Canada's Drug Agency
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Drugs Health Technologies **Health Systems**

Methods and Guidelines

Best Practices and Standards to Enhance the Quality of Rare Disease Registries in Canada

Key Messages

Why Are We Doing This Work? Why Is This Important?

In 2023, the federal government announced up to $1.5 billion over 3 years to support the National Strategy for Drugs for Rare Diseases to improve the affordability of, and access to, drugs for rare diseases. While prospectively planned randomized controlled trials (RCTs) are the most robust study design for estimating the causal effects of interventions, the conduct of RCTs is not always feasible because of low disease prevalence and/or a limited number of patients, a lack of other treatment options, or populations for which it is not ethical to conduct RCTS, such as children or other vulnerable populations.

A key component of the 2022–2025 Canada's Drug Agency (CDA-AMC) Strategic Plan is to advance innovative approaches to evidence generation to inform decision-making, which is consistent with a pillar of the Drugs for Rare Diseases Strategy. Rare disease registries (RDRs) represent an additional data source that may produce real-world evidence (RWE) to address evidentiary uncertainties and provide additional context outside traditional clinical trials to inform health care decision-making related to drugs for rare diseases. As of June 2024, 66 RDRs in Canada and 82 international RDRs that include patients living in Canada have been identified in an inventory of RDRs published by CDA-AMC. There is a need to understand differences in scope and quality when assessing RDRs and their potential to inform the evidence needs of regulatory and health technology assessment (HTA) agencies.

This guidance presents a set of recommended best practices and standards for RDRs in Canada that align with international recommendations and were developed through a consensus-building approach including representatives of RDRs in Canada, patient groups, data holders, HTA agencies, industry, and academia. This guidance establishes a set of recommended best practices and standards to enhance the transparency, content, and quality of RDRs to increase confidence in RDRs as real-world data sources that can help inform decision-making.

What Did We Do?

This guidance was developed through a scoping review of previously published international recommendations for improving the quality of RDRs and a modified panel process in collaboration with 23 representatives of RDRs, patient groups, data holders, HTA representatives, industry, and academia. Best practices and standards had to have been rated by

Key Messages

the panel as both important and feasible to implement in Canada to be included in the guidance.

What Did We Find?

The scoping review of previously published guidance identified 109 potential best practices and standards, which were categorized into the 3 domains — governance, data, and information technology infrastructure. A Delphi panel review identified 52 best practices and standards that were deemed both important and feasible to implement, including 33 governance elements, 13 data elements, and 6 information technology infrastructure elements.

What Does This Mean?

This guidance, developed in collaboration with multiple partners and in alignment with international recommendations, establishes recommended best practices and standards tailored specifically for RDRs in Canada. While this guidance provides best practices and standards to support the enhancement of RDR quality, meeting all best practices and standards does not guarantee that a registry is suitable to inform regulatory, HTA, or payer decision-making. Moreover, the recommended best practices and standards serve as a guide to improve the architecture and quality of RDRs, and it is not mandatory for an RDR to meet all 52 elements to be considered suitable for informing specific decision-making needs. The suitability of a registry to address specific decision-making needs depends on multiple factors, including its relevance, timeliness, and alignment with specific evidence needs. By focusing on best practices and standards deemed both important and feasible within the Canadian context, we aim to provide a framework that strengthens the capacity of RDRs to contribute meaningfully to health care decision-making. This document may be periodically updated or added to as the generation of RWE from RDRs evolves over time.

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Abbreviations

CDA-AMC	Canada’s Drug Agency
HTA	health technology assessment
RCT	randomized controlled trial
RDR	rare disease registry
REQueST	Registry Evaluation and Quality Standards Tool
RWE	real-world evidence

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This guidance was developed through a collaborative effort, including representatives of patient organizations, data holders, HTA organizations, industry, and academics.

This work was led by Dr. Jean-Eric Tarride and Dr. Alfonso Iorio from the Department of Health Research Methods, Evidence, and Impact at McMaster University, with their team, and in collaboration with CDA-AMC. The McMaster team led the development of the guidance, which involved 23 experts, including 12 representatives from rare disease registries and 11 representatives of patient groups, data holders, HTA representatives, industry, and academics.

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Background and Rationale
There are between 6,000 and 8,000 rare diseases worldwide, each affecting a small number of individuals.[1] In Canada[2] and Europe,[3] rare diseases are defined as diseases or conditions that affect fewer than 1 in 2,000 people. In the US, a rare disease is one that affects fewer than 200,000 people.[4] Depending on the definition, it is estimated that between 1 and 3 million people in Canada,[1,2] two-third of whom are children,[2] live with a rare disease. Despite the chronic, debilitating, and potentially life-threatening nature of many rare diseases, treatments are often unavailable.[1] In 2023, to enhance patient access to drugs for rare diseases in Canada, Health Canada announced an investment of up to $1.5 billion over 3 years to support the National Strategy for Drugs for Rare Diseases.[1] One of the objectives of this strategy is to improve the collection and use of evidence to support decision-making.[1,5]

High-quality prospectively planned RCTs continue to be the most rigorous design to generate safety and efficacy data to assess the causal effects of drugs. In the context of rare diseases, the conduct of RCTs is not always feasible or ethical due to the lower prevalence of disease and small number of pediatric or adult patients, limited or no treatment comparators, high heterogeneity in disease symptoms and severity, and variability in disease progression.[6-9] Even when RCTs are available, their generalizability may be limited as they do not provide evidence of effectiveness and harms in routine settings. These evidence uncertainties impact decision-making, which can result in suboptimal access to new and emerging therapies or technologies. RWE can provide complementary and supplementary evidence on the use, safety, effectiveness, and cost of drugs from a variety of real-world data sources, such as electronic medical records and administrative databases.[10]

RDRs are an additional source of real-world data that may address evidence uncertainties and provide evidence to complement traditional clinical trials to inform health care decision-making. Registries are organized systems that use observational methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition, and can serve 1 or more stated scientific,

clinical, or policy purposes.[8] However, RDRs are diverse as they collect a wide range of data from patients with different diseases and are at varying levels of maturity in their development and operations. This presents challenges for regulatory and HTA agencies when assessing the quality of data and the subsequent evidence produced from RDRs.[9,11-13]

Many recommendations and guidelines have been developed to improve the architecture and quality of data from registries.[9,12,14-21] For regulatory and HTA purposes, the European Network for Health Technology Assessment (EUnetHTA) released 23 criteria in the Registry Evaluation and Quality Standards Tool (REQueST) in 2019.[12,22] This tool was piloted in 25 RDRs in Canada[23] based on publicly available information and confirmed that RDRs collect data that could be used for decision-making. However, there was considerable variability across RDRs in Canada in several domains of REQueST, highlighting the need for a shared set of best practices and standards for RDRs in Canada.[23]

Based on recommendations and guidance consolidated from previous international work,[19] we developed this guidance to support the National Strategy for Drugs for Rare Diseases.[1] This guidance presents a set of recommended best practices and standards that are specific to RDRs in the Canadian context and were deemed both important and feasible by representatives of RDRs, patient groups, data holders, HTA agencies, industry, and academia. This guidance will support regulatory and HTA agencies to understand the quality of RDRs and help establish the trust that RDRs can help inform regulatory, HTA, and other health care decision-making needs. Meeting all best practices and standards does not guarantee that an RDR is suitable to inform decision-making needs as the suitability of a registry to address specific needs depends on multiple factors, including its relevance to address specific evidence gaps and ability to generate and report decision-grade data in a timely manner. Moreover, the recommended best practices and standards serve as a guide for registry holders, and it is not mandatory for an RDR to meet all of the elements to be considered for addressing specific evidence needs.

