Table 9.

The Global Landscape

Worldwide, evidence is growing that disease registries can enhance the understanding of rare diseases. In 2010, the National Institutes of Health (NIH) in the United States organized a workshop "Advancing Rare Disease Research: The Intersection of Patient Registries, Biospecimen Repositories, and Clinical Data" held in Bethesda Maryland. Over two days,

Table 9: Possible Registry Features and Case Examples

REGISTRY FEATURES	EXAMPLE
Simple database software collects electronic data centrally or at local sites. Paper forms might help to mediate the electronic data collection. There is no electronic access to data by sites and no sharing of data in real time.	Simple clinic database at a single site (e.g. an Access database in a neuromuscular clinic).
Complex database software collects electronic data from registry participants and other sources such as electronic health records. Data is collected at local sites and entered over the World Wide Web. Paper forms may be used to mediate data collection. Sites do have access to local data and reporting is available in real time.	US ALS Registry [160] http://wwwn.cdc.gov/ALS/AboutRegistry.aspx
Complex database software collects electronic data from registry participants and other sources such as electronic health records. Data is collected at local sites and entered over the World Wide Web. Paper forms may be used to mediate data collection. Sites do have access to local data and reporting is available in real time. Additionally, aggregate data can be made available to participating centres or the broader research community.	Duchenne Connect [161] https://www.duchenneconnect.org/
Complex database software collects electronic data from registry participants and other sources such as electronic health records. Data is collected at local sites and entered over the World Wide Web. Paper forms may be used to mediate data collection. Sites do have access to local data and reporting is available in real time. Additionally, aggregate data can be made available to participating centres or the broader research community. This type also adds practitioner research networking through support mechanisms such as a portal, email, and other tools.	MS Base[162]; EULAR [163] https://www.msbase.org/msbase/en/msbase/pub/home;jsessionid=dlygajmrqijx188ceum70m3h0 http://www.eular.org/
Complex database software collects electronic data from registry participants and other sources such as electronic health records. Data is collected at local sites and entered over the World Wide Web. Paper forms may be used to mediate data collection. Sites do have access to local data and reporting is available in real time. Additionally, aggregate data can be made available to participating centres or the broader research community. This type also adds practitioner research networking through support mechanisms such as a portal, email, and other tools. Finally this type also includes patient networking and direct access through forums, portal tools, newsletters etc.	Patients Like Me [164] http://www.patientslikeme.com/

From the [1]University of Calgary, Calgary, Alberta; [2]Western University – London Health Sciences Centre, London, Ontario; [3]University of Calgary Department of Community Health Sciences, Calgary, Alberta; [4]Parkinson Society of Canada, Toronto, Ontario; [5]McGill University, Montreal, Quebec; [6]University of Manitoba, Winnipeg, Manitoba; [7]Institute of Public Health, University of Calgary, Calgary, Alberta; [8]Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada.

several hundred attendees discussed the creation of a global internet-based rare disease registry.[165] In 2011, the EPIRARE (European Platform for Rare Disease Registries) project conducted a survey to examine the currently functioning rare disease registries across Europe and other countries and explore problems, needs, resources and expectations with the goal of developing tools to support existing registries and to facilitate the development of new registries where needed.[166] As of July 16, 2012 over 80% [62% (2000-2011) and 20% (1990-1999)] of the registry custodians responding to the survey indicated they had collected their first case within the last 20 years. Ninety percent of registries responding were actively collecting data[166]. Of particular note was the fact that approximately 75% of the registries responding to the survey had fewer than 2000 patients enrolled.[166] This clearly demonstrates a factual basis for assertions made at the NIH workshop indicating that a key barrier to implementing a global rare disease registry platform was a lack of compatibility across existing registries and especially a lack of ability to use existing pockets of data.[165]

Another notable result was that over 50% of the registries indicated that they were either using their own diagnostic coding system or no coding system at all.[166] This is likely a direct result of the lack of rare disease codes in the World Health Organization's International Classification of Diseases 10th edition (ICD-10) featuring codes for only 500 of the perhaps 6000 rare diseases currently described worldwide.[167]

Over 80% of registries completing the EPIRARE survey indicated they obtained some of their information from clinics and only 8% indicated that data was collected online from patients.[166]

Finally, approximately 70% of registries completing the EPIRARE survey indicated that it would be helpful for the EPIRARE initiative to provide IT tools including for example database software or secured data exchange.[166] Attendees at the NIH workshop identified a clear gap associated with the IT infrastructure required to facilitate a global rare disease registry. Specifically, while the technology exists and can be relatively easily implemented a more pressing question was addressing the multi-faceted definitions associated with the possible data fields across potentially millions of enrollees and thousands of diseases.[165] While it was clear that an online platform would provide efficiencies of scale and cost with respect to data collection and recruitment, the exact method by which the software would be designed and constructed would be the subject of substantial follow-up discussion.[165] It is clear that considerable discussion around the ideal online registry scenario remains. This guideline therefore outlines the basic elements that can be implemented and the considerations that should be made in carrying out your own registry discussions.

Relevant Literature

Online databases and websites can be used to increase recruitment of participants into investigator-driven drug trials. Bergin et al successfully implemented an internet database that allowed physicians to register patients for epilepsy trial recruitment online from routine clinics.[62] The database was also effective at randomizing patients for controlled trials. This method proved to be useful with three quarters of neurologists indicating a willingness to participate. Information was collected

easily and efficiently and allowed participants to be recruited from multiple locations from eight cities in New Zealand.

The feasibility of web-based online registries was examined by Wild et al. who developed a free, international, internet registry of femoral nail complications.[168] Participation was voluntary and access was open to anyone. Agreement to consecutively enter all cases was required. Participants from 25 countries submitted anonymized patient data through online questionnaires. Originally results produced 13.4% incomplete and 19.3% inconsistent data. However, after revision of questionnaires to include a minimal data set, only drop boxes and check boxes and the inclusion of automated plausibility checks to rule out wrong data, incomplete and inconsistent data decreased to 2.9% and 0% respectively. Automatic, real-time evaluation of the data was also implemented displaying graphical results. This method provides fast, easy access to international registry data.

The internet may also be used to recruit registry participants via social networking websites. Tweet et al examined the feasibility of developing a virtual multi-centre registry of individuals with spontaneous coronary artery dissection using an online disease specific social media support network.[169] A pilot study of 12 participants proved this method to be fast and feasible for recruitment, case ascertainment, retrospective and prospective data collection. Researchers were able to identify and notify potential participants through the social media networking site, send and collect consent forms and questionnaires and collect and analyze medical records and imaging data. This innovative method could be potentially useful to create multi-centre, online rare disease registries at a low-cost.

Web-based systems of data collection have been developed in order to reduce manual data entry, improve quality, recruit patients and link patient data. Hess et al 2005 created a data collection system that used touch-screen computers to collect self-reported patient data in a pilot study of 86 consecutive patients aged 19 to 84 seen at a general medicine practice.[27] This system proved to be time efficient and user-friendly. Results showed that all patients completed the questionnaire (majority within 15 minutes), 81 individuals reported no difficulty using the tool, five patients reported some difficulty and no patients reported considerable difficulty. Additionally patients were asked if they would like to join a research registry project and be placed on a prospective subject list for notification when they are eligible for research studies. Fifty-five percent of individuals agreed to join the registry and 49% wished to be added to the prospective subject list. This study demonstrated that a web-based system can potentially be used to recruit registry and study participants, reduce selection bias, protect patient privacy and link patient responses to electronic medical records.

Web-based registries can potentially be used to share resources internationally[170] and provide fast and easy reporting of electronic patient data.[100] Mitri et al developed a web-based registry of patients with congential heart defects at a hospital in Saudi Arabia.[170] This internet method allowed for any web browser to perform registry functions such as: data-entry, data viewing, charting and exporting data.

A multi-centre web-based registry was developed by Prince et al to create a more effective method of data collection than paper based case record forms.[100] This method was tested by

entering data from 161 juvenile idiopathic arthritis patients. Treating physicians from nine centres found electronic data collection to be user-friendly with a reliable layout, sufficient amount of data collected and an acceptable amount of time needed to enter data.

Internet-based data collection may not be feasible for all age groups. Rolfson et al performed a study that examined the reliability of internet patient reported questionnaires and compared the response rates to mailed pen-and-paper questionnaires in 2,290 randomized participants from the Swedish Hip Arthroplasty register.[171] Internet questionnaires demonstrated adequate reliability in 100 participants and can provide immediate online access, a decrease in manual errors, elimination of missing values and a reduction in human resources required to manually register data. Sixty-seven percent of responders felt secure answering questions online. However, response rates of internet questionnaires were significantly lower (49%) when compared to (92%) to pen-and-paper questionnaires (p<0.01). The study also found that internet response rates declined with increasing age (p<0.001). In this population internet questionnaires are feasible, but should be supplemented with a pen-and-paper based option.

Participant access to the internet and willingness to complete questionnaires need to be considered when planning data collection methods. Bhinder et al performed a study to determine the feasibility of online collection of health-related quality of life data in Canadian tertiary care patients.[18] Fifty-seven percent of 644 patients surveyed were willing to complete questionnaires over the internet through an emailed link. Of these patients, 78% completed at least one questionnaire. Lack of time was the most common reason patients failed to complete the questionnaire. This study found that young, single urban dwellers that were working, or in school were more likely to have internet access and willing to participate. These results suggest that online data collection is feasible, but alternative methods of data collection should be included.

Overall the literature cited several effective, economical methods that may improve registry data. Internet based recruitment methods are proving to be very cost effective and efficient at recruiting large number of patients quickly.[62,168,169,172] Web-based databases are associated with a reduction in the time and resources needed for data management.[27,52,100,168,173,174]

OTHER CONSIDERATIONS

Data Collection Strategies

The different types of registries and methods of data collection are discussed in the Data Collection and Registry Configuration section of this document.

Managing Expectations

When developing registries and particularly online registries, a key element of success is to identify all potential stakeholders associated with the registry and ensure that their expectations are managed. Stakeholders might include physicians or other clinical staff; researchers and research support staff; patients and their families; pharmaceutical industry or government data end users; legal and ethics committees or offices; patient organizations or charities and the internal registry team which might include any

or all of the above. Table 10 shows the possible expectations of each stakeholder group based on a review of literature in the area and this project's patient focus groups.

With these expectations in mind, key guiding themes to registry modalities and formatting should include:

1) Participation in the registry should not be onerous on any party.
    a. Minimize time for data collection for both the patient and the provider
    b. Minimize additional visits for patients and providers
    c. Minimize total clinic burden through efficient datasets and software
2) Registry policies and procedures should be documented in clear and plain language.
    a. Make these available to all stakeholders to ensure transparency.
3) Online registries should be designed with easy access and compatibility as key priorities.
    a. Enables rapid sharing of data across sources and research teams
    b. Enhances participant experience in contributing data.
4) Registries can be used to form and enhance investigator networks and patient experience.
    a. Powerful communication vehicle with patients for educational and research recruitment purposes
    b. Powerful mechanism for administering and monitoring clinical standards.

