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Reflections on the Canadian Bleeding Disorders Registry: Lessons Learned and Future Perspectives

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Abstract

The evolution of care of patients with inherited bleeding disorders (like hemophilia) in Canada has benefited from the development of a Canadian national database and registry to support clinical practice, individualized treatment, and patient participation in care and research, as well as the supply of treatments. The Canadian Bleeding Disorders Registry (CBDR) has become the national registry for comprehensive care and research in hemophilia in Canada with patient, clinical, and research module connectivity. Attention has been paid to ensure administration, governance, and security of infrastructure with strict adherence to privacy and ethics concerns, which has required continued resourcing and collaboration. The CBDR has served as a robust resource to inform epidemiology of disease, burden of disease, and disease changes and variation over time as new treatment modalities are introduced. Information on the utilization of blood products to treat hemophilia has and can be retrieved and used by Canadian blood product procurement agencies to inform decision-making for past and future purchases. In the future, there is the opportunity to develop the registry for the purposes of implementing outcome-based performance agreements for new therapies to treat hemophilia. The successful multistakeholder coordination and alignment achieved over decades with the development and function of the CBDR is an exemplar that could, with specific customizations to ensure relevance, usefulness, and effectiveness, be extended to other rare disease areas.

For author information see Appendix 1.

Background

The purpose of this report is to describe experiences with establishing, operating, and using evidence retrieved from the Canadian Bleeding Disorders Registry (CBDR). In addition, lessons learned, opportunities, and future perspectives will be discussed. Over time, the CBDR has evolved to integrate with additional tools such as the Canadian Bleeding Disorders research module (CBDR-R); the patient and caregiver module (myCBDR); the Patient Reported Outcomes, Burdens, and Experiences (PROBE) study, and the Web-Accessible Population Pharmacokinetic Service (WAPPS). Partnerships with Canadian stakeholders have been ongoing and will continue moving forward, including similar partnership experiences with other national registries (Australia, Italy, US) and with the World Bleeding Disorders Registry. The experiences described aim to serve as a resource to support the growing interest in real-world data generation for other rare diseases. Ideally, this report is timely and relevant for planning and deploying infrastructure to support optimal care in Canada and beyond for patients with other rare diseases.

With the intent of making this material more useful, and awareness that there are many different ways of learning, this content has been organized in 2 different ways — a narrative of the background, development, planning, and use of the CBDR, followed by a discussion of the strengths and limitations. In the appendix, the same material is organized as questions and answers, to facilitate finding specific information of interest without the need to scan the entire document.

Introduction

Inherited bleeding disorders are rare diseases caused by the deficiency or dysfunction of plasma proteins in the blood required for the development of desired clotting processes, known as physiologic hemostasis. Von Willebrand disease, hemophilia A, and hemophilia B are the most common among the rare inherited disorders of hemostasis, comprising a family of 50-plus bleeding syndromes.[1,2] These inherited disorders primarily affect males and in their severe forms are life threatening. Starting in the late 1960s, mostly in high-income countries, understanding of the pathophysiology and advances in treatment options enabled even severely affected patients to experience the same life expectancy as the general male population.[3,4] Treatment involved the replacement of the deficient plasma proteins, originating from blood donors, which were then prepared into concentrated form by manufacturers and provided to patients as plasma-derived factor concentrates. Coinciding with these advances in treatment during the 1970s, a preliminary data capture infrastructure was established in Canada.

Very unfortunately, the dream of a cure morphed into a nightmare when there was widespread transmission of blood-borne HIV and hepatitis C virus within the blood collection and donation system worldwide. As a result, for the vast majority of patients in Canada who received treatment in the 1970s and 1980s, life expectancy was estimated to be 35 to 40 years shorter than the general population.[5] This created strong motivation for a close partnership among patients and their advocates, clinicians, regulators, and factor concentrate product manufacturers to ensure continuous improvement, primarily in the safety of replacement therapy.[6]

In the early 1990s, the community welcomed the first generation of recombinant clotting factor concentrates, which were synthetic instead of derived from human blood plasma. These provided a high degree of safety relative to the risk of blood-borne transmission of pathogens, as evidenced by the absence of reported transmission of blood-borne viruses in persons with hemophilia since the late 1980s to now.[7-10] With the advent of recombinant clotting factor concentrates, and the associated safety improvements, regular prophylaxis (regular administration of clotting factor concentrate) was proven effective in preventing bleeding and the predominant adverse health outcome for patients, hemophilic arthropathy.[11] This is permanent joint disease due to repeated bleeding into joints; the associated inflammation can develop, to some degree, in as many as 30% to 50% of patients.[12,13] In turn, prevention of bleeding and improved health-related quality of life (HRQoL) has become the primary objective of care in developed countries.