Purpose and Main Objectives

The overall purpose of this guidance is to present a set of recommended best practices and standards for RDRs in Canada to enhance their quality to be better positioned to produce decision-grade evidence to inform regulatory, HTA, and payer decision-making in Canada, in order to support access to effective treatments for patients in Canada living with rare diseases.

The main objectives of this guidance are to provide a set of best practices and standards for RDRs in Canada that are:

- important and feasible to implement in Canada
- developed through a consensus-building approach that involved representatives of RDRs in Canada, patient groups, data holders, HTA agencies, industry, and academia
- aligned with international best practices and standards to improve the quality of RDRs.

About This Guidance

When developing this guidance, it was crucial to consider that RDRs serve small, diverse populations with limited resources, which may impact their readiness to implement best practices and standards. Therefore, it was critical that the best practices and standards included in this guidance were deemed both important (i.e., their absence would make it challenging to assess an RDR for decision-making) and feasible (i.e., there were no perceived barriers to implementing them in the Canadian context) by RDRs and multiple partners.

The recommendations of this guidance are not intended to be one-size-fits-all; rather, they are meant to assist RDRs in Canada in identifying and implementing best practices and standards to improve the quality of RDRs. This guidance is also meant to assist regulatory and HTA agencies in Canada in determining whether RDRs can be valid data sources to inform regulatory and HTA evidence needs and decisions. This guidance was not developed to be used for accrediting or scoring RDRs and is not meant to replace the recent CDA-AMC Guidance on Reporting Real-World Evidence[10] as these 2 documents should be viewed as complementary. The guidance applies to "1 registry per rare disease or condition." The guidance may be applied separately for each rare disease or condition in multidisease RDRs. This guidance is not intended to be a step-by-step guide to design an RDR or a guide to design registry-based studies. This guidance is a framework for identifying recommended best practices and standards to improve the quality of RDRs that were deemed important and feasible to implement in the Canadian context, overall aligned with international recommendations, and can support decision-makers to understand the quality of RDRs.

This guidance will remain a living document that may require periodic updates or extensions as lessons are learned through the implementation of these guidelines. For example, additional best practices and standards may be adopted in the future if the current barriers to their implementation are overcome (e.g., new funding to support a particular activity).

Methods

This work was led by Dr. Jean-Eric Tarride and Dr. Alfonso Iorio from the Department of Health Research Methods, Evidence, and Impact at McMaster University, with their team, and in collaboration with CDA-AMC. The McMaster team led the development of the guidance, which involved 23 experts (12 representatives from RDRs and 11 representatives of patient groups, data holders, HTA representatives, industry, and academics) using a modified Delphi panel methodology. This methodology is commonly used as a reliable means of determining consensus for a defined problem and has been recently applied in the context of RDRs and in the CDA-AMC Guidance on Reporting Real-World Evidence.[10,24-26] A schematic of the methods is presented in Appendix 1, while the details of the methods are presented in Appendix 2. A brief summary of the methods is given in this section.

The process of identifying recommended best practices and standards to improve the quality of RDRs in Canada included 3 iterative steps. The first step was a scoping review[19] of existing recommendations and guidance for improving the quality of RDRs published between 2010 and April 2023, from which 64 documents were reviewed. Aligned with the international literature and the framework developed by Ali

et al. (2021),[15,16,19,20,27] the findings were mapped into 3 domains (i.e., governance, data, and information technology infrastructure) and corresponding subdomains.[19] Based on the results of the scoping review, a list of 109 potential best practices and standards to improve the quality of RDRs were included in a survey for voting and commenting by an expert panel.

In the second step, the survey was shared with an expert panel comprised of representatives of RDRs (N = 12), patient groups (N = 2), HTA agencies (N = 3), data holders (N = 2), industry (N = 2), and academia (N = 2). As aligned with the methodology applied during the development of the CDA-AMC Guidance on Reporting Real-World Evidence,[10] a threshold of 70% was used for inclusion or exclusion. To be included in the guidance, at least 70% of the expert panel had to agree that the item was both important (i.e., the item's absence would make it challenging to assess an RDR for decision-making) and feasible to implement in Canada (i.e., there were no perceived barriers to the implementation of this item). Items deemed not important by at least 70% of panellists were excluded.

The survey results were shared with the panellists before a virtual meeting organized to discuss the survey results (which took place on May 7, 2024). Items that did not reach consensus (i.e., scores greater than 30% and lower than 70%) were discussed during the online meeting. Additionally, items that did reach consensus for inclusion, but for which there were differences in the importance and feasibility scores between RDR and non-RDR members of the panel, were also discussed. Following the discussion, the panellists voted again for final inclusion on each of the items raised for discussion. Items that did not reach at least a 70% agreement for inclusion were excluded from the final list of best practices and standards. The experts also had the opportunity, before or during the meeting, to flag items that required further clarification.

In the last step, the guidance was drafted and shared with the expert panel for their review and feedback. Comments were collated by the authorship team and a revised version of the guidance document was shared with the panellists for final review.

Overview and Structure

The guidance is organized into 3 main domains and several subdomains of recommended best practices and standards to enhance the quality of RDRs.[19] Each section presents a brief overview related to a particular domain or subdomain before listing the recommended best practices and standards that reached consensus for inclusion in terms of importance and feasibility of implementation. Appendix 3 presents the list of the 52 recommended best practices and standards that reached consensus in a tabular form, while Appendix 4 presents the list of the 57 items that were not included in this guidance (i.e., those that were deemed important but not feasible to implement in Canada).

Best practices and standards are presented for the following domains and subdomains.

1. Governance (33 best practices and standards)
    1.1. RDR purpose and description
    1.2. Population

Section 1: Governance Best Practices and Standards

Governance broadly refers to the formalized processes, structures, and systems that guide RDR leadership's high-level decision-making, strategic planning, and oversight.[8,11,14] Governance is organized around 8 elements, including the RDR purpose and description; population; governance structure; sustainability and funding; ethics, legal, privacy; data governance, documentation; and training.[19]

1.1. RDR Purpose and Description

A comprehensive description of the RDR's purpose, objectives,[8,11,14] and key characteristics[12,14,16,28] allows potential partners to recognize the possible utility of evidence generated from RDR data to support decision-making. As terminology and other descriptors can vary for different RDRs, the RDR should define and describe terms as appropriate (e.g., if national coverage is defined as an RDR being implemented in several provinces versus "all" provinces and territories in Canada).