Participant Enrollment in Online Registries

A key consideration in operating an online registry is a mechanism for verifying that enrolling participants are indeed from the registry jurisdiction and desired target population. The Internet's configuration leaves substantial opportunities for accidental foreign participant involvement and/or involvement of participants outside of the target population. These situations could occur through accidental channels such as mis-reporting of target population characteristics, or deliberate activities such as internet protocol (IP) address re-routing or participant profile fabrication. One mechanism to prevent these occurrences is linking of registry enrollment with known clinic populations for participant verification. This could be done during registration via manual (e.g. physician messaging) or electronic methods (e.g. physician record search) or it can be done post-registration via auditing through linkage with administrative data for the appropriate jurisdiction. In a randomly selected sample, the NARCOMS (North American Research Committee on Multiple Sclerosis) Registry demonstrated a 98% agreement between patient self-reported diagnosis and physician reported diagnosis,[187] and demonstrates that robust methodology can contribute to successful recruitment of target population participants regardless of the registry type selected in the formation of the online registry.

Privacy and Confidentiality in Online Registries

In addition to the above challenges with relation to enrollment of participants, online registries also face challenges with respect to ensuring appropriate privacy and confidentiality for participants. Many of the data safeguards outlined in the Data

Table 10: Managing Stakeholder Expectations

STAKEHOLDER	TIME	DATA COLLECTION MODALITY	DATA SECURITY	DATA VISIBILITY	USER KNOWLEDGE	DELIVERABLES
			AREAS OF EXPECTATION			
Physicians	Burden is minimal.[100]	Data entry is efficient and low cost.[100,175]	Data security should be monitored by a committee not an individual.[48]	Data can be freely exchanged and is comparable to other sources[50,175] Online registries may help to facilitate free exchange.[100]	Physician input has been present during registry design.[176].	Results are relevant to clinical practice or research interest.[176,177] Educational outreach is a useful activity paired with registries.[178]
Clinical Staff		Data entry is efficient and pay is reasonable.[100]			Clear procedures for registry execution are outlined.[49]	Can be used as a tool to standardize clinical practice.[177]
Researchers	Using registries for recruitment can save time.[179]			Rapid access to registry data may be helpful.[179]		
Research Staff				Rapid access to registry data may improve recruitment.[179]		
Patients	No extra visits will be required for data collection to minimize transportation hassles and cost.[180-182]	Graduated levels of consent may increase participation.[48] Willingness to share medical information is higher than personal information.[183]		Data will be kept confidential and not shared with employers, insurance providers etc.[48] Identifiers are acceptable data points if the information will be used for follow up contact about research opportunities.[184]	Data collection purpose and methods for release will be clearly communicated.[48] Desire for prompt information after diagnosis.[185] Perception for equal knowledge and information sharing between patients and healthcare practitioners.[185]	Data will be used by responsible people for legitimate purposes.[48] Data will contribute to increased knowledge of the disease, possible elucidation of treatment and improved patient quality of life in the long-term.[186] Regular educational outreach specific to disease type and featuring the latest information on research and knowledge.[48,185,186]
Families						Access to family support and services (counseling, equipment, peer support).[33]
Ethics committee				Research or parties accessing data will have the access/data release reviewed by ethics.[12]		Regular reporting on registry activities is required.[12]
Patient organizations						
Registry Team		To maximize registry success central data collection and curation should be considered.[50,51]			Clear procedures for registry execution are outlined.[49]	A research network that can provide technical assistance and guidance helps to ensure registry success.[52]

Storage and Curation chapter apply to the construction of online registries just as they apply to other types of registries. Participant log-in credentials must be appropriately derived and should be stored in an encrypted manner. Additionally strategies to verify participant identity may be worthwhile such as personal verification questions or tokens utilized for other secure online functions such as online banking. When planning an online registry, ensure appropriate IT security and network consultants are involved in the registry design. Many institutions conducting research have these individuals' available and strict policies in place.

Follow Up

With all registries, the issue of attrition must not be overlooked. This may be a greater challenge for online registries which may have a higher degree of automation and depend less on the provider-participant relationship (e.g. patient driven registries). In Internet-delivered healthcare interventions attrition is a bigger concern than in interventions that are provided face to face.[188] Possible sources of attrition might include declining interest in the registry; death; transfer out of the target clinic population and other attrition from follow-up. Attrition is a critical issue because it may introduce a selection bias into the registry data. There is a need for greater research in the areas of predictors of attrition and methods to address attrition specifically within the context of registries. One study did find a reduction in attrition using a blended follow-up approach where participants received both automated email reminders and telephone or in-person follow-up.[188] Substantial literature discussing retention and attrition in longitudinal cohort studies may be helpful. For example, below are some general strategies to maximize retention based on the work of Hunt and White[189] and Given et al.[190]

1) Assess participant willingness to participate over the long term during initial consent and baseline visits.
2) Cultivate participant bonding and commitment to the study through the use of logos and themes used on all communication with study participants.
3) Strive to contact participants at least once in a 6 – 24 month interval and track all follow-up activities.
4) Study staff should be well trained, communicate enthusiastically and openly, be flexible and respond promptly to questions or concerns.
5) Providing small branded tokens of appreciation; providing regular feedback about study progress and cash or other incentives for survey completion may help to improve participant retention.

Internet Access

According to the Canadian Internet Use Survey (CIUS) administered by Statistics Canada in 2010, 79% of households had access to the internet and over half used multiple devices (e.g. desktop, laptop, mobile phone, game console) to access the Internet.[190] Ninety-four percent of internet users over the age of 16 utilized email and 75% of these users reported accessing the

internet at least once a day.[191] Additionally, regardless of age over 60% of users accessed the internet to search for medical or health information.[191] On average only 19% of users contributed content to the internet including activities such as message boards, blogging or posting images and this was in stark contrast to the average use of social networking sites at 58%.[191]

The level of access was higher among urban metropolitan households compared with rural households (81% in urban metropolitan vs. 71% in areas outside of metropolitan or agglomerate areas).[190] Rates of access varied nationally and were highest in British Columbia, Alberta and Ontario. Rates of access were also highest in the upper income quartile ($87,000 per household or more). Also, internet access also varied by household size with higher access rates in households with more than three members.[190] About 75% of Canadian households have access to high speed home internet access.[190] Over half of households that did not have internet access indicated that they had no need for internet access while other reasons for lack of access including lack of devices to access the internet; the cost of the service or equipment; and a lack of confidence about internet skills.[190]

Based on these data, limitations in internet access alone should not significantly contribute to online registry enrollment bias in Canada. However, lowered participation in activities requiring the contribution of content on the internet such as social networking and other activities should be considered a concern with respect to registry enrollment, online data collection and attrition potential. Further examination of motivations behind these statistics is likely warranted. A best practice strategy to addressing these knowledge gaps and the potential biases they may introduce would be to have a toll-free number available to all people interested in joining any online registry and a postal mailing option for any email correspondence.[192] This would help to ensure that access was not a factor limiting enrollment and will not substantially increase time consumed by registry activities.[192]

Knowledge Translation

Knowledge translation, the ethically sound application of knowledge to improve the health of populations[193] is an important obligation for registries. The immediacy and accessibility of online registries inherently lends themselves to knowledge translation activities. Some evidence suggests that patient engagement levels relate to attrition rates and that higher engagement will reduce attrition[188] Some studies have expressed that registry participants desired regular communication of results (e.g. annual reports, newsletters) in lay language[185] however it should be noted that while it was preferred that these were interactive, sophisticated technologies such as videos were not preferred.[185] This indicates that a knowledge translation strategy such as an e-newsletter might be a very effective strategy with minimal cost. Additionally, registries that involve a network of practitioners may serve as good vehicles for enabling practice improvement.[177] Our guideline for the development of knowledge translation plans for neurological registries includes the following steps based on the work of Melanie Barwick and Donna Locket[193]:

1) Identify your target audience(s) – remember that this might include patients and families, disease organizations or charities, researchers, scientists, clinical providers, and institutional decision-makers depending on the purpose of your registry.
2) Engage members of your target audience(s) at appropriate times – plan engagement with members of your audience into your registry operations and determine at what intervals this engagement will occur at.
3) Determine main messages for each target audience – what is the minimum and critical information that must be communicated to each target audience. Think of the simplest way to express these elements.
4) Consider the packages for these main messages and what methods you will use to circulate them – there are no right or wrong strategies; consider planning an evaluation of each strategy to determine its effectiveness.
5) Determine the desired impact of your messages – identify the possible outcomes you hope for with the distribution of your messages. Plan how you will evaluate your success.

RECOMMENDATIONS

✓ Consider registry objectives and data collection plans before establishing an online registry as the planned deployment.

✓ Identify all potential stakeholders and ensure expectations are adequately managed.

✓ Ensure a mechanism exists to verify that enrolled registrants are from the desired target population and registry jurisdiction.

✓ Ensure participants are aware of registry expectations and willing to participate in the long-term.

✓ Ensure activities are undertaken by the registry to cultivate participant bonding and commitment. Strive to contact participants at least once every 6 – 24 months depending on registry needs. Track all follow-up activities.

✓ Ensure study staff are well trained and highly knowledgeable. Communication needs to be open, flexible, and prompt.

✓ Provide regular feedback to participants. Consider other ways in which appreciation may be expressed.

✓ Ensure non-electronic methods of communication are open to participants (e.g. mailing address; fax number; toll-free telephone number).

✓ Ensure a knowledge translation plan has been created and is actualized.

Part II - Registry Quality

Quality and data validation are key factors in assessing the successes and failures of a registry. Often, very little discussion of data quality and validation are undertaken during registry dataset design. Additionally, standardized quality methodologies are often difficult to apply to registry applications especially those that are not population-based.

High quality registries have these characteristics in common:

- A quality management plan derived during registry design and considering the big picture
- Methodologies to address inconsistencies in data collection and data sources
- Employ pilot testing or iterative deployment of data collection to ensure quality metrics are achievable
- Employ rigorous, consistent, and documented processes for data cleaning and correction.
- Train personnel to maximize initial data quality.
- Have an audit system including defined triggers initializing audit processes.

The interpretation of registry data necessitates some relationship between the data and the outside world. In most cases this involves some measure of validation. When analyzing and validating registry data the following should be considered:

- Clear and transparent hypotheses should be configured during registry design
- Comparison of data against external sources may be helpful.
- Influences of data collection and patient recruitment strategies must be assessed to determine the potential for selection bias within registry data.
- Assess site to site variations and pay close attention to missing data prior to conducting external analyses.
- Define clear procedures for handling missing data and site data collection variances.

Neurological Registry Quality Control and Quality Assurance

James Marriott[1], Vanessa K. Noonan[2], Elizabeth Donner[3], Mark Lowerison[4], Darren Lam[4], Lundy Day[4], Janet Warner[4], Eric E. Smith[4], Jean K. Mah[4], Paula de Robles[4], Nathalie Jette[4,5], Megan Johnston[4], Tamara Pringsheim[4], Lawrence Korngut[4]

This section of the guideline discusses procedures and best practices around quality control and quality assurance. In developing this section of the guideline we reviewed available literature and best practice; consulted with registry and disease experts; and derived consensus recommendations.