Over time, a multidisciplinary approach to care (e.g., psychosocial support, physiotherapy, integration into community life), not just the prophylactic infusion of the deficient plasma clotting factor, has been made available to the patient and their family, with the goal of providing the opportunity for optimal health.[14,15] In keeping with this goal, the bleeding disorders community, particularly in Canada, expanded and enhanced the existing data capture infrastructure to capture not only replacement plasma clotting factor utilization and adverse events, but also to measure clinical outcomes, HRQoL, and the lived experience of patients with bleeding disorders. The registry infrastructure of today has evolved on the foundation of this preliminary data collection tool. Key learnings, barriers, and facilitators to implementation and the strengths and limitations of the tool to support optimal care for rare bleeding disorders in Canada are discussed in the following.

Genesis of the Canadian Data Collection System for Rare Bleeding Disorders

As mentioned, starting in the late 1970s, the functional, efficient, and accountable system of hemophilia care has been developed in Canada mostly at the initiative of the comprehensive hemophilia treatment centres, without formal official mandates.[16-18] However, some Canadian province have since designated provincial hemophilia programs in specific treatment centres.[19] Building on the initiative of the comprehensive hemophilia treatment centres, national standards of care for hemophilia were first promulgated in May 1978 at the Comprehensive Care for the Canadian Hemophiliac conference in Winnipeg. This was a multistakeholder initiative jointly organized and cochaired by the Canadian Hemophilia Society (represented by Durhane Wong-Rieger) and the Association of Hemophilia Clinic Directors of Canada (AHCDC) (represented by Dr. Jerome Teitel). Successful collaboration among stakeholders has been ongoing since then, and the several incremental improvements in the standard were most recently consolidated in the June 2020 publication of the second edition of the Canadian Integrated and Comprehensive Care Standards for Inherited Bleeding Disorders. These are endorsed by health care provider groups and the patient organization.[20] The existing system of hemophilia care, ongoing collaboration, and commitment to improving care standards is thus an eloquent testimony to the goodwill and constructive collaboration among patients and their families, health care providers, and funders.

The establishment of national care standards has necessitated ongoing evolution of the data collection system and capacity to measure the provision of care against those standards. Further, in response to the tainted blood tragedy in the late 1990s, the first implementation of the Canadian Hemophilia Registry (CHR) and Canadian Hemophilia Assessment and Resource Management System were established. The purposes were to track delivery of specific lots of plasma clotting factor products to individual patients and allow easy and quick recall of batches of products in the event of safety-related issues.[16,18,21,22]

Another major milestone was when the European Haemophilia Safety Surveillance System, a prospective surveillance program ongoing since 2008 and based on regular monitoring of more than 40,000 European patients,[23-25] was introduced into Canada in 2015. This was introduced as the Canadian Hemophilia Surveillance System (CHESS) and captures data related to treatment safety and efficacy, plasma clotting factor utilization, and HRQoL.

So, by the early 2010s, several data collection resources related to hemophilia care were operating in Canada — CHR, the Canadian Hemophilia Assessment and Resource Management System, and CHESS.

Transition to the Canadian Bleeding Disorders Registry

Administration

Between 2014 and 2016, the system of 3 separate databases and resources was transitioned to the current CBDR to extend the registry scope to more broadly support clinical and administrative needs, to update privacy compliance to contemporary requirements, and to give the registry a more robust funding and sustainability framework.[26] As a result of an initial scoping review, a technical solution was acquired from the National Blood Authority of Australia with McMaster University and the AHCDC investing resources for the initial setup and staffing of what would eventually become the CBDR. The registry became a partnership among the AHCDC (the clinical pillar), the Canadian Hemophilia Society (the patient association pillar), McMaster University (the technical and scientific pillar), and the Canadian provincial and territorial governments (the institutional funding pillars). The Canadian provinces and territorial governments aligned to support the registry via Canadian Blood Services (CBS) Canada's blood and blood products provider (with the exclusion of the province of Quebec). This raised the number of collaborators in the development of the registry to 5 with McMaster University coordinating the collaboration effort. Further development of the registry was facilitated with the participation and endorsement of all stakeholders with a vested interest to ensure robust data collection. In late 2016, once the registry was established and rolled out to treatment centres, a business case was prepared by the AHCDC to the provincial and territorial representatives, including Quebec provincial government representatives, with a request for continued support. The proposal was discussed and approved, with funding flowing to AHCDC via CBS and the Ministère de la Santé et des Services Sociaux du Québec (MSSS) responsible for Héma-Québec, the blood and blood product provider in Quebec. It was at this time that with successful partnership among patients, clinicians, scientists, blood product providers, and public health care funders, the CBDR of today was established.