1. The registry's primary purpose and objectives are described.
2. The registry time frame is documented (i.e., when was the registry created, is it ongoing, and the final data collection date, if applicable).
3. The registry design and/or methodology is described (e.g., retrospective, prospective).
4. Geographical coverage is described (e.g., local, regional, provincial, national, international).
5. The organizational settings from which the registry providers and patients are recruited are described (e.g., community, specialized clinics, hospitals).

6. Each data source is described (e.g., physician assessment records, patient-reported data, laboratory).
7. Current linkages to other data sources are reported.
8. Documentation of key RDR characteristics is available upon request.

1.2. Population

Understanding the specific composition of an RDR population is critical to understanding the relevance of the data to address research questions.[12,14,16,22,28-30]

1. Predefined inclusion and exclusion criteria are specified for patient entry into the registry.
2. The case definition of the rare disease captured in the RDR is documented.
3. The diagnostic method(s) for the rare disease captured in the registry are documented.
4. The current number of patients in the RDR is documented.
5. The current number of sites recruiting patients is documented.
6. For international RDRs, the number of countries participating in the RDR and the number of patients per country are documented.

1.3. Governance Structure

The governance structure of an RDR[11,15,28,30-35] and its decision-making process[16] should be documented. For transparency, all parties engaged with the RDR need to declare any potential conflicts of interest.[12,28,36] In alignment with CDA-AMC policy, a timeline of 2 years to declare conflicts of interest when submitting RDR data to regulatory or HTA agencies in Canada is encouraged.

1. An organizational chart describing the roles and responsibilities of each party involved in the registry is available upon request.
2. The registry has a named lead, and current contact information is documented and available.
3. The registry governance includes a board of directors and/or steering committee that provides oversight of all registry activities.
4. The frequency of meetings with members of the governance structure (e.g., board of directors, steering committee, advisory board) is documented.
5. The declarations of conflicts of interests (e.g., financial, academic) for all parties involved in the registry, including for members of the governance structure (board of directors, steering committee, advisory board) and registry funders are documented using a standard process.
6. The decision-making governance structure and related processes for both internal registry activities and collaboration with external parties are documented.

1.4. Sustainability and Funding

The long-term sustainability of RDRs is dependent on funding, which might include multiple funding sources (e.g., public or private organizations, public-private partnerships, nonprofit foundations, patient groups, professional societies).[14,28,37,38] Full disclosure of all funding sources will ensure transparency.[12,16,17] A time

frame of 2 years for disclosing funding sources has been previously proposed[12,22] and has been adopted in this guidance.

1. All funding sources over the past 2 years are disclosed.

1.5. Ethics, Legal, Privacy

All activities of the RDR must comply with the appropriate regulations.[14,28,29,32,39-41] This includes documenting ethics approval, data collection and consent processes (including assent for pediatric populations), data security controls, and patient recruitment.[8,12,14,16,17,30,42,43]

1. The registry's compliance with relevant (i.e., international, national, regional, and local) ethical, legal, and privacy requirements is documented.
2. Ethics approvals are documented.
3. The consent process for patient contact, data collection, data storage, and data use and reuse is described.
4. Data security controls are specified on the patient consent form.
5. The patient recruitment process, including incentives to encourage participation, is documented.

1.6. Data Governance

RDRs are often data custodians and, as such, are responsible for managing and monitoring data usage, data access policies, and data sharing agreements.[11,14,16,33,43,44] An integral part of this responsibility is transparency regarding data ownership and use of data by external parties.[8,11,29,33,36,44] Special consideration should be taken for research involving First Nations,[45] Inuit, and Métis populations.

1. The data ownership rights are documented, including who owns the data, who owns the registry, and who is the registry data custodian.
2. The policies for the use or disclosure of data to external parties for academic or research purposes or nonresearch purposes (e.g., regulatory, HTA agencies, payer, industry) are documented.

1.7. Documentation

Proper documentation facilitates a shared understanding, transparency, and consistency for RDR processes, procedures, and activities.[9,14-16,34,35,39] To ensure timeliness and relevance, key documents (e.g., standard operating procedure manual, data dictionary) are updated as needed.[8] The REQueST (tool) suggests that the status of documents should be checked with the registry if the documentation is more than 5 years old.[12,22]

1. A manual on the RDR's standard operating procedures is available.
2. The RDR has standardized consent forms and participation information sheets that describe the extent of patient contact, data collection, data storage, and data use and reuse.
3. Protocols for RDR-based or industry-funded studies are published or available on request.
4. Key documents are updated as needed and dated.

1.8. Training

Training relevant to the specific RDR is essential for RDR staff and data providers to ensure consistency and quality across governance, data, and information technology infrastructure domains.[14-16]

1. All RDR staff and data providers receive training on RDR procedures.

Section 2: Data Best Practices and Standards

Data broadly refers to the structures, policies, and processes required to ensure RDRs can maintain high-quality data.[14] Assurance that the data are fit-for-purpose to produce reliable, relevant, timely, and replicable evidence is required to support regulatory, HTA, and payer assessments.[8,14,16,21,27,46]

Best practices and standards around data are organized around 6 elements, including health-related interventions, the data dictionary, common data elements, data collection, data quality and assurance, and data analysis and reporting.

2.1. Health-Related Interventions

Information on health-related interventions is needed to support the life cycle assessment of therapies and health technologies and should be documented if health-related interventions are captured in an RDR.[12,14]

1. If health-related interventions (e.g., medication, surgery) are captured in the database, they are documented.
2. For each health-related intervention captured in the registry, the source of the information is documented (e.g., patient recall, clinical report, electronic medical records).

2.2. Data Dictionary

An up-to-date data dictionary is invaluable for the maintenance of a quality RDR.[8,10,12,20,28,37,42,47]

1. A data dictionary that defines all data elements, permissible values, representation classes, data types, formats, if data elements are mandatory versus optional, and which data elements are collected at baseline compared to follow-up is available.
2. Any relevant changes to the registry content (e.g., variables, coding) over time are documented, including dates and specific changes.

2.3. Common Data Elements

Although reaching a consensus on a core group or minimum set of common data elements can be challenging,[48] common data elements collected across all contributing sites of an RDR facilitate harmonization.[11,17,43,49,50]

1. Common data elements (i.e., a core group of data elements or minimum dataset collected across all centres that contribute to the registry) are used.

2.4. Data Collection

Standardized data collection processes support the collection of high-quality data.[14,28] Information on the data collection tools[8,51-54] and type of data being collected at baseline and over time[9,12,16,54] are documented.

1. Standardized data collection guidelines (e.g., processes and pathways) are used.
2. Standardized data collection forms (paper or computer based) are used.
3. Data collection tools to enter the data are documented (e.g., web-based platform, direct import from electronic medical records, smartphone, manual data entry).
4. The data collected at baseline and during follow-up visits (e.g., demographics, clinical data, biological specimens, health care resource utilization, patient-reported outcome measures) are documented.
5. The follow-up methods and frequency are documented (e.g., at regular intervals, ad hoc, or both, when patients come to the clinic).

2.5. Data Quality and Assurance

Data quality and assurance plans reflect the various dimensions of data quality.[14,28,46] At a minimum, the methods used to avoid duplication and the percentage of patients lost to follow-up must be documented to support data quality efforts.[28,29]

1. Methods to avoid duplication of registered cases are documented.
2. The percentage of patients lost to follow-up is documented.