Quality, as defined by the International Standards Organization (ISO) in standard ISO 8402:1994, is the "totality of characteristics of an entity that bear on its ability to satisfy stated and implied needs."[194] In the context of registries, this means that registry data characteristics must altogether satisfy the intended and implied needs of the registry purpose. For example, if the purpose of your registry is to study all female adults of child-bearing age with epilepsy; then your registry data must consist only of female adults of child-bearing age who have a diagnosis of epilepsy. It is important to note that quality and registry purpose are inherently related. Registry creators will therefore need to define what quality means for their specific purpose(s).

While quality control and quality assurance are related concepts it is important to understand that they are different. Quality assurance (QA) is the process that maintains a desired level of quality.[195] QA is a proactive process done in advance of obtaining an outcome. Examples of QA activities might include audits, training, procedure documentation, selection of quality tools etc. Quality control (QC) is the assessment of whether an outcome meets quality expectations.[195] QC is a reactive process done once an outcome has been obtained. Examples of QC activities might include testing a product sample to determine if it meets requirements; or conducting a site inspection visit. Useful registries must have good quality data.[196,197]

RELEVANT LITERATURE

Quality Attributes

Without high standards for capturing data in registries, data quality can be compromised. The absence of high quality data in a registry may limit its use and generalizability. Arts et al[196] conducted a literature review on the subject of registry quality between 1990 and 2000. The two most frequently cited attributes that determine registry usability were accuracy and completeness. Based on an amalgamation of the definitions discussed in the literature these attributes were defined as[196]:

Accuracy – the extent to which registry data represent the truth

Completeness – the extent to which all necessary registry data has been entered

The above definitions were further supported in additional literature.[197]

Types and Causes of Data Errors

Many types and causes of error can be identified. The literature reviewed by Arts et al[196] divided data errors into three types: interpretation errors, documentation errors, and coding errors. Causes for these errors fall into two classifications: systematic and random.[197] Systematic data errors might be caused by computer programming errors; poor data dictionary definitions; inadequate or poor training; or data collection methodology violations or errors.[196,197] Random errors might be caused by incorrect data transcription (e.g. typing error), incorrect data collection (e.g. source documentation is illegible), or data are incorrectly entered into the data field (e.g. correct data in wrong location).[196,197] The most frequently cited errors in the literature reviewed by Arts et al[196] were inaccurate data transcription and computer programming errors. The average error rate found in the literature, accounting for both systematic and random data errors on Case Report Forms (CRFs) is 976 errors per 10,000 fields.[197] Overall, this is an error rate of approximately 1%.

Table 11: QA Activities

QA Action	Activity
Prevention	• Select and train adequately motivated personnel. • Design a data collection protocol including standardized definitions for data fields and guidelines for data collection method(s).
Detection	• Routinely monitor data and compare with the original data source; this could include centralized audits or site audits. • Utilize automated field parameters to detect errors within known value ranges. • Consider using dual entry or visual check methods to reduce random errors.
Action	• Correct identified errors • Identify and remedy root causes of errors

Case Report Forms

The literature reviewed by Arts et al[196] discussed a number of factors that would influence data quality on CRFs. Quality can be improved by the use of closed rather than open-ended questions on the CRF; and collecting data promptly from the original data source whenever possible or having data entered by a clinician if the original source is not available. Additional literature suggests direct connection between electronic medical records and CRFs to reduce transcription errors and capitalizing on the functionality of online CRFs[197] with easy to use fields and self-explained fields (e.g. pop up help).

Quality Control

Arts et al[196] found that the two main mechanisms discussed in the literature for registry QC were completeness checks and site visits.

Quality Assurance

Arts et al[196] found a number of quality assurance activities that should be undertaken in high quality registries. (see Table 11 above)

Other validation studies have also reiterated or reported additional points for maintaining and improving data quality in registries (Table 12). A review of the literature suggests that a number of strategies can be utilized. These include having motivated, well-trained, up-to-date, and accountable staff,[102,196,198-211] user-friendly data collection forms,[104,196,200] clear data collection methods,[202,212] clear objective definitions,[102,104,196,201,203-205,211], uniform data collection methods across sites,[93,201,205,209,212] a minimum set of necessary data elements in the registry,[104,196] drop down menus (as opposed to free text fields),[196] a system for automated data checks (e.g. software algorithms),[102,196,202,208,213] and an integrated delivery system between medical facilities for sharing patient records and information.[214] In addition, drafting and evaluating data

Table 12: Strategies to Maintain and Improve Data Quality in Registries

Strategy	Article(s)
Having motivated, well-trained, up-to-date, and accountable staff	102,196,198,211
Having user-friendly data collection forms	104,196,200
Having clear data collection methods	202,212
Having clear objective definitions	102,104,196,201,203-205,211
Having uniform data collection methods across sites	93,201,205,209,212
Having a minimum set of necessary data items	104,196
Having drop down menus	196
Having a system for automated data checks (e.g. software algorithms)	102,196,202,208,213
Having a minimum set of necessary data elements in the registry	104,196
Having an integrated delivery system between medical facilities for sharing patient records and information	214
Drafting and evaluating data collection protocols	196,215
Routine monitoring of data	102,196,197,199,202-204,208,215,216
Limiting the number of steps when collecting registry data	102,104,201,205,217
Collaboration and communication between staff, sites, and the registry	196,199,206,212,218-220
Providing constant feedback to participating sites for quality control	196,200
Comparing data with external sources to ensure complete case ascertainment	104
Collecting data in a time a location sensitive manner from those directly involved in the patients' care	196
Mandatory reporting	204,221

collection protocols,[196,215] routine monitoring of data,[102,196,197,199,202-204,208,215,216] limiting the number of steps when collecting registry data (e.g. electronic forms can directly collect data to reduce entry error affiliated with paper forms),[102,104,201,205,217] collaboration and communication between staff, sites, and the registry,[196,199,206,212,218-220] providing constant feedback to participating sites for quality control,[196,200] comparing data with external sources to ensure complete case ascertainment,[104] collecting data in a time and location sensitive manner from those directly involved in the patients' care,[196] and mandatory reporting[204,221] can all aid in maintaining and ensuring that registry data is of high quality.

OTHER CONSIDERATIONS

Quality Assurance Considerations – Data Collection

Appropriate and accurate data collection is inherently linked to the success of a registry so it is of paramount importance that the ultimate goals of the registry be reflected in the development of data collection procedures. This involves keeping the "big picture" in mind from the outset. To that end, case report forms (CRFs) should be designed to only collect the minimum amount of information needed for the registry. It is important to note that the minimum amount of information needed for the registry may not just be the minimum dataset. Sometimes it may be necessary to collect items beyond the minimum dataset needed for research in order to engage key stakeholders, or provide the registry with long-term funding sustainability. However, collecting the minimum amount of data serves multiple purposes. It reduces the burden on the front-end individuals (clinicians, researchers, data abstracters), minimizing the chance for survey fatigue to lead to errors or neglect of the registry. Interrelated to this, the data being collected should be seen as valid and important to the front line individuals (e.g.; patients of physicians) completing CRFs to keep them engaged and enthusiastic about the registry itself.

The CRFs should be designed to allow accurate data collection of uniform quality. This involves the creation of a data dictionary to explicitly define each variable being collected and the precise range of values allowed for all variables. For example, formatting of dates should be standardized throughout the CRFs and registry databases. These technical considerations need to be addressed early in the registry and CRF process. CRFs should also be constructed with a logical flow for the benefit of those entering the data. In registries which will be utilizing various primary data sources (egg; patient questionnaires, health care databases), CRFs should be identified so the appropriate data is collected from the best source for that data to help ensure data quality. Alternatively, if different sources are going to be used, methods for achieving consensus for data points needs to be identified a priori and mechanisms built-in to the registry to resolve discrepancies among data sources.

CRFs should also be designed with the needs of the content provider in mind. In the case of clinicians, as mentioned above, this means ensuring that registry data entry process is fluid and not overly time-consuming. When patients will be contributing to data collection, additional considerations are also needed. For example, limited dexterity might make typing or pencil/paper data collection time-consuming or impossible in some populations. Similarly, those with hearing deficits may find it challenging to complete a phone interview. It is therefore

essential for the modality of data collection be tailored to suit the needs of the population providing the content. If a diverse patient population with varying abilities is involved, the same information may need to be captured through different CRFs. In that case, it is important track the mode of data collection utilized for each dataset. This can be used to evaluate registry quality despite different data collection modalities and can allow for comparison between the methods.

Some registries will be collecting information from pre-existing datasets. These might include governmental health-care databases or office/hospital based electronic medical records (EMRs). Similar to when data is being collected initially from a patient or a clinician, it is important that the registry not become overloaded with extraneous data from the pre-existing dataset that does not suit the purpose and goals of the registry. Related to this issue, some administrative datasets may contain information that may comprise confidentially or privacy and should be stripped from the dataset used to construct the registry.

In some cases, it may be desirable to compare the registry data with an external database. For example, this may be needed to ensure the validity of the registry. If this is planned for a specific registry, it is important to consider data linkage up front during the CRF and registry design. It should be noted that creating database linkages may increase the burden of data collection. Nevertheless, this may be justified given the purpose of the considered linkage. More information on Data Linkage and Validation can be found in other sections of this document. Overall, it is paramount that the design of the data collection instruments and the registry as a whole be focused on collecting the least data amount of data necessary and collecting this through the easiest modality possible. It is also important that the tasks of data validation and data cleanup be delegated to those running the registry and not the front-line personnel providing registry content.

Data Cleaning

Data cleaning refers to the process in which errors in the registry's dataset are identified and corrected. Errors can include incorrect data (such as out-of-range values), absent data (missing values), duplicate entries or contradictory, mutually-exclusive data entered into different fields. As with other aspects of registry production, it is important that data cleaning be considered upfront in the design of the registry. This involves the production of a "data management manual" that explicitly details how data will be queried and the steps that will be taken to resolve data conflicts. The data dictionary and data validation rules will need to be specified. Data cleaning methodology might include automatic periodic query reports, automatic data cleaning algorithms and manual data cleaning and query reports.

As with other aspects of registry initiation, it would be important to include data cleaning in any pilot testing phase to ensure that the data cleaning procedures are adequate.

When anomalies or errors are found in data cleaning routines, it is important that problematic data is (at least initially) retained with the registry without being removed until the uncertainty is addressed. The data cleaning routines should go back to the original source of the data whenever possible. This will minimize the potential for bias to be introduced by a third party causing further errors by incorrectly assuming what value the

anomalous data should take; (i.e.: a registry technician thinking that they know "what that person meant"). Furthermore, the registry needs to have a mechanism to track and record when data changes are made which can be analyzed in the future as needed. This applies not only to data cleaning, but also in situations where incomplete records are later appended.

If multiple data entry methods are being used to populate the database, the data cleaning routines may need to take this into account. While this could be used as a way to help ensure data accuracy (eg: if different data sources contain the same information), the data management manual will have to explicitly detail how to resolve conflicts that arise because of different values in different data sources.