The direct costs of the CBDR program are approximately CA$700,000 per year, not including in-kind contribution of the Canadian academic and health care institutions hosting the hemophilia treatment centres (HTCs), and the patients' direct contribution to the data collection. More than 95% of the previously noted direct costs are supported by the provincial and territorial stakeholders. This is approximately 0.002% of the yearly cost of treating hemophilia in Canada. Roughly 57% of the budget covers the software licensing cost, maintenance and updating, database and website hosting; 25% covers project coordination and governance and a data analysis team; and 21% covers the help desk service.

Governance

The CBDR data are owned by the patients, the database is owned by the AHCDC, and McMaster University is the data custodian. McMaster University entered into data transfer agreements (DTAs) with each participating hemophilia treatment centre, either via a home institution (hospital or university) or via the respective provincial ministry of health. All of Canada, with the exception of British Columbia, is covered with a DTA (discussed in the following).

The CBDR Committee (CBDR-C), a body of the AHCDC, oversees the registry and develops and presents action plans and recommendations to the AHCDC executive board for routine and special activities. The committee meets monthly, and reports to the AHCDC's General Assembly yearly.

The CBDR Stakeholder Advisory Group (CBDR-SAG), including health care professionals, patients, and technical staff from the core team, meets monthly and provides input into the ongoing development of the CBDR data structure and web interface, the data quality assurance activities, and the educational initiatives.

Security

The CBDR is a secure, centralized, encrypted at rest and transmission database, hosted on a cluster of servers physically located at the Health Information Research Unit at McMaster University. The facility has a level I security rating, with physical access controlled by personal swipe cards and closed-circuit video cameras; it undergoes periodic threat and security assessments and is audit logged. The database is hosted on an array of disks and is logically backed up daily with weekly physical copies stored offsite for redundancy. The database is accessible with a secure login procedure from the web.

The CBDR was created as a stand-alone software program and is not currently integrated with electronic medical record (EMR) functions at local hospitals. While integration would be beneficial in avoiding duplicate data entry, the multiplicity of the EMRs used in Canada, and the significant amount of resources needed to ensure successful integration, has delayed considering this development.

That said, the CBDR is integrated with the Web Accessible Population Pharmacokinetic Service for Hemophilia (WAPPS-Hemo).[27,28] This is the dominant software tool used to estimate how long plasma clotting factor replacement products will remain in a patient's blood after each infusion (also known as an individual's pharmacokinetic profile). This information allows clinicians to prescribe optimal plasma clotting factor regimens and provides patients with an estimate of their own plasma clotting factor levels in real time. Ultimately, this ensures individualized treatment adjustments and recommendations and

the prevention of bleeding events. Additionally, the respective patient modules for the 2 platforms (myCBDR and myWAPPS) are connected with a single sign-on procedure to help avoiding multiple data entry. Similarly, a single sign-on integration has been developed with myPROBE,[29] the patient-oriented app to collect a set of patient-reported outcome measures in the field, as well as data collection through the Pain Treatment Planning Questionnaire. To date, the only generic tool in use is EQ-5D 5-Levels, but other measures (like the Edmonton Symptom Assessment Scale) might be considered in the near future.

CBDR data have been successfully linked to ICES data as part of a project investigating the impact of hemophilia on the risk of fractures.

Privacy and Ethics

The CBDR can be considered a national disease registry (as it includes virtually all patients diagnosed in the country), a clinical database, or a prospective cohort study. Considering this latter concept, the database structure, data collection design, and patient consent form for data collection were submitted for ethical approval to the Hamilton Integrated Research Ethics Board. Submission to this board is a requirement of all research projects involving McMaster University. Signing the consent form is proposed by HTCs to the patients under their care, and patients electing to use myCBDR will e-sign a Term of Use module when creating their credentials to access and use the registry. Both consents include authorizing the use of data for standard reporting to the AHCDC, CBS, and Health Canada, as well as participation in ethically approved retrospective research without requiring further patient consent. This includes consent for linkage of data to other administrative databases. The CBDR has a privacy policy, and myCBDR has both a privacy policy and terms of use policy. Both were developed by the legal office at McMaster University, approved by the legal counsel of the AHCDC, and ratified (or sometimes modified) by the hospital or provincial counsels during the DTA negotiations between McMaster and prospective CBDR users.

Canadian Bleeding Disorders Registry: Structure

Data Collection and Organization

Data from patients are collected via 2 main mechanisms. Patients enter information about their treatment and the bleeding events they experience (the primary clinical outcome) into the myCBDR app (which is further described in the following). Patients or caregivers also periodically provide patient-reported outcomes via linked apps (e.g., myPROBE) and portals (e.g., the Pain Treatment Planning Questionnaire).