2.6. Data Analysis and Reporting

A statistical analysis plan for each RDR-based study supports the transparency of methods and results.[8,14]

1. Statistical analysis plans are in place for each registry-based study.

Section 3: Information Technology Infrastructure Best Practices and Standards

Information technology infrastructure refers to the critical technology infrastructure required to collect, share, link, and use patient and clinical data,[11,41,52] as well as to securely store, transmit, and manage patients' personal health information in the virtual space.[39,41,55]

3.1. Physical-Virtual Infrastructure

RDRs have a fundamental responsibility to ensure that their digitally stored data are safe and secure.[15,28,41,56-59] Procedures are in place to give users access to data,[15] to transfer and receive data,[14,60] and to erase or release personal data when requested.[15,61,62]

1. Data security protocols are in place and documented (e.g., encryption, firewall).
2. Data breach procedures are in place and documented.

3. The RDR's policies outlining the ability of the RDR to transfer data to and from external parties are documented.
4. Procedures to grant authorized users access to RDR data are in place and documented.
5. The registry has clear procedures to erase personal data when requested.
6. The registry has a policy on releasing data to registry participants on request.

Forward-Looking Statement and Conclusion

This guidance describes a set of recommended best practices and standards to enhance the quality of RDRs in Canada. Based on recommendations and standards synthesized from prior international work,[19] this guidance includes best practices and standards that were deemed important and feasible to implement for RDRs in Canada, in partnership with representatives of RDRs, patient groups, HTA agencies, data holders, and other health system partners. This guidance will help RDR holders identify a set of recommended best practices and standards to improve the quality of registries and will also support regulatory and HTA bodies to understand the quality of RDRs and whether RDRs can serve as credible sources of real-world data to inform regulatory, HTA, and payer decision-making in Canada.

This guidance is overall consistent with the European Medicines Agency checklist[16] for evaluating the suitability of registries for registry-based studies and the FDA guidance[20] on using registry data to support regulatory decision-making. The European Medicines Agency checklist[16] and FDA guidance[20] present additional guidance specific to registry-based studies. For instance, the FDA guidance[20] includes recommendations on completeness, traceability, and timing of data collection. Compared to the international literature, some recommendations were not implemented in this guidance as several items were rated important but not feasible to implement in the Canadian context. For example, this guidance does not include best practices and standards regarding processes for data quality assurance plans, auditing, or reporting on representativeness. Future initiatives are needed to understand the barriers and facilitators to make important items more feasible for RDRs in Canada.

This guidance will be implemented and operationalized with consideration of the scope and quality of different RDRs, while also addressing the evidence needs of decision-makers. RDRs have varying resources that may impact their readiness to implement best practices and standards. By including best practices and standards that were deemed both important and feasible to implement in the Canadian context by multiple RDRs and health systems partners, this guidance aims to increase the number of RDRs that meet these best practices and standards. While this guidance is designed to support the enhancement of RDR quality, meeting these best practices and standards does not guarantee that a registry is suitable for regulatory, HTA, or payer decision-making. Moreover, the recommended best practices and standards serve as a guide for registry holders, and it is not mandatory for an RDR to meet all 52 elements to be considered a credible real-world data source to inform specific decision-making needs.

This document may be updated or expanded over time to reflect learnings from the implementation of this guidance. For instance, best practices and standards that were rated as important, but not feasible in the

existing Canadian context, may need to be added if current barriers to their implementation are addressed (e.g., funding to support specific activities). This flexibility will ensure that RDRs can successfully develop and maintain the quality, consistency, and transparency required for regulatory and HTA decision-making while also recognizing the challenges and opportunities for implementation by RDRs.

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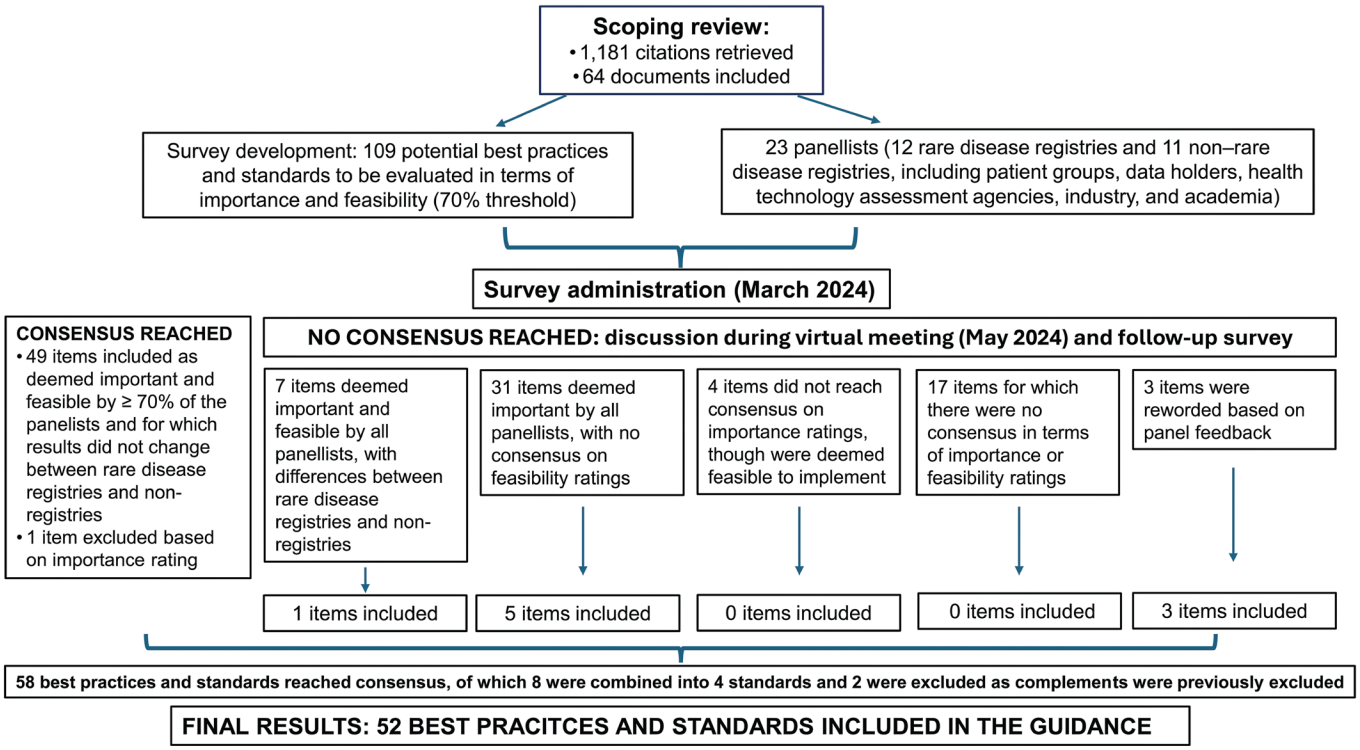
Appendix 1: Methods Schematic

Figure 1: Methods Schematic for the Identification of Best Practices and Standards



Appendix 2: Detailed Methods and Results Overview

This guidance was developed in 3 steps. In step 1, a list of potential best practices and standards were consolidated through a scoping review of international recommendations and guidance for improving the quality of RDRs.[19] Step 2 involved using a modified Delphi process to identify best practices and standards that were deemed both important and feasible to implement in Canada by representatives of RDRs, patient groups, HTA agencies, data holders, and other health system partners. Step 3 involved a consultation process with health system partners to finalize the guidance.