Quality Control

In addition to data cleaning, more comprehensive auditing of the registry contents may be required. As with all aspects of registry design and implementation, audits will vary in scope, frequency and location (i.e.: either onsite at data collection points or remotely) depending on the requirements of a specific registry and the funding constraints. Audits are important to ensure that training of data collectors is adequate and that data is complete and consistent. Audits can be conducted on a random basis or alternatively, for-cause audits can be created it there is a concern for example about a particular data collection site or a particular data field. The procedure for future planned audits should be incorporated into the registry design so that data collection methods are audit friendly. Furthermore, the registry should be structured such that a certain level of change within the collected data elements automatically triggers an audit. Such an audit would help to identify the root cause(s) of the change; is it because of simple error, or is there a systemic issue.

Quality Plan

Registries should document their quality management practices into a quality management plan. Quality management plans will address how, when and where quality activities will take place and who is responsible for them. Two key best practices in constructing quality plans include flowcharts and checklists. Flowcharts are diagrams that show the flow of data through the registry process and identify points at which quality breakdowns may occur. Checklists can be used to help to control quality and to communicate components of quality within a given process. The quality management plan can either be integrated into the data management plan, or developed as a separate standalone document.

RECOMMENDATIONS

✓ Consider the big picture when designing data collection procedures with quality in mind. Especially consider reducing data collection burden and enhancing participant engagement.

✓ Determine the best source for data being collected. If multiple sources are to be used ensure a methodology to address discrepancies is in place. Address uncertainties produced by vague data directly at the source.

✓ Consider the population from which data is being collected and tailor the data collection modality(ies) to suit the population's needs.

✓ Reconcile registry data with external data to ensure external validity.

✓ Ensure data collection process can be modified if quality assessments or pilot testing detect the need.

✓ Do not change data based on assumptions. This could distort the data or introduce bias.

✓ Develop a data cleaning plan during the registry design stage. Ensure the plan addresses any data linkage needs.

✓ Track when data are changed and the manner in which they are changed. Consider keeping multiple versions of a record instead of overwriting a single record.

✓ Define clear triggers for auditing. Audits should be random and for cause. Data should be collected in a manner that facilitates auditing.

✓ Develop a quality management plan. Ensure quality acceptance criteria and acceptable range (if applicable) are documented in the data management plan or quality plan.

Validation and Interpretation of Neurological Registry Data

Tamara Pringsheim[1], Darren Lam[1], Lundy Day[1], Angela Genge[3], David B. Hogan[1], Michael Shevell[3], Claire Marie Fortin[4], Colleen Maxwell[5], Guillermo Fiebelkorn[2], Karen Barlow[2], Moira K. Kapral[6], Steve Casha[1], Theo Mobach[1], Megan Johnston[1], Nathalie Jette[1,7], Lawrence Korngut[1]

This section of the guideline addresses considerations with respect to the validation and interpretation of registry data. In developing this section of the guideline we consulted with registry, disease, and statistical experts in addition to reviewing the available literature.

RELEVANT LITERATURE

Methods of Validation

Several methods can be used to assess completeness of registry data. Completeness of registration can serve as an indicator of registry effectiveness - an ideal registry will capture all cases of a given disease within a defined population. Completeness is defined as the proportion of diagnosed cases that are registered. Possible methods for estimating completeness include:

1. Estimates based on cases confirmed through death certificates and the mortality to incidence ratio
2. The historic data method: comparing current rates of registration to appropriate numbers of cases from the past within the same registry
3. Comparison to a reference registry with complete ascertainment
4. Capture-recapture methodology
5. Independent case ascertainment (linking registry data to an independent database)
6. The flow method
7. Estimating completeness based on mortality/incidence ratios.[222]

Schmidtmann et al[222] performed a survey of 195 cancer registries in Europe to determine which methods were most commonly applied to estimate data completeness. The survey found that the historic data method, comparison to a reference registry, estimates based on death certificates and the mortality to incidence ratio, and mortality/incidence ratio were the most commonly used methods. The quality of these indicators of completeness was not assessed.

Although comparative studies on the performance of indicators of completeness are lacking,[222] there are many studies that assessed individual methods of validation. The literature suggests that record-linkage methods and comparison with other data sources were most frequently used to investigate data quality. For validation purposes, registry data has been compared to medical records,[19196,201,203-205,207,209,214,216,220,221,223-225] a national population-based registry,[102,200,202,227,232] a clinic-based registry,[233] a regional database,[219,234] multiple registries,[221,235-237] administrative records,[210,232,238,239] or independent sources such as a quality improvement project,[199] study data,[240,241] in-person or telephone queries,[242] and a research project database.[243] The common variables assessed were case ascertainment, data completeness, data accuracy, reliability and sensitivity.

Several studies reported using the capture-recapture method to estimate completeness of registered cases and degree of under-reporting.[218,228,235,237,244,245] Schmidtmann et al[246] performed a simulation study to evaluate capture-recapture methods for estimating completeness of cancer registries under real conditions. They concluded that all capture-recapture methods underestimated completeness. The flow method,[218,247] mortality incidence ratio,[218] and historic data method[218] were less commonly reported to estimate completeness of case ascertainment.

In order to ensure consistency of data collection and reliability of registry data, a number of approaches have been employed by registries. These include examining inter-rater reliability,[248] comparisons of independent recoding or refilling of data,[249,250] and test-retest reliability.[251] In all cases, the data were found to be accurate, thus allowing for generalizability, research, audit, and review.

Byrne et al performed a systematic review of studies that investigated the validity of administrative registers in psychiatric

research.[252] Studies varied by validity methods and quality. Methods included applying diagnostic criteria to registry data, comparing registry data with case notes, or applying diagnostic criteria with case notes. In two studies, clinical interviews and case note reviews were assessed using operationalized criteria. The review found no gold standard for the assessment of registry data validity.

Having an objective process of data validation can improve data accuracy and staff accountability of data collection. Protech and Chappel implemented a data validation system to improve the data accuracy of a trauma registry.[253] The data validation model included staff participation in a review of key areas of registry data trends and errors and development of a standardized rating tool included as part of the data abstraction process. The validation method required data abstractors to use an electronic signature for each data abstract and the validity of abstracts were checked using an objective rating system. This process assisted with training of new staff members by providing email summaries of assigned ratings for each data abstract and any detected errors on a weekly basis. The validation tool was useful for providing performance feedback of data collectors and analyzing overall accuracy of data.

Studies that compare the feasibility of various methods of assessing data quality and validating data is limited,[222] thus, future studies are needed that evaluate the performance of different methods of data validation.

Lessons Learned from Improving the Validation of Registry Data

As mentioned earlier, there are a number of different methods that can be used for data validation and these may be associated with varying degrees of data accuracy and reliability. To improve methods of validation, a number of strategies have been proposed. It has been suggested that auditing be undertaken at regular intervals.[199,204,215,223] Frequent assessment of registry data can identify culprits that jeopardize accuracy and/or reliability. Using multiple sources of data can allow for retrieval of missing data and continuous validation.[204,223] Furthermore, randomly selecting participating sites[223] and at random time points[215] is appropriate for the proper evaluation of data quality. If registry staff from the coordinating center visit participating sites, errors may be more easily detected.[196] Selecting clear, objective, and easy-to-evaluate outcomes and variables for validation has been frequently suggested to improve the validation process.[202,223] Lastly, using patient identifiable data for linkage can improve the validation of data.[102]

OTHER CONSIDERATIONS

Registry Design

Registries evaluating safety, effectiveness, or evaluating an association between specific exposures and outcomes should specify hypotheses a priori to improve design, execution, and acceptance of results. It is important to have some a priori hypotheses. Without an a priori hypothesis, there is concern that the registry may be too broad in terms of its scope or may neglect to collect key information and evaluate specific outcomes. Disease registries with descriptive goals (e.g., clinical features, natural history, disease progression) often will not have an a

priori hypothesis. In this case, the registry may serve as a platform through which hypotheses may be generated. Long term project funding for a descriptive registry may allow hypotheses to evolve and new objectives to be generated in a prospective fashion.

In order to secure long-term funding, registries might need to develop new hypotheses or questions over time. Consider beginning the registry with an initial question, but constructing the registry in a manner to allow adding of questions in a prospective manner that can be answered through the registry's work.

Registry Development

It is essential to be transparent about the goals of the registry and methodology employed by the registry. A key question is how well do the study results apply to the target population? Are the results generalizable to them? Can they be extrapolated to other populations that are of interest? Case ascertainment must also be considered. It is important to minimize selection bias and determine whether the registry is capturing data across the entire applicable spectrum of the target population (i.e. not just the sickest or most disabled patients are included). Case ascertainment may be improved through partnering with patient organizations and recent census data. It is important to have a mechanism for assessing/tracking disease severity in order to ensure that the entire spectrum of the disease is represented.

With respect to assessing data quality, it is important to ensure relevant variables are collected, whether data collection is complete, and how missing data were handled. Assessment of completeness and accuracy of data has to make sense with respect to the disease. It has to be acknowledged that data assessment methods will evolve with increasing knowledge of the disease.

Sometimes registries are used for purposes other than those that were pre-specified. It is important to ensure that when a registry database is used for a purpose that was not pre-specified, that the registry contains all the information necessary to answer the new question. It is often difficult to ascertain what and how much to ask initially. Flexibility to modify what is asked is beneficial. As registries can help address new questions, the ability to add new modules/concepts is beneficial.

Validating Completeness, Accuracy and Quality of Data

It is important for registries to define how missing data will be handled, and develop a strategy to try to minimize missing data. For example, some registries use the internet (online contact information) to facilitate the collection and follow up of missing data. However, internet data collection may be less accurate than face to face data collection. Completeness must be balanced against accuracy. Collecting data from multiple sources may ensure completeness but can potentially compromise data accuracy. It is important for the registry to report data completeness, especially if data are being published.

Registry completeness can also be assessed across different demographics (e.g. age, Socioeconomic status, rural/urban) so that any biases in the registry are apparent. Additionally, there should be plans for site monitoring, quality assurance and data verification. Data review is and should be a standard practice.

With respect to hypothesis-driven registries, it is important to have a plan for statistical analyses that describes the analytic principles and statistical techniques employed to address the primary and secondary objectives. Statistical analyses need to be planned at appropriate intervals while considering the possible time dependency of data within the registry. It is important to ensure that a sufficient number of events have occurred and that sufficient time has passed in order to ensure that it is biologically plausible for a specific event to have occurred. It may be necessary to consider the natural history of the disorder. Registry analyses should provide information on: (1) patient population, (2) exposure or treatment, (3) endpoints or outcomes, (4) time, and (5) potential for bias.

For analyses, the use of internal comparator groups is preferable. If they cannot be found, an effort should be made to use external comparator groups. For internal comparator groups, one can make comparisons of individuals with varying disease severity, different disease subtypes, or by individuals presenting with disease at different times. Non-diseased spouses may be used as a comparator but they are potentially exposed to the same environment. It may be necessary to find an alternately derived control group. One potential concern with external comparators is that the data is not collected the same way. In order for the use of the external comparator to be fair, outcomes must be "hard", such as death, institutionalization, or hospitalization.

There is the potential that analyses performed by different investigators using data from multi-site registries may address the same question but produce different results. Methodological differences may explain the deviations. It is important to ensure that centers are interpreting things in the same way (standardization of responses).