Step 1: Development of a List of Potential Best Practices and Standards to Improve the Quality of RDRs in Canada

A scoping review[19] of international guidelines and studies that included recommendations for improving the quality of RDRs published between 2010 and April 2023 was conducted through a systematic search of the MEDLINE and Embase databases and the websites of regulatory bodies and HTA agencies. The search strategy was developed by a CDA-AMC research information specialist and included terms such as RDR, quality, guidance, recommendations, and standards. The base year 2010 was selected to align with the publication of the guidance on RDRs by the European Rare Disease Task Force (*Patient Registries In The Field Of Rare Diseases: Overview Of The Issues Surrounding The Establishment, Management, Governance And Financing Of Academic Registries*) initially published in 2009 and updated in 2011.[63] Guidance cited in the RDR literature that was not specific to RDRs was also reviewed, including the *European Medicines Agency Guideline On Registry-Based Studies*[16] and REQueST.[19] Of the 1,135 unique sources identified through the search strategy, 93 were assessed for eligibility based on a full-text review and 47 were included for data abstraction. In addition, 35 documents were identified through a grey literature search, of which 18 were assessed for eligibility based on full-text review and 6 were included for data abstraction. An additional 11 documents were identified by scanning the references cited in the included papers. In total, 64 documents were included in the review (refer to Appendix 5 for a full list). Based on the framework developed by Ali et al. in 2021 (*The Quality Evaluation of Rare Disease Registries—An Assessment of the Essential Features of a Disease Registry*),[15] the recommendations and guidance for improving the quality of RDRs cited in the literature were mapped according to 3 domains (i.e., governance, data, and information technology infrastructure) and several subdomains (9 for governance, 7 for data, and 2 for information technology infrastructure).[19] Based on the results of the scoping review, a list of 109 potential best practices and standards was established through an interactive process in which the authorship team reviewed each potential best practice and standard identified through the scoping review to ensure clarity and avoid duplication.

Step 2: Modified Delphi Process

Composition of the Delphi Panel

A diverse group of experts and data users, including representatives of RDRs in Canada, patient groups, data holders (i.e., the Canadian Institute for Health Information, IQVIA, Statistics Canada), HTA agencies,

industry, RWE experts in Canada, and international RWE experts were invited to participate in the Delphi panel. Out of 36 invitations sent, 23 panellists agreed to participate in the Delphi panel process, including representatives of RDRs (N = 12), patient groups (N = 2), data holders (N = 2), HTA agencies (N = 3), industry (N = 2), and academia (N = 2).

Survey Development

The 109 potential best practices and standards were programmed into an online survey using the Qualtrics Online Survey program (Qualtrics, Provo, UT) with 2 questions per potential best practice and standard. The first question was to determine if a potential best practice and standard was "important" using a scale from 1 to 4 where 1 indicated "unimportant," 2 indicated "somewhat unimportant," 3 indicated "somewhat important," and 4 indicated "very important." Best practices and standards were defined as important if their absence would make assessing an RDR for decision-making challenging.

Recognizing that RDRs are diverse, characterized by small populations, often with limited resources, and at different development levels, a second question was included to determine whether implementation of the potential best practice and standard would be "feasible" (i.e., if there would be barriers to implementation in Canada). In the affirmative, participants were asked to provide details about the barriers. Participants could also provide other feedback in the comment box. Comments were not mandatory.

The online survey was piloted with the authorship team members as well as with 2 representatives from CDA-AMC who were familiar with RDRs but not directly involved in this research or its design, and 2 PhD students who were not involved in the project. Comments and/or feedback were addressed by the authorship team before the survey was piloted a second time for final feedback before administration.

Survey Administration and Analyses

The survey was circulated to the 23 expert panellists on March 27, 2024. One week prior, the panellists received a document providing the rationale for developing the best practices and standards, as well as background information on the development of the 109 potential best practices and standards mapped across 3 key quality domains (i.e., governance, data, and information technology infrastructure) and their correlated subdomains. Supporting documents included draft tables from the scoping review developed by the McMaster team (subsequently published[19]) and 2 publications that provided a comprehensive set of recommendations for improving the quality of RDRs: *Recommendations for Improving the Quality of RDRs*[27] and *The Quality Evaluation of Rare Disease Registries—An Assessment of the Essential Features of a Disease Registry*.[15]

Panellists received instructions on how to complete the survey. The instructions stated that to be included as a best practice and standard, an item must be both important and feasible in the Canadian context. Panellists were also instructed that the final set of best practices and standards would apply to "1 registry per condition" and that RDRs that collect data on several rare diseases will be expected to apply best practices and standards for each rare disease in their registry. The survey panellists had 14 days to complete the survey, with reminder emails sent on day 5 and day 11. All 23 panellists completed the survey.

In alignment with the CDA-AMC reporting guidance on RWE,[10] items with a score of 1 or 2 on the importance levels were coded “not important,” while items with a score of 3 or 4 were coded “important.” The consensus level was established at 70% for the importance and feasibility scale. Specifically, items that were rated 3 (somewhat important) or 4 (important) by at least 70% of the respondents **and** at least 70% of the respondents did not foresee any barriers were included. Items that were rated either 1 (unimportant) or 2 (somewhat unimportant) by at least 70% of survey respondents were excluded. Items that were rated 3 (somewhat important) or 4 (important) by at least 70% of the respondents but were considered infeasible by at least 70% of the panellists were excluded.

All other items were flagged for discussion at a virtual meeting held on May 7, 2024. This discussion included items that were rated 3 (somewhat important) or 4 (important) by at least 70% of the respondents with no consensus for feasibility (score greater than 30% and lower than 70%); items that did not reach consensus on importance, though did reach consensus for feasibility; and items that did not reach consensus for importance and feasibility. In addition, items that had reached consensus in terms of importance and feasibility but for which there were important differences in terms of importance or feasibility between RDR and non-RDR panellists were also flagged for discussion.

Survey Results — Round 1

Based on the survey responses of the 23 panellists, 49 items were included as best practices and standards as these items were deemed important and feasible by at least 70% of RDR and non-RDR panellists. This included 30 of 63 potential best practices and standards in the governance domain, 12 of 34 in the data domain, and 7 of 12 in the information technology domain. One item from the data domain was excluded in round 1 because it was deemed unimportant by at least 70% of the panellists. All other items were flagged for discussion during the online meeting on May 7, 2024, including 7 items for which disparities between RDR and non-RDR panellists were observed in terms of importance or feasibility. Table 1 presents the results.