RECOMMENDATIONS

✓ A priori hypotheses may improve the design, execution, and acceptance of results and serve to clearly define the scope and nature of the information being collected by a registry. Registries which seek to prove a premise need hypotheses; registries with descriptive goals do not need hypotheses.

✓ Registries should consider a design and permissive policies that allow for new hypotheses to be generated and followed up on as the registry develops. This may generate opportunities to obtain new funding and may ensure long-term viability.

✓ Be transparent about the goals and methodology of the registry.

✓ Ensure the entire spectrum of the disease or condition is represented if registry results are to be generalized.

✓ Ensure data collection includes important and relevant variables.

✓ Address confounding variables where possible.

✓ Clearly define inclusion/exclusion criteria to maximize data quality and maximize target population capture.

✓ Use internal comparator groups where possible. If external comparator groups are being used, recognize potential limitations and try to utilize unambiguous outcomes.

✓ Have a plan in place to minimize the amount of missing data. Where data are missing, ensure that this is addressed. Ensure the risks associated with supplementary data collection modalities have been addressed.

✓ Ensure that registry completeness and potential sampling biases are reported.

✓ Ensure that resources are in place for proper and thorough data analyses. Registry analyses should provide information on: (1) patient population, (2) exposures, (3) endpoints or outcomes, (4) time, (5) potential for bias.

✓ Address deviations in data collection and interpretation that occur between sites.

Part III - Registry Impact

The impact of patient registries is a key factor in evaluating registry success. Registries can have impacts in many ways including but not limited to the following:

- Impact on consistency of clinical care and/or clinical practice
- Impact on knowledge of the natural history of disease through the monitoring of real-world cohorts
- Evaluation of the effectiveness of novel clinical therapeutics from a post-marketing perspective
- Facilitation of research design
- Facilitation of research study recruitment
- Reduction in research study/clinical trial start-up costs (due to efficient recruitment practices and site selection)
- Evaluation of health service utilization and service availability across jurisdictions.

Registries with a high degree of impact have the following characteristics in common:

- Careful advance planning of registry design and implementation
- Adequate human and monetary resources
- Retain registry participants and stakeholders through regular communication
- Ensure data collection efficiency (minimal time, minimal frequency, pilot tested data forms etc).
- Operate in a transparent manner.

In order to facilitate the evaluation of registry impact clear objectives and criteria for success should be established during registry planning. The use of common data elements across registries may afford the opportunity for comparative analysis where appropriate. Registry impact will be affected by the quality of registry data and this in turn is affected by the available budget and human resources. Resource planning during registry design must therefore consider the desired impact and level of quality to be achieved.

Neurological Registry Feasibility and Sustainability

*Tamara Pringsheim[1], Ruth Ann Marrie[2], Elizabeth Donner[3],
Michael Shevell[4], Darren Lam[1], Lundy Day[1], Megan Johnston[1],
Nathalie Jette[1,5], Lawrence Korngut[1]*

The feasibility and sustainability of a registry depend on many factors, including researchers, clinicians, administrators and participants. The development and maintenance of a successful registry may be improved by considering the following elements in the design and implementation of registry procedures.

RELEVANT LITERATURE

Factors That Negatively Affect Feasibility

Several factors can negatively influence registry feasibility. They include confidentiality and privacy issues, barriers to participation, issues related to multiple centres and locations, issues related to human and financial resources, poor data quality(non-uniform, missing, or incomplete data), and potential biases.

In the past, concerns over maintaining privacy have led to patients declining to give personal / sociodemographic information, concealing their diagnosis, or even submitting false information.[254] The ethical concerns surrounding participant consent,[41,255] and privacy legislation[39] can also complicate registries, especially when disagreement exists regarding whether individual privacy can be overridden for the greater public good for quality assurance projects. Differences in legislation across jurisdictions can add further complexity to the design of registries whose source populations are widely dispersed. Issues of confidentiality are not unique to patients; physicians have also been concerned about privacy. In one study, surgeons expressed concerns about who has access to patient outcomes data.[256] Finally, concerns about security when recording and transmitting participant data online have been raised.[257]

Registries often depend on the participation of multiple stakeholders, and low participation and response rates by any stakeholder, including health care providers, institutions, and participants are problematic. Many physicians may be reluctant to participate if the commitment involves a large amount of time, effort, or money.[53,256] Ensuring low physician burden by providing adequate financial and human resources to enable data collection may increase the likelihood of retaining physicians.

Anonymity at the physician level may also be important in the design of some registries. In one study, some surgeons declined to participate if they were fearful of revealing their outcomes when outcomes may appear worse than those of other surgeons.[256] Troubles securing cooperation from hospitals and staff have also been reported.[254,258] For example, in establishing a statewide mammography database in Arkansas, potential participating mammography centres were concerned about patient confidentiality, lack of space, computers and staff time to orient employees on data collection procedures. Some centres' regulations prevented non-employee access to centre data and equipment[258].

Overly demanding data collection requirements and the frequency of data collection may affect patient participation and retention. Several studies have reported that tools and forms that are not user-friendly may prohibit participation and proper functioning of a registry.[36,103] Multimodal data collection (online, paper based) and tailoring the mode of data collection (e.g. support mobile application) to the needs of the participants may increase enrollment and retention. Registries may be more successful with respect to recruitment and retention if the patients have a relationship with people collecting data, and regular clinical follow up may help to enhance relationships. Members of some ethnic groups may be less willing to participate in registries than others.[18,41,61] For example, in analyzing a large comprehensive data set of participants recruited into clinical research programs on Alzheimer's disease in the United States, only 3.6% of the total population studied was non-white[61].

While some registries are limited to a single centre, many involve multiple sites, and obtain data via multiple sources. Multi-centre registries may face challenges due to inconsistent data collection methodology, which can limit completeness and data comparability. Definitions for a condition may differ by site,[40,106,257,259] and reporting of outcomes may also differ.[259] Conflict on policy development[106] what data to collect,[39] and differences in the availability of experts and resources[42] may also arise. Data quality may differ as well due to non-uniform, missing, or incomplete datasets. As mentioned earlier, the lack of uniform definitions and data heterogeneity can lead to

inconsistencies in data sets.[40,106,257,259] Fragmented data sets can also result from insufficient coverage of a population.[42,259]

Other factors that can affect registry feasibility include financial and funding constraints, lack of time, effort, and resources, and potential biases. Insufficient financial support can critically limit the development and sustainability of registries.[40,42,260] Studies have reported a need for trained, dedicated staff for the maintenance of a registry.[39] Asking hospital staff to incorporate registry work into existing duties may not be sustainable and can lead to poor data quality.[39] There may be a lack of interest and motivation with staff attending to the registry, especially when personnel turnover is high.[258] This is also accompanied with the need to train new personnel that are unfamiliar with the registry. Others have documented a lack of resources such as staff (including experts in the field), space, computers, and time.[42,258] Finally, selective reporting can result in selection biases that lead to biased results.[256,261]

Enabling Factors that Enhance Feasibility

The literature outlines enabling factors that enhance the feasibility of registries including establishing a purpose that reflects the needs of registry users, adequate funding, consistent human resources, implementing a user friendly data entry process with a minimal data set and international collaboration when appropriate.

Clear Purpose

It is essential for a registry to have a predefined purpose that reflects the needs of its users. Having a predefined goal enables registry personnel to focus on a specific objective rather than simply collecting data.[39] The purpose should be explicitly defined and agreed upon before the implementation of the registry,[36] as along with explicit aims for data collection and usage. This includes planning and selection of data items to be included.[39]

Data Collection

Data collection should be focused based on the goals of the registry and limited to the data necessary to meet those goals. For registries that seek to gather data regarding many patients, limiting the data collection beyond that required to routine clinical care to five to ten minutes per patient encounter may increase the likelihood of ongoing participation. For registries that are gathering data involving small numbers of patients, it may be more feasible to gather larger amounts of data per encounter. A nurse or other allied health professional supported registry might require less physician resource time. Larger amounts of data collected increase the potential for inconsistent and missing data.

Several other factors must be considered during registry development including communication and organizational frameworks, infrastructure and costs[41] and who should have access to participant information and for what purpose.[256] It is also important to ensure the registry population will be large enough to support the conduct of valid scientific research and if using the registry design will best answer research questions.[41]

Stakeholder Engagement

For a registry to be sustainable it needs support from stakeholders at political, administrative and clinical levels.[39] Active collaboration among researchers, policy makers, patient advocates and healthcare providers is important.[40] Support for a registry can be influenced by establishing a steering committee, or expert panel.[39] Steering committees help ensure timelines are met, objectives are clear, and that the interests of the general community are met.[39] All stakeholders, including patient advocates, funding agencies, researchers and people involved in the operation of the registry should be considered for involvement in the steering committee. The level of enthusiasm and involvement of the steering committee, site champions, and principal investigators can determine the success or failure of the registry. Both ethical and scientific oversight committees can be established to address key issues related to registry design and implementation and make recommendations.[41]

Communication

Regular communication (e.g. teleconferences) from the data coordinating centre is vital to the success of the registry, by sustaining enthusiasm and a sense of purpose among participating centres. It is important to emphasize community building among the coordinating centre and participating sites and establish visibility at relevant national meetings. Registry sustainability can be enhanced by regular communication with the participating centres and site retention tools such as a website, newsletters, instruction manuals, training meetings, regular data reports, presentations at conferences, and the ability of participating providers to publish based on registry data. Centre specific data reports could be offered and this information may be attractive to centre representatives because it could enhance their institutional databases, or provide a means of quality assurance. Visible products should be clinically relevant to people contributing to data collection.

Finances

Financial feasibility must also be addressed when planning a registry. It is important to note that the scale of cost of a registry is not in a linear relationship with the scope of the registry. As the scope of a registry increases, the cost to implement further changes with the registry may rise at a greater rate than the change in scope. Ideally registry investment should be considered in the context of both benefit to society and minimized costs. The point at which the benefit to society equals the minimized cost is the ideal investment.[260] Adequate funding is needed to support ongoing data collection and quality assurance efforts.[36,40,42] Requests for proposals for registry projects should have funding terms that are appropriate and meet the needs to fund a planning phase, execution phase, and analysis phase. It is important to be clear about what role sponsors have in registry planning and analysis, and who has access to data. Obtaining and sustaining funding requires a long-term commitment from an expert group, retention of experienced staff and attracting funding for additional research projects.[39] Publication of registry results and other knowledge translation activities will improve the success of future applications for funding and may attract philanthropic funding sources.