Table 1: Results From the First Round of the Expert Panel Consensus (Survey)

Subdomain	Number of items	Items included, n (%)	Items excluded	Items for discussion (round 2), n (%)
Governance				
Registry purpose and description	14	4 (29)	0	10 (71)
Population	11	6 (55)	0	5 (45)
Funding and sustainability	5	1 (20)	0	4 (80)
Governance structure	6	5 (83)	0	1 (17)
Partner engagement	6	1 (17)	0	5 (83)
Ethics, legal, privacy	6	5 (83)	0	1 (17)
Data governance	3	3 (100)	0	0 (0)

Subdomain	Number of items	Items included, n (%)	Items excluded	Items for discussion (round 2), n (%)
Documentation	8	4 (50)	0	4 (50)
Training and support	4	1 (25)	0	3 (75)
Data				
Disease classification	1	0 (0)	0	1 (100)
Health-related interventions	2	1 (50)	0	1 (50)
Data dictionary	2	2 (100)	0	0 (0)
Common data elements	3	0 (0)	0	3 (100)
Data collection	10	5 (50)	1	5 (50)
Data quality and assurance	9	2 (22)	0	7 (78)
Data analysis and reporting	7	2 (29)	0	5 (71)
Information technology infrastructure				
Physical and virtual infrastructure	10	7 (70)	0	3 (30)
Software infrastructure	2	0 (0)	0	2 (100)
Total	**109**	**49 (45)**	**1**	**59 (55)**

Round 2: Discussion With the Expert Panel and Follow-Up Survey

One week before the online meeting, tables that presented the detailed survey results from round 1 were sent to the panellists. The tables included the items that reached the threshold for inclusion and the items to be discussed during the meeting. Each table included the overall scores for the importance and feasibility of each potential best practice and standard and the individual scores by RDR to non-RDR status. Panellists also had the opportunity to provide comments before the meeting.

Out of 23 panellists, 17 attended the online meeting to discuss items that did not reach consensus. Several observers from CDA-AMC and the authorship team also attended the meeting. The observers did not engage in the discussion except to answer questions posed by the panellists. The observers also did not participate in the voting process.

The importance and feasibility scores and the key themes emerging from the comments collected during round 1 of the survey were presented for each item that did not reach a consensus. After a brief discussion with the panellists led by an experienced moderator, participants voted on these items for final inclusion using the online poll function of the Zoom platform. As some items were not discussed during the meeting due to time constraints, a follow-up survey was sent to the 17 panellists who attended the meeting to vote on the remaining 17 items that did not reach consensus in terms of importance and feasibility during round 1. Panellists voted on both importance and feasibility for these 17 items. Additionally, 3 items discussed at the online meeting were reworded and included in the follow-up survey. Items were excluded if a threshold

of at least 70% was not reached. All 17 panellists who attended the online meeting completed the follow-up survey. Table 2 presents the results of round 2 of the Delphi panel process.

Table 2: Results From the Second Round of the Expert Panel Consensus

Subdomain	Number of items that did not reach consensus in round 1 survey	Items included after round 2 panel discussion, n (%)	Items excluded after round 2 panel discussion
Governance			
Registry purpose and description	10	4 (40)	6
Population	5	2 (40)	3
Funding and sustainability	4	0 (0)	4
Governance structure	1	0 (0)	1
Partner engagement	5	0 (0)	5
Ethics, legal, privacy	1	0 (0)	1
Data governance	0	0 (0)	0
Documentation	4	1 (25)	3
Training and support	3	0 (0)	3
Data			
Disease classification	1	0 (0)	1
Health-related interventions	1	1 (100)	0
Data dictionary	0	0 (0)	0
Common data elements	3	1 (33)	2
Data collection	4	0 (0)	4
Data quality and assurance	7	0 (0)	7
Data analysis and reporting	5	0 (0)	5
Information technology infrastructure			
Physical and virtual infrastructure	3	0 (0)	3
Software infrastructure	2	0 (0)	2
Total	**59**	**9 (15)**	**50**

Final Results

Following a review of round 1 and round 2 of the Delphi panel results, 4 included best practices and standards that were originally presented as 2 separate items in the survey were combined for clarity. The specific items are listed in the following.

- International registries (domain: governance; subdomain: population)
  - Original best practices and standards:
    - For international RDRs, the number of countries participating in the RDR is documented.

        - For international RDRs, the number of patients per country is documented.
    - Combined best practices and standard:
        - For international RDRs, the number of countries participating in the RDR and the number of patients per country are documented.
- Policies on the use or disclosure of data (domain: governance; subdomain: data governance)
    - Original best practices and standards:
        - The policies for the use or disclosure of data to external parties for academic or research purposes are documented.
        - The policies for the use or disclosure of data for external parties for nonresearch purposes (e.g., regulatory, HTA agencies, industry) are documented.
    - Combined best practices and standards:
        - The policies for the use or disclosure of data to external parties for academic or research purposes or nonresearch purposes (e.g., regulatory, HTA agencies, industry) are documented.
- Protocols for RDR-based studies (domain: governance; subdomain: data documentation)
    - Original best practices and standards:
        - Protocols for RDR-based studies are published or available on request.
        - Protocols for industry-based studies are published or available on request.
    - Combined best practices and standards:
        - Protocols for RDR-based studies are published or available on request (as industry is a subset of RDR-based studies).
- Policies to transfer data to external organizations (domain: information technology infrastructure; subdomain: physical-virtual infrastructure)
    - Original best practices and standards
        - The RDR’s policies outlining the ability of the RDR to transfer data to external organizations are documented.
        - The RDR’s policies outlining the ability of the RDR to receive data from external organizations are documented.
    - Combined best practices and standards:
        - The RDR’s policies outlining the ability of the RDR to transfer data to and from external parties are documented.

In addition, 1 item from the population subdomain of the governance domain that was initially included as part of round 1 of the survey has been excluded from the final best practices and standards as its complement was excluded in round 2.

- Survey #30 — included in round 1: The method for calculating the representativity of the registry's population is described.

- Survey #29 — excluded in round 2: The representativity of the registry's population is documented (percentage of patients in the registry versus the overall disease population in the coverage area). For international registries, provide the representativity for each country.

Similarly, 1 item from the data analysis and reporting subdomain of the data domain originally included in round 1 of the survey has been excluded from the final best practices and standards as its complement was excluded in round 2.

- Survey #94 — included in round 1: Safety reporting processes for adverse events are modifiable, if applicable (e.g., new adverse events can be introduced).
- Survey #93 — excluded in round 2: The process for identifying and reporting adverse events ascertained during primary data collection is documented.

Three best practices and standards were also reworded based on feedback from panellists during the round 2 online meeting. These 3 reworded best practices and standards were voted on in the follow-up survey that immediately follow round 2.

- Survey #23 original — The diagnostic methods for the rare disease captured in the registry are provided (e.g., International Classification of Diseases, Nineth Edition or International Classification of Diseases, Tenth Edition, hospital codes, genetic tests, laboratory tests, links to clinical guidelines).
  - Survey #23 revised wording — The diagnostic methods for the rare disease captured in the registry are documented.
- Survey #55 original — All documents are regularly updated as needed and the registry documentation is not older than 5 years.
  - Survey #55 revised wording — Key documents are updated as needed and dated.
- Survey #65 original — The interventions captured in the database are documented (e.g., medication, surgery).
  - Survey #65 revised wording — If interventions (e.g., medication, surgery) are captured in the database, they are documented.