Human Resources

Registries need trained and skilled researchers and clinicians to coordinate, collect and analyze data.[39,42] A full-time individual should be hired and trained to improve data quality.[36] For example, to maintain long-term interest from collaborators, the Victorian State Trauma Registry aimed to train postdoctoral fellows and newly graduated specialists.[39]

Change Management

Proper change management is essential for registry success.[5] It is recommended that registries have a manual which describes – in detail – policies, procedures, protocols, the governing body if the registries and the roles and responsibilities of its members, and processes and infrastructure for ongoing training of registry staff.[5] Furthermore, it is recommended to have in place a standard procedure for communicating about change in a timely manner.[5]

Data Collection Practices that Promote Feasibility

Depending on the goal of the registry, data collection should be population-based to provide unbiased data and enable monitoring and evaluation of the entire health care system.[39] Mandatory participation by centre, where feasible, increases efficiency and accuracy of outcome results.[256] Depending on the ethical and social landscape of the population, a combination of ascertainment methods may be required to include under-represented groups.[41]

Minimum core dataset

There is a need for a minimum core data set that is complete enough to fulfill the purpose of registry, but limited enough to ensure feasibility and high quality of the data collected.[36,106] From a clinical perspective all data items should be included, but from an epidemiological perspective more data collected reduces the focus on data quality and completeness; these perspectives need to be balanced to meet the goals of the registry and ensure data quality.[39] To limit heterogeneity of data, a consensus around core data elements should be developed.[257] It is helpful to re-evaluate the data items annually for completeness and relevance and to refine the data collection tool if needed.[39] Data accuracy and completeness should be monitored regularly at all participating sites.[36,40]

Data entry

The data entry process should be user friendly, involving easy to use data entry forms with straightforward, universally accepted definitions and a focused data collection strategy.[36,39,40,103] It is recommended that data collection be standardized, easy to access, reported regularly and entered without requiring interpretation.[39,106] Online data submission via a secure web-based system can ease data reporting,[103,259,262,263] but requires enhanced efforts to protect confidentiality of the data.[103,259] Data quality can be improved by using clear coding guidelines, proper instructions for data collectors and using patient identifiable data for data linkage and validation.[111] Pilot testing of registry elements prior to recruitment and the use of an advisory board to add transparency and credibility are good practices to ensure registry burden is minimized.

Consent

Linkage to other data sources in order to obtain key long term outcomes data on patients who are lost to follow-up may be helpful, such as vital statistics to determine whether the patient has died. Such linkages would need to be included in the consent form. It is beneficial to seek permission for future direct contact (without the consent/intervention of any associated health care providers) at the time of enrollment. Consent forms can be developed providing the option of participating, including data linkage and permission for future contact. Providing yes and no options for each choice allows participation to be tailored to individual patient needs. Developing integrated data systems can be useful to improve data quality by linking clinical data sources such as hospital medical records to registries,[106] or to create a comprehensive registry combining information from multiple registries.[264]

Collaboration

At times, national and international collaboration between registries may be needed to ensure an adequate sample size to study an outcome of interest, such as in the case of rare disease registries. Pregnancy registries in epilepsy, for example, require collaboration to identify a sufficient number of women exposed to various medications to examine occurrence of congenital malformations.[265] Collaboration between registries through shared expertise and funding may also be a useful strategy to overcome challenges such as weak infrastructure, poor registry quality and insufficient coverage in a population.[42] When combining registries, an integrated approach that supports an efficient exchange of information can minimize duplication and facilitate information exchange within the community.[264] However, there are challenges associated with sustaining multi-jurisdictional registries including annual renewal for multiple centres, and multiple ethics review boards for the same registry. A national registry review board may help overcome these challenges. Internet-based registries and online data submission are feasible ways of gathering data from multiple countries.[103,259,262,263] Collaboration between state and federal registries is also effective for building national registries to ensure the data process is uniform and comparable.[40]

Innovative Ways to Increase the Likelihood of a Feasible Registry

In addition to the enabling factors described above, there are innovations that may be useful for increasing the likelihood of the implementation of a successful registry.

Harmonization of Data Collection

The EuroTARN group (http://eurotarn.man.ac.uk/)[266] was established by several European collaborators and aimed to develop a common core dataset to assess the feasibility of collecting anonymous data as part of a trauma registry.[263] A website that contained a new online data submission form was designed. To facilitate the creation of the dataset and consensus of opinions between contributors, the Delphi technique was used (views from the expert panel were collected through a series of online questionnaires). This online technique was beneficial for each stage of the technique to be completed on time and was less

costly than meetings. The first stage involved asking participants to document as many clinical data points that they felt were necessary in the core dataset and document ideas for inclusion/exclusion. The second stage involved the categorization of and subsequent agreement ratings for all core data points submitted in stage one. The third stage involved voting on remaining core data points where an overwhelming rate of agreement was not achieved. The core dataset allows for the possibility to collect and combine outcome data in established trauma registries from representatives of 14 countries across Europe using a web-based system. It was successfully developed and trial data collection demonstrated the potential to collect clinical and epidemiological trauma data from a pan-European perspective.

The National Institute for Neurological Disorders and Stroke initiated a common data elements project in order to streamline data collection for clinical research. The NINDS common data elements website (http://www.commondataelements.ninds.nih. gov/#page=Default)[267] serves as a repository of common data elements for clinical investigators. It provides access to NINDS common data elements definitions, as well as sample data collection forms. In addition to general common data elements, disease specific common data elements have been created for Amyotrophic Lateral Sclerosis, Congenital Muscular Dystrophy, Epilepsy, Friedrich's Ataxia, Multiple Sclerosis, Parkinson's Disease, Spinal Cord Injury, Stroke, and Traumatic Brain Injury.

Timeliness of Data Reporting

Since traditional sources of information (publications and presentations) lack timeliness in terms of recognition and reporting, Hauser et al established an Internet-based registry of pacemaker and ICD pulse generator and lead failures.[262] This Internet-based registry could recognize and report device problems quickly. Quarterly data summaries are posted on the website and emailed to participants. When unexpected trends were observed, emailed alerts were issued to participants. Through the use of an Internet-based registry with data from multiple centers, important data can be transmitted in a timely manner. Registries may adopt such a system to report data quickly.

The Global Registry of Acute Coronary Events (GRACE) study tested the feasibility of a simplified data collection tool and provision of a quarterly feedback to index individual hospital management practices to an international reference cohort.[268] They provided sequential, longitudinal data that enabled health care providers to identify potential care gaps, implement appropriate changes to the appropriate diagnostic management approach to patients with a suspected acute coronary syndrome, and measure the impact of changes on quality measures and clinical outcomes. GRACE successfully showed that individual hospitals can index their data management practices to an international reference cohort using simplified data collection tools. This allows health care providers to identify care gaps and potentially implement changes to diagnostic and management approaches.

To encourage researchers and clinicians to collaborate and share information for Disorders of Sex Development (DSD) in the European DSD registry, a web-based registry and virtual research environment (VRE) was developed.[257] Consensus around a core data model was developed to eliminate heterogeneity in data. This VRE allows clinicians to enter data to assist researchers in finding eligible patients for study recruitment. This can allow for the collection of standardized data internationally, thereby, allowing collaborative research to be performed globally.

In certain instances, the existence of multiple independent registries on the same topic area may reduce their effectiveness. Non-collaborating registries in the same topic area result in the need for investigators to identify and visit several resources to obtain required information. Duplication amongst these resources will further complicate effective use of the registry data, impacting its overall value to the scientific community.[264] One solution to this problem is for individual databases to be complementary and interlinked.[264] This integrated approach could support efficient information exchange. Another possibility is the creation of a comprehensive registry that contains information currently provided by existing independent registries.[264]

OTHER CONSIDERATIONS

Incentives for Patient Participation

Some registries provide patients with small tokens to express appreciation for participating, for example, if a participants does not miss follow up sessions, they would be awarded "super participant" status, gold star, or a small gift such as an article of clothing with the registry logo on it. Incentives for patient participants such as newsletters, or compensation are particularly beneficial. The NARCOMS registry distributes a 20 page magazine, 'NARCOMS Now', to participants every three months (http://narcoms.org/narcomsnow/home)[269]; it provides participants with information about MS, recent research findings, and includes updates on the contributions of participants.

The ability to perform telephone or video-link follow-up visits or to do web-based follow-up visits may be beneficial for participants living in remote areas, and permission to perform various types of follow-up visits should be addressed during the initial consent process. Additional incentives such as: paying for parking when appropriate, giving community service points to those who need them to graduate from school, and/or giving small gifts such as movie passes may assist in retaining patients in a registry.

RECOMMENDATIONS

A feasible registry with a high degree of impact will:

✓ Have adequate advance planning and infrastructure (including human and monetary resources).

✓ Incorporate minimal data collection time and frequency while tailoring the mode of data collection to participant needs.

✓ Pilot test data collection practices to ensure they work as designed.

✓ Have a diverse advisory board representing ethics, legal, operational, participant and sponsor interests.

✓ Employ regular communication amongst all stakeholders.

✓ Utilize graduated consent, and other participant retention tools such as a registry website and newsletter.

✓ Regularly engage providers through training meetings, regular data reports and presentations at conferences.

✓ Cultivate long-term funding through activities that raise awareness about the importance of the registry.

✓ Act in a transparent manner.

✓ Utilize common data elements to enhance registry compatibility.

✓ Link with vital statistics to determine whether patient has died and address other accessible information that may be of interest (seek patient consent for this).

✓ Address challenges associated with recruitment and retention of members of minority groups to ensure representativeness.

Evaluation of Neurological Patient Registries

Jean K. Mah[1,3], Janet Warner[1,3], Ruth Hall[2], Eric E. Smith[1,3], Thomas Steeves[2], Elizabeth Donner[2,4], James Marriott[5], Megan Johnston[1], Mark Lowerison[1,3], Paula de Robles[1,3], Vanessa K. Noonan[6], Essie Mehina[1,3], Nathalie Jette[3,7], Tamara Pringsheim[1,3], Lawrence Korngut[1,3]

Over the past decade, there has been an appreciable increase in the number of national as well as international registries for a variety of neurological conditions, with corresponding increase in the amount of publications arising from these efforts [ref]. The registries were established for determining the natural history of a specific disease, the effectiveness of new treatments, the quality of care and/or other patient-related outcomes. The purpose of this chapter is to provide an approach to registry evaluation and quality assessment.

In preparation of this chapter, we reviewed current literature and consensus guidelines on registry evaluations. We also consulted with medical experts and registry/database specialists as part of a national registry meeting to provide feedback and consensus on criteria to be used for evaluation of disease registries in Canada.

RELEVANT LITERATURE

Despite the importance of registry evaluation, there is currently a paucity of reports related to neurological disease registry evaluation. Other examples were related to diseases such as rheumatoid arthritis,[270] trauma,[271] liver transplantation,[104] and cancer[272]. Domains of the registries that were evaluated include recruitment numbers, missing data, reporting, audit of guidelines, access to national and institutional health databases, patient involvement and collaborations. Key references and tables are provided as resources to assist with registry evaluation.

Research Quality

Detailed discussion of registry quality assurance and quality control can be found in Chapter 7 of this guideline. A further discussion on the validation and interpretation of registry data including from a quality perspective can be found in Chapter 8 of this guideline.

Existing Guidelines for the Reporting of Research Studies

The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement[273] is a 22-item checklist intended for use with observational studies. The list provides 18 general and 4 specific guidelines for complete reporting of cohort, case-control and cross-sectional studies. The authors had intended for the statement to be a tool (instead of a rigid standard) to help assess the quality of reports arising from observational-based studies. They acknowledged the inherent limitations of the STROBE statement, including an inability to address the reporting of all types of studies. Nonetheless, for registries based primarily on observational methods, the STROBE statement is a useful guide.

Similar guidelines are available for the reporting of randomized clinical trials, meta-analysis, and systematic reviews. The QUOROM (Quality of Reporting of Meta-analyses)[274] and the CONSORT (Consolidated Standards of Reporting Trials)[275] statements are guidelines for assessing the quality of reports that were developed at separate consensus meetings. Like the STROBE statement, these guidelines are consisted of checklists of domains that should be considered as part of the evaluation. These domains are pre-defined and the ways in which they should be assessed are described. Similarly, guidelines on how best to report perform systematic reviews include SQUIRE (Standards for Quality Improvement Reporting Excellence) and STREGA (Strengthening of Reporting of Genetic Association Studies); the latter is an extension of the STROBE statement.[276] Other types of publications should be graded based on strength of the evidence as presented in the research articles.[277]

In reality, there are often variations in the reporting of observational studies. In the article titled Issues in the reporting of epidemiological studies: a survey of recent practice[271], seventy-three articles in observational epidemiology were reviewed in search of limitations in reporting. The articles were picked from 20 journals, and included 37 cohort, 25 case-control, 10 cross-sectional, and one case-cohort studies. For the most part, the articles investigated cancer or cardiovascular disease with 31% of the articles investigating other diseases. The authors found a variety of issues that may have led to erroneous conclusions, including insufficient information on participant

selection process, data quality, sample size consideration, and rationale for grouping and sub-analyses. Adjustment for potential confounders (or effect modifiers) and multiple comparisons were at times inadequate. As well, the epidemiological literature in general may be prone to publication bias. Additional attention to details and efforts are needed to avoid similar bias in the reporting of disease registries.

Quality of Evidence: Consistency, Precision and Avoidance of Bias

It is important to have clear guidelines for grading the strength of evidence. According to one publication[278], evidence should be graded according four domains: risk of bias, consistency, directness and precision. The reference includes recommendations on how to rate the evidence for each of the four domains. Additional considerations included dose-response association, potential confounding factors, strength of the association, and publication bias. The authors recommended that these assessments should be incorporated into an overall grade of the strength of the evidence; as well, the report should provide an explanation of the reasoning for the grade and which domains played the most important role in influencing the overall grade.

Data Comparability, Validity, and Timeliness

In a review article on data quality in the cancer registries[279] is based on experience from a cancer registry. Part 1 highlighted the importance of the comparability, validity and timeliness of data. Comparability is the extent to which statistics generated by different groups are to be compared to one another. In order to have data comparability, it is important to have consistent definitions and adherence to mutually agreeable standards and operational procedures. Validity refers to the proportion of cases in the registry that actually have a particular characteristic. Validity depends on accurate abstracting, coding/recoding, as well as the precision of documentation. Common methods of assessing validity include re-abstracting and recoding, diagnostic criteria (or histological) verification, missing information analyses, and internal consistency assessments. More information on Validation of Registry Data can be found in Chapter 8 of this guideline.

Re-abstracting involves independently collecting data from the source and comparing it to the initial data abstraction that has been recorded in the registry. Greater degree of agreement is associated with greater validity of data. Recoding involves reassigning codes to the abstracted information and assessing the agreement with records in the database. While this method is easier and less expensive, it will not allow one to detect problems with abstraction. Reliability studies involve multiple people coding identical source documents under controlled conditions to assess the level of agreement. Histological verification involves assessing the accuracy of a diagnosis through a histological examination by a pathologist. This method is particularly relevant for disease based on tissue biopsies or pathological analyses. Death certificate only (DCO) registrations involve registering patients post mortem based only on a death certificate which mentions some form of cancer. The problem with this method pertains to the degree of accuracy of death certificate. One possible solution is to minimize the amount to

death certificate only registrations. Death certificate notification registrations involve identification of a cancer patient through a death certificate and verification of the information through other sources. This practice is generally more accepted than death certificate only registration due to the increased validity.

Lack of access to source documents, problems with items and code values, misapplication of coding rules and inadequate case histories can often lead to unknown values or missing information. Internal consistency, item validity and inter-record consistency are all important concepts to evaluate the quality of evidence in a registry. Timeliness deals with access to current data; the more current the data, the more likely it is to be complete and accurate. While there is no formal definition of timeliness, some guidelines suggest that capturing within 6-23 months is considered as "timely". Efficient procedures, well trained staff and electronic data capture can all enhance timeliness.

Comprehensiveness of Data

Comprehensiveness is the extent to which the information of the registry is representative of the population.[280] To assess comprehensiveness it is important for the incident rates and survival proportions generated by the registry to be as close as possible to those of the general population. Both semi-quantitative and quantitative methods were outlined in this review to help determine the completeness of data in a cancer registry.

OTHER CONSIDERATIONS

Registry Impact

The impact and cost-effectiveness of disease registries remains largely undetermined. As well, the potential impact of registries on patients, families as well as the scientific communities will require further studies. Timely dissemination of available information will help disease registries to achieve their greatest impact.

RECOMMENDATIONS

✓ Assess registry quality with the registry purpose in mind.
✓ Criteria for evaluating the outcomes and/or success of the registry are available and should be specified as part of registry planning.
✓ Research and evidence quality will depend on available resources and budget. These should be planned accordingly to achieve the desired quality.

Common Data Elements for Neurological Registries

Janet Warner[1], Megan Johnston[1], Lawrence Korngut[1], Nathalie Jette[1,2], Tamara Pringsheim[1]

At the outset of this project, one aim was to define a set of core data fields to include in all neurological registries in Canada. This project targeted neurological registries in Canada for all priority neurological conditions identified in the call for proposal including: Alzheimer's disease (AD) and other dementias, amyotrophic lateral sclerosis (ALS), brain tumours, cerebral palsy (CP), dystonia, epilepsy, Huntington's disease (HD), hydrocephalus, multiple sclerosis (MS), muscular dystrophy (MD), Parkinson's disease (PD), spina bifida, spinal cord injuries (SCI), Tourette syndrome and traumatic brain injury (TBI). The project team sought to identify all existing neurological condition registries in Canada to consult as stakeholders in this project. Disease experts from all of the above priority conditions were included in the process. Neurological registries represented in the project included:

• The Canadian Cerebral Palsy Registry – a voluntary registry including children with CP across several jurisdictions in Canada. (Edmonton, Alberta).
• The Canadian Neuromuscular Disease Registry (CNDR) – a voluntary registry which includes MD, ALS and all other adults and children with neuromuscular disease in Canada (Calgary, Alberta, www.cndr.org)
• Hydrocephalus Registry (under development)
• The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry - a voluntary online registry for patients worldwide with MS (Birmingham, Alabama, www.narcoms.org)
• The Ontario Stroke Registry – formerly known as the Registry of the Canadian Stroke Network, a mandatory registry under Ontario's Personal Health Information Protection Act (PHIPA) based at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario. http://www.ices.on.ca/webpage.cfm?site_id=1&org_id=26&morg_id=0&gsec_id=7071&item_id=7071
• The Quebec Myotonic Dystrophy Registry – a voluntary registry for Quebec patients with myotonic dystrophy (a form of MD) (Quebec, Quebec http://www.dystrophiemyotonique.chuq.qc.ca/ENG/registry-why.html)
• The Rick Hansen Spinal Cord Injury Registry (RHSCIR) – a voluntary registry which includes individuals with SCI from across Canada (Vancouver, British Columbia, www.rickhansen registry.org)

• The Southern Alberta Dementia Registry (under development)
• The Sudden Unexplained Death in Epilepsy (SUDEP) Registry (under development)
• The Tourette syndrome International Consortium (TIC) Database – an international database of Tourette's patients from 27 countries housed at the BC Children's Hospital in Vancouver, British Columbia.

BACKGROUND

In selecting elements for a registry, several factors must be considered:

• Importance of the elements for the integrity of the registry
• Reliability of data collection in each element
• Necessity for analysis of the primary outcome of the registry
• Burden of data collection in each element (time and cost)

Data element selection can be simplified if clinical data standards exist for the disease or condition of interest. Utilizing data elements that adhere to clinical standards can facilitate comparisons across registries; improve efficiency during the establishment of registries; promote effective sharing and data linkage between registries; and can help to ensure the meaning of information collected by different registries is the same.

We identified a number of potential sources of core data fields available worldwide including:

1) National Institute of Neurological Disorders and Stroke (NINDS) based at the National Institutes of Health in the United States maintains a list of common data elements for 8 of the priority neurological conditions including ALS, PD, HD, MD, epilepsy, SCI, MS, and TBI.
2) Ontario Brain Institute based in Ontario Canada is preparing common data elements for CP, and epilepsy.
3) Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disease (TREAT-NMD) has prepared common data elements for number of neuromuscular conditions including Duchenne, congenital, and myotonic muscular dystrophies.
4) The EURO-MOTOR project in Europe is defining common data elements for ALS databases in Europe.

5) The Patient-Reported Outcomes Measurement Information System (PROMIS) project created a web-based resource that features data field banks, case report form banks, and centralized access to computerized-adaptive testing for some measures.

6) The EPIRARE project based in Europe has been discussing common data elements for rare disease registries in Europe and globally.

Overall, inclusion of core data elements in registries can enhance registry feasibility and sustainability by providing the opportunity for sharing of data between registries in a meaningful way.

METHOD

In May 2012, the project team held its first team meeting and initial discussion around core data fields occurred. At that meeting a brief review of potential items based on the above identified data sources was presented. Consensus at the meeting was to hold a Delphi method consultation among all investigators and stakeholders to identify potential common data elements.

Over the summer, the Delphi method consultation was configured and held using the web-based survey platform Survey Gizmo (Boulder CO, www.surveygizmo.com). Thirty-one people received the survey and there was a 71% completion rate.

The survey featured two questions regarding each proposed data element:

1) Should the item be collected from registry participants?
2) Is the proposed field for collecting the information from participants appropriate?

Participants could respond on a radio button scale featuring the options Strongly Disagree, Disagree, Neutral, Agree, Strongly Agree, and No Opinion.

In September 2012, the results of the survey were reviewed the second project team meeting and final discussion around the proposed core data fields occurred.

DISCUSSION

In general, the results of the Delphi method consultation did not provide clarity on core data elements for neurological registries in Canada. The registry team decided at the September meeting that very few elements could be recommended based on the results of the Delphi consultation. Additionally, substantial challenges in collecting any elements across the entire neurological disease spectrum were identified due to the heterogeneity of the diseases/conditions being considered and the relevant clinical measures and outcomes especially when considering the spectrum of the diseases across pediatric and adult audiences. The mobility of patients between regions within Canada was identified as being a major concern due to the lack of a consistent identifier apart from a Social Insurance Number (SIN). Focus group data collected in the spring of 2012 indicated that patients were highly unwilling to share their SIN number for registry purposes. There were also substantial concerns regarding a duplication of effort against the other identified organizations creating common data elements within some of the

disease groups and a considerable issue as to how to address adequate stewardship of the dataset beyond the scope of this project.

RECOMMENDATIONS

The project team recommended that neurological core data elements are essential and should be developed but the process required is beyond the capability of the current project. Core data elements will require a national group of registry leaders and experts to provide oversight and updating of core data elements to ensure validity and relevance over time.

The project team arrived at the consensus recommendation that neurological disease registries with patient contact in Canada should collect the following elements to maximize the compatibility of data between registries and prevent overlap.