Finally, out of 6 potential best practices and standards for the subdomain partner engagement of the governance domain, only the item "The frequency of meetings with members of the governance structure (e.g., board of directors, steering committee, advisory board) is documented" was deemed important and feasible by the panellists. This item was moved to the governance structure subdomain as it relates to another item ("The RDR governance includes a board of directors and/or steering committee that provides oversight of all RDR activities"). As such, the final list of best practices and standards does not include the subdomain partner engagement. Similarly, as neither of the 2 potential best practices and standards from the software infrastructure subdomain were included in the guidance, this subdomain was excluded from the guidance.

In total, 52 best practices and standards were included, of which 4 were combined (as previously outlined) and 2 were excluded (as shown in Table 3). Appendix 3 presents the detailed list of best practices and

standards included by domain or subdomain while Appendix 4 presents the list of excluded items and reasons for exclusion.

Table 3: Final Results of the Expert Panel Consensus Study

Subdomain	Number of items	Number of items included, n (%)	Number of items excluded
Governance			
Registry purpose and description	14	8 (57)	6
Population	10	6(60)	4
Funding and sustainability	5	1 (20)	4
Governance structure	7	6 (86)	1
Partner engagement	5	0 (0)	5
Ethics, legal, privacy	6	5 (83)	1
Data governance	2	2 (100)	0
Documentation	7	4 (57)	3
Training and support	4	1 (25)	3
Data			
Disease classification	1	0 (0)	1
Health-related interventions	2	2 (100)	0
Data dictionary	2	2 (100)	0
Common data elements	3	1 (33)	2
Data collection	10	5 (50)	5
Data quality and assurance	9	2 (22)	7
Data analysis and reporting	7	1 (14)	6
Information technology infrastructure			
Physical and virtual infrastructure	9	6 (67)	3
Software infrastructure	2	0 (0)	2
Total[a]	**105**	**52 (50)**	**53**

[a]The initial survey presented 109 potential best practices and standards for consideration. However, for simplicity and brevity, 4 sets of best practices and standards that were similar in nature were combined following the survey. As a result, the final number of potential best practices and standards was reduced from 109 to 105. Additionally, 2 best practices and standards initially included after the round 1 survey were subsequently excluded as the corresponding complementary best practice and standard was excluded in round 2 of the survey. As a result, the included items were reduced from 58 to 52 and the excluded items increased from 51 to 53.

Step 3: Consultation Process to Finalize the Guidance

The guidance was drafted and shared with the expert panel for their review and feedback. Comments were collated by the authorship team and a revised version of the guidance document was shared with the panellists for final review.

Appendix 3: Best Practices and Standards to Improve the Quality of RDRs in Canada

Table 4: List of Best Practices and Standards Included in the Guidance

Subdomain	Number	Best practices and standards
Governance		
Registry purpose and description	1	The RDR's primary purpose and objectives are described.
	2	The RDR time frame is documented (i.e., when was the RDR created, is it ongoing, and the final data collection date, if applicable).
	3	The RDR design and/or methodology is described (e.g., retrospective, prospective).
	4	Geographical coverage is described (e.g., local, regional, provincial, national, international).
	5	The organizational settings from where the RDR recruits providers and patients are described (e.g., community, specialized clinics, hospitals).
	6	Each data source is described (e.g., physician assessment records, patient-reported data, laboratory).
	7	Current linkages to other data sources are reported.
	8	Documentation of key RDR characteristics is available upon request.
Population	9	The case definition of the rare disease captured in the RDR is documented.
	10	Predefined inclusion and exclusion criteria are specified for patient entry into the RDR.
	11	The diagnostic methods for the rare disease captured in the RDR are documented.
	12	The current number of patients in the RDR is documented.
	13	The current number of sites recruiting patients in the RDR is documented.
	14	For international RDRs, the number of countries participating in the RDR and the number of patients per country are documented.
Governance structure	15	The RDR has a named lead, and the contact information is documented and available.
	16	An organizational chart describing the roles and responsibilities of each party involved in the RDR is available upon request.
	17	The RDR governance includes a board of directors and/or steering committee that provides oversight of all RDR activities.
	18	The frequency of meetings with members of the governance structure (e.g., board of directors, steering committee, advisory board) is documented.
	19	The declarations of conflicts of interests (e.g., financial, academic) for all parties involved in the RDR, including for members of the governance structure (board of directors, steering committee, advisory board) and registry funders are documented using a standard process.
	20	The decision-making governance structure and related processes for both internal RDR activities and collaboration with external parties are documented.
Funding and sustainability	21	All funding sources over the past 2 years are disclosed.

Subdomain	Number	Best practices and standards
Ethics, legal, privacy	22	The RDR compliance with relevant (i.e., international, national, regional, and local) ethical, legal, and privacy requirements is documented.
	23	Ethics approvals are documented.
	24	The consent process for patient contact, data collection, data storage, and data use and reuse are described.
	25	The patient recruitment process, including incentives to encourage participation is documented.
	25	Data security controls are specified on the patient consent form (e.g., encryption systems, intrusion detection, secure access).
Data governance	27	The data ownership rights are documented, including specifying who owns the patient data, who owns the RDR, and who is the RDR data custodian.
	28	The policies for the use or disclosure of data to external parties for academic or research purposes or nonresearch purposes (e.g., regulatory, health technology assessment agencies, industry) are documented.
Documentation	29	The RDR's standardized consent forms and participation information sheets describe the extent of patient contact, data collection, data storage, and data use and reuse.
	30	A manual on the RDR's standard operating procedures is available.
	31	Key documents are updated as needed and dated.
	32	Protocols for RDR-based are published or available on request (as industry is a subset of RDR-based studies).
Training	33	All RDR staff and data providers receive training on RDR procedures.
Data		
Health-related interventions	34	If health-related interventions (e.g., medication, surgery) are captured in the database, they are documented.
	35	For each health-related intervention captured in the RDR, the source of the information is documented (e.g., patient recall, clinical report, electronic medical records).
Data dictionary	36	A data dictionary that defines all data elements, permissible values, representation classes, data types, formats, if data elements are mandatory vs. optional, and which data elements are collected at baseline compared to follow-up is available.
	37	Any relevant changes to RDR content (e.g., variables, coding) over time are documented, including dates and specific changes.
Common data elements	38	Common data elements (i.e., a core group of data elements or minimum dataset collected by all rare disease RDR centres) are used.
Data collection	39	Standardized data collection guidelines (e.g., processes and pathways) are used.
	40	Standardized data collection forms are in place (paper or computer based).
	41	Data collection tools to enter the data are documented (e.g., web-based platform, direct import from electronic medical records, smartphone, manual data entry).
	42	The data collected at baseline and during follow-up visits (e.g., demographics, clinical data, biological specimens, health care resource utilization, patient-reported outcome measures) are documented.
	43	The follow-up methods and frequency of follow-up are documented (e.g., at regular intervals, ad hoc, or both, when patients come to the clinic).

Subdomain	Number	Best practices and standards
Data quality and assurance	44	Methods to avoid duplication of registered cases are documented.
	45	The percentage of patients lost to follow-up is documented.
Data analysis and reporting	46	Statistical analysis plans are in place for each RDR-based study.
Information technology infrastructure		
Physical and virtual infrastructure	47	The RDR's policies outlining the ability of the RDR to transfer data to and from external parties are documented.
	48	Data security protocols are in place and documented (e.g., encryption, firewall).
	49	Procedures are in place to grant authorized users access to RDR data.
	50	The RDR has data breach procedures in place.
	51	The RDR has clear procedures to erase personal data when requested.
	52	The RDR has a policy on releasing data to RDR participants on request.

Appendix 4: Items Excluded as Potential Best Practices and Standards

Table 5: Items Excluded as Best Practices and Standards in the Guidance and Reason for Exclusion

Domain	Excluded item	Round excluded	Reason for exclusion	
			Not important	Not feasible
Governance				
Registry purpose and description	1. Any changes over time to the registry's scope or population are documented.	Round 2	—	Yes
	2. The registry has the ability to conduct prospective studies.	Round 2	Yes	Yes
	3. Procedures for future data linkages are described.	Round 2	Yes	Yes
	4. Average follow-up period per patient in months/years is described.	Round 2		Yes
	5. The registry describes if and how registry data have been used by decision-makers (e.g., regulatory and HTA agencies, payers).	Round 2	Yes	Yes
	6. A list of registry-based publications is publicly available.	Round 2	Yes	Yes
Population	7. The registry differentiates between confirmed and suspected cases, if applicable.	Round 2	—	Yes
	8. The number of new patients entering the registry over the last 3 years is provided.	Round 2	Yes	—
	9. The representativity of the registry's population is documented (% of patients in the registry versus the overall disease population in the coverage area). For international registries, provide the representativity for each country.	Round 2	—	Yes
	10. The method for calculating the representativity of the RDR's population is described.	Round 2	Complement was excluded	
Funding and sustainability	11. The percentage of total dollars from each funding source is provided for the last 2 years.	Round 2	Yes	Yes

Domain	Excluded item	Round excluded	Reason for exclusion	
			Not important	Not feasible
	12. In the case of industry funding, specify whether the industry funding over the past 2 years was used for the core activities of the rare disease registry, for specific rare disease registry-based studies, or both.	Round 2	—	Yes
	13. The registry has established plans for long-term sustainability.	Round 2	—	Yes
	14. The registry has a financial audit process in place.	Round 2	Yes	Yes
Governance structure	15. An advisory board providing clinical guidance is in place.	Round 2	—	Yes
Partner engagement	16. The registry involves a broad range of partners in the registry decision-making (e.g., patients or patient groups, physicians, industry).	Round 2	—	Yes
	17. The frequency of communication with registry users is described (e.g., monthly, yearly).	Round 2	Yes	Yes
	18. The methods of communication with registry users are described (e.g., websites, newsletters, scientific journals, and institutional bulletins).	Round 2	Yes	—
	19. The registry has at least 1 scientific committee meeting per year with the reporting of key data.	Round 2	Yes	Yes
	20. The registry collects routine feedback on user satisfaction.	Round 2	Yes	Yes
Ethics, legal, privacy	21. The consent process to link with other registries or databases is described.	Round 2	—	Yes
Documentation	22. Contract templates for collaboration between the registry and external party users are available.	Round 2	Yes	Yes
	23. Registry-based studies are registered.	Round 2	Yes	Yes
	24. Regular reports on registry activities are available (e.g., annual, bi-annual).	Round 2	—	Yes
Training and support	25. Training resources for registry staff, data providers, and new users are available.	Round 2	—	Yes

Domain	Excluded item	Round excluded	Reason for exclusion	
			Not important	Not feasible
	26. Training logs and other documentation are maintained and reviewed regularly.	Round 2	Yes	—
	27. A support team or help desk for data users and providers is in place.	Round 2	—	Yes
Data				
Disease classification	28. The registry uses standardized terminology and disease classifications that comply with international, national, and local standards, as applicable.	Round 2	—	Yes
Common data elements	29. When applicable, common data elements are harmonized with other registries with the same rare disease (i.e., when there is more than 1 similar registry in Canada or outside of Canada).	Round 2	—	Yes
	30. Justification for the common data elements captured by the registry is documented (e.g., based on clinical practice guidelines, and regulatory guidance documents).	Round 2	Yes	Yes
Data collection	31. The registry has designated personnel for capturing/entering the data.	Round 2	Yes	Yes
	32. Strategies to minimize selection bias and loss to follow-up are described.	Round 2	—	Yes
	33. Potential confounders are identified.	Round 2	Yes	Yes
	34. The time between primary data collection and data entry into the registry database is provided.	Round 1	Yes	—
	35. The reason for loss to follow-up is described and dated for each patient (e.g., date of death, consent withdrawal, lost contact, moved, other/unknown).	Round 2	—	Yes
Data quality and assurance	36. A data quality assurance plan is in place.	Round 2	—	Yes
	37. The registry defines and uses quality indicators and reports on these quality indicators regularly (e.g., monthly, yearly).	Round 2	—	Yes
	38. Routine data quality checks and data cleaning are performed.	Round 2	—	Yes

Domain	Excluded item	Round excluded	Reason for exclusion	
			Not important	Not feasible
	39. Data quality audits are performed, and triggers for initializing the audit processes are available.	Round 2	—	Yes
	40. Regular audits are performed to ensure compliance with data protection rules.	Round 2	—	Yes
	41. Results for the latest data quality audit are provided.	Round 2	—	Yes
	42. The percentage of missing data is provided for variables in the core/ minimal dataset.	Round 2	—	Yes
Data analysis and reporting	43. Organizations usually performing data analyses are identified (registry, academics, contract research organizations).	Round 2	Yes	—
	44. The process for identifying and reporting adverse events ascertained during primary data collection is documented.	Round 2	—	Yes
	45. Safety reporting processes for adverse events are modifiable (e.g., new adverse events can be introduced).	Post round 2	Complement was excluded	
	46. The methods to deal with potential confounders are described.	Round 2	Yes	Yes
	47. The methods to deal with missing data are described.	Round 2	—	Yes
	48. The methods to deal with censored data are described.	Round 2	Yes	—
Information Technology Infrastructure				
Physical and virtual infrastructure	49. The registry has the capability for data linkage (e.g., access to patient identifiers).	Round 2	—	Yes
	50. Methods for data linkage to administrative or other databases are described, if applicable.	Round 2	—	Yes
	51. The registry strengthens its security system through regular risk assessments.	Round 2	—	Yes
Software infrastructure	52. The registry complies with FAIR principles at the data source. FAIR principles are the capacity of data systems to Find, Access, Interoperate, and Reuse the data.	Round 2	—	Yes

Domain	Excluded item	Round excluded	Reason for exclusion	
			Not important	Not feasible
	53. The registry has a web interface that facilitates the upload and download of data.	Round 2	Yes	Yes

HTA = health technology assessment; RDR = rare disease registry.

Appendix 5: Documents Reviewed to Identify Potential Best Practices and Standards

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