✓ Full legal name
✓ Date of birth
✓ Place of birth
✓ Sex
✓ Disease/Diagnosis
✓ Provincial Health Number (if required for data linkage based on registry needs)

It should be noted that the above elements incorporate the participant's full legal name, date of birth and place of birth as the sole "unique" identifier for a registry participant. Provincial health numbers are not considered a unique identifier as they change from province to province if a registry participant moves. This is important for multi-jurisdictional registries to avoid having a patient who moves provinces registered twice.

Gender, date of birth, and provincial health number will be required if the registry desires linkage with administrative data. For registries with the sole purpose of linking to administrative data it may not be possible to ethically justify the collection of the legal name.

The project team also recommended that registries examine relevant core data elements as previously identified from international and other applicable groups. It is recommended that registries be willing to share case report forms to enhance the ability to collaborate with new and existing registries.

Finally, it is recommended that registries designing case report forms consider validated sources of questions available in Canada such as the Canadian Community Health Survey (CCHS) and other Statistics Canada surveys.

Appendix A - Literature Search Strategy

MEDLINE
Cochrane CENTRAL Register of Controlled Trials
Cochrane Database of Systematic Reviews

1. exp *Registries/
2. ((patient or patients or disease* or population surveillance) adj5 (registry or registries or register or registers)).tw.
3. 1 or 2
4. exp Population Surveillance/mt [Methods]
5. Data Collection/lj, mt, og, st [Legislation & Jurisprudence, Methods, Organization & Administration, Standards]
6. models, theoretical/ or models, organizational/
7. "organization and administration"/ or exp governing board/ or knowledge management/ or mandatory programs/ or organizational objectives/ or planning techniques/ or program development/ or public health administration/ or total quality management/ or voluntary programs/
8. Accreditation/
9. "Forms and Records Control"/
10. Benchmarking/
11. (barrier* or best practice* or creating or creation or design* or develop or developing or development or establish* or evolving or evolution or facilitator* or guidelines or implementing or implementation or infrastructure* or lessons learned or maintenance or maintain* or methodology or model or models or quality or standards or trends).tw.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 3 and 12
14. exp *Registries/mt, og, st [Methods, Organization & Administration, Standards]
15. 13 or 14
16. limit 15 to English
17. limit 16 to animals
18. limit 16 to (animals or humans)
19. 17 not 18
20. 16 not 19
21. limit 20 to (comment or editorial or letter)
22. 20 not 21
23. exp *Tissue Donors/ or exp *"Tissue and Organ Procurement"/
24. ((organ or organs or tissue*) adj5 (donor* or donat*)).tw.
25. education.fs.
26. exp "substance-related disorders"/
27. exp "drug and narcotic control"/
28. exp street drugs/
29. ((drug or drugs or pharmaceutical*) adj5 (registry or registries or register or registers)).tw.
30. exp vital statistics/
31. ((marriage or birth or death) adj5 (registry or registries or register*)).tw.
32. exp *vaccination/ or exp *immunization/
33. (immunisation* or immunization* or vaccination* or vaccine*).ti.
34. (cochrane adj5 register).tw.
35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. 22 not 35

PubMED

1. Registries[Majr]
2. ((patient or patients or disease* or population surveillance) AND (registry or registries or register or registers))[tiab]

3. 1 or 2

4. Population Surveillance/mt [Methods][MeSH]

5. Data Collection/lj, mt, og, st [Legislation & Jurisprudence, Methods, Organization & Administration, Standards][MeSH]

6. models, theoretica[MeSH] or models, organizational[MeSH]

7.("organization and administration" or governing board or knowledge management or mandatory programs or organizational objectives or planning techniques or program development or public health administration or total quality management or voluntary programs)[MeSH]

8. Accreditation[MeSH]

9. "Forms and Records Control"[MeSH]

10. Benchmarking[MeSH]

11. (barrier* or best practice* or creating or creation or design* or develop or developing or development or establish* or evolving or evolution or facilitator* or guidelines or implementing or implementation or infrastructure* or lessons learned or maintenance or maintain* or methodology or model or models or quality or standards or trends)[tiab]

12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

13. 3 and 12

14. Registries/mt, og, st [Methods, Organization & Administration, Standards][Majr]

15. 13 or 14

16. limit 15 to English

17. limit 16 to animals

18. limit 16 to (animals or humans)

19. 17 not 18

20. 16 not 19

21. limit 20 to (comment or editorial or letter)

22. 20 not 21

23. Tissue Donors[Majr] or "Tissue and Organ Procurement"[Majr]

24. ((organ or organs or tissue*) and (donor* or donat*))[tiab]

25. education[fs]

26. "substance-related disorders"[MeSH]

27. "drug and narcotic control"[MeSH]

28. street drugs[MeSH]

29. ((drug or drugs or pharmaceutical*) and (registry or registries or register or registers))[tiab]

30. vital statistics[MeSH]

31. ((marriage or birth or death) and (registry or registries or register*))[tiab]

32. vaccination[Majr] or immunization[Majr]

33. (immunisation* or immunization* or vaccination* or vaccine*)[ti]

34. (cochrane register)[tiab]

35. 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36. 22 not 35

EMBASE

1. *register/

2. ((patient or patients or disease* or population surveillance) adj5 (registry or registries or register or registers)).tw.

3. 1 or 2

4. *model/ or *process model/

5. *"organization and management"/

6. *management/ or *total quality management/

7. *planning/ or *strategic planning/

8. *organization/

9. methodology/ or *quality control/ or standard/

10. data collection method/

11. *quality control/

12. *"board of trustees"/

13. *knowledge management/

14. *program development/

15. *planning/

16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 3 and 16
18. ((barrier* or best practice* or creating or creation or design* or develop or developing or development or establish* or evolving or evolution or facilitator* or guidelines or implementing or implementation or infrastructure* or lessons learned or maintenance or maintain* or methodology or model or models or quality or standards or trends) adj5 (registry or register or registers or registries) adj5 (patient or patients or disease* or surveillance)).tw.
19. 17 or 18
20. limit 19 to English language
21. limit 20 to animal studies
22. 20 not 21
23. limit 22 to (conference abstract or "conference review" or editorial or letter or note or proceeding or report or trade journal)
24. 22 not 23
25. exp *donor/
26. exp *transplantation/
27. ((organ or organs or tissue*) adj5 (donor* or donat*)).tw.
28. exp *drug dependence/ or exp *drug abuse/ or exp *substance abuse/ or exp *alcoholism/ or exp *addiction/
29. exp *drug control/
30. ((drug or drugs or pharmaceutical*) adj5 (registry or registries or register or registers)).tw.
31. exp *birth certificate/
32. exp *death certificate/
33. exp *"cause of death"/ or exp *marriage/
34. exp *vital statistics/
35. ((marriage or birth or death) adj5 (registry or registries or register*)).tw.
36. exp *vaccination/
37. exp *immunization/
38. (immunisation* or immunization* or vaccination* or vaccine*).tw.
39. (cochrane adj5 register).tw.
40. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 24 not 40

PsycINFO

1. ((barrier* or best practice* or creating or creation or design* or develop or developing or development or establish* or evolving or evolution or facilitator* or guidelines or implementing or implementation or infrastructure* or lessons learned or maintenance or maintain* or methodology or model or models or quality or standards or trends) adj5 ((patient or patients or disease* or population surveillance) adj5 (registry or registries or register or registers))).tw.
2. ((organ or organs or tissue*) adj5 (donor* or donat*)).tw.
3. ((drug or drugs or pharmaceutical*) adj5 (registry or registries or register or registers)).tw.
4. ((marriage or birth or death or vital statistics) adj5 (registry or registries or register*)).tw.
5. (immunisation* or immunization* or vaccination* or vaccine*).ti.
6. (cochrane adj5 register*).tw.
7. 2 or 3 or 4 or 5 or 6
8. 1 not 7
9. limit 8 to English language
10. limit 9 to (abstract collection or chapter or "column/opinion" or "comment/reply" or dissertation or editorial or letter or review-book or review-media or review-software & other)
11. 9 not 10

ABI Inform
BIOSIS Previews
PAIS (Public Affairs Information Service)

1. ((patient or patients or disease* or population surveillance) and (registry or registries or register or registers))[Keyword]

2. (barrier* or best practice* or creating or creation or design* or develop or developing or development or establish* or evolving or evolution or facilitator* or guidelines or implementing or implementation or infrastructure* or lessons learned or maintenance or maintain* or methodology or model or models or quality or standards or trends)[Keyword]
3. 1 and 2
4. ((organ or organs or tissue*) and (donor* or donat*))[Keyword]
5. ((drug or drugs or pharmaceutical*) and (registry or registries or register or registers))[Keyword]
6. ((marriage or birth or death) and (registry or registries or register*))[Keyword]
7. (immunisation* or immunization* or vaccination* or vaccine*)[Keyword]
8. (cochrane register)[Keyword]
9. 4 or 5 or 6 or 7 or 8
10. 3 and 9

Appendix B - Glossary

Aboriginal – a term used to refer collectively to all First Nations, Métis, and Inuit peoples in Canada.

Biobank/biobanking – the collection of biological samples including but not limited to blood, tissue, skin, nails, and hair in a centralized repository. This may or may not include information about the individuals who provided the samples.

Capacity – with respect to the provision of informed consent, capacity is the individual capability to understand information presented and to understand the potential consequences of any decision made based on such information. .

Clinical Trial Registry – a clinical trial registry is typically a registry created during a clinical trial. Clinical trial registries may include device or treatment registries and may be run by investigators or by for-profit entities.

Informed Consent – in Canada this is consent provided by an individual participating in research in a manner that is voluntary and given after the individual has been made fully aware of the nature of the research and the possible risks and benefits of participation. Informed consent must also be ongoing and able to be withdrawn at any time.

Intellectual property (IP) – the basic legal right conferred by patents, trademarks, copyright and other similar concepts which allows the owner of such property to exclude others from using that property without permission. Typically the property is derived from some form of creative pursuit and thus is referred to as intellectual.

Research ethics board (REB) – an appointed institutional body consisting of researchers, community members and other experts (e.g. legal, ethics, medical) which reviews the ethical acceptability of all research activities conducted at the institution or under its jurisdiction.

Standard operating procedure (SOP) – a prescribed procedure that is followed every time a task occurs.

Substitute decision maker – a person with the necessary legal authority to make decisions on behalf of an individual who lacks the capacity to consent to participate or to continue to participate in a particular research project

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NOTES
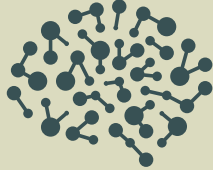
Canadian Registry Network
Réseau canadien de registres

The Canadian Registry Network consists of 9 registries which seek to share science and connect researchers everywhere. By working together on projects, the Canadian Registry Network specifically aims to improve the design, quality and impact of registries. The first project on which the Canadian Registry Network collaborated is the Neurological Registries Best Practice Guidelines and Implementation Toolkit project.

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Correspondence: Lawrence Korngut
Department of Clinical Neurosciences
University of Calgary
Email: lawrence.korngut@albertahealthservices.ca