Clinicians and others involved in the care of the patient can enter select data as part of documenting clinical interactions with the patient. In particular, treatment plans and treatment orders to CBS and Héma-Québec are generated via the system, while pharmacokinetic profiles, standardized joint scores (a clinical outcome), and adverse events are recorded at the clinic level. Finally, genotyping information is entered into CBDR centrally by the National Genotyping Laboratory in Kingston, Ontario. The database consists of 4 categories of data.

1. Patient demographics: CBDR stores patients' demographic data, as this is required to provide efficient and error-safe support to clinical care. General demographics, anagraphic data, educational attainment, employment status, and links to other database are collected.
2. Clinical data: This section includes diagnostic testing results, clinical evaluation scores, treatments, and so forth. A subset of clinical data is adverse event reporting, managed according to a specific routine to ensure completeness of the reporting. HTCs are required to provide a statement of all (or no) adverse events observed for the period.
3. Treatment usage data: This section includes treatment recommendations, the amount of plasma clotting factor ordered through CBS and Héma-Québec and dispensed to the patient, as well as the log (time and dose) of the self-infusion of plasma clotting factor at home.
4. Outcome data: This is both clinical outcome data (like the Hemophilia Joint Health Score) and patient-reported outcomes (via the PROBE study) that captures information such as difficulties with activities of daily living, use of pain medication and mobility devices, and EQ-5D 5-Levels data).[29-33] All data are collected longitudinally over the patient's lifespan. For patients with severe hemophilia, data are entered many times per year, while patients with mild disease are required to enter data yearly at a minimum.

Patient Module: myCBDR

myCBDR is a patient-oriented reporting system, available via a web portal or tablet/smartphone app, with native versions for iOS and Android, allowing the patient/caregiver to record self-administered treatment infusions and bleeds in real time. The patient/caregiver can also access their own record. myCBDR displays the patient's basic clinical characteristics, treatment plan and records the inventory of plasma clotting factor vials dispensed to the patient and then self-infused. The patient/caregiver can review bleed frequency, severity and location and treatment requirements for further discussion with the clinician. The principal advantage for the patient/caregiver is easy and accurate record-keeping in the home treatment environment, allowing rapid and effective individualization of care. Access to the portal and apps is password protected.

Research Module: CBDR-R

The CBDR-R is a companion database and web interface that supports ad hoc data collection. The CBDR logic is built around the concept of an electronic case record form for a clinical study. CBDR-R users are associated with a CBDR HTC and have access to the records of patients registered with their centre. The software allows definition of a new study, assigning of primary and local investigators, and the setting of inclusion and exclusion criteria desired for study. For multicentric studies, which are the majority in the field, the primary study investigator has immediate access to the number of eligible patients by centre across all participating centres, while each local investigator has access to the actual list of eligible patients within their own centre. The software allows enrolling and consenting a patient, and sending specific links (and reminders) for completing ad hoc patient-reported outcomes tools and questionnaires beyond those included in the CBDR dataset (e.g., the Bleeding Assessment Tool, the Hemophilia Activity List, the Standardized Form 36, the Pain Treatment Planning Questionnaire, and others, per each study protocol). All relevant information is pulled from the appropriate specific dataset within CBDR when available, or via ad hoc forms.

Comprehensiveness and Quality of Data

Registration of patients in the registry is voluntary, as is a patient's choice to obtain care at 1 of the 26 treatment centres associated with the AHCDC. However, the vast majority of patients with bleeding disorders in Canada attend 1 of the AHCDC HTCs, as demonstrated by triangulation exercises, comparison of epidemiologic indicators, and trends over time.[34-36] All Canadian HTC physicians are AHCDC members, and all but those in British Columbia participate in the CBDR data collection. British Columbia has developed a separate data collection platform, the Inherited Coagulopathy and Hemoglobinopathy Information Portal (iCHIP), not directly connected with CBDR. However, British Columbia historically contributed data to CHR, and CHESS, as previously mentioned. When the CHR and CHESS were dismantled and absorbed into the CBDR, specific functions were developed in the CBDR to allow centres in British Columbia to generate a national unique patient identifier, which is used as a secondary identifier in iCHIP, and to report adverse events to the CBDR without identifying the patient.

There is no gold standard approach for assessing the completeness of capture of all affected patients within a disease registry, but there are useful indicators. For example, the constant intake of new cases registered over time, as expected for inherited disorders, or the agreement between the amount of treatment prescribed, dispensed, and recorded as being administered by individual patients over time. In terms of the level of completion of individual patient records, it needs to be acknowledged that the data collection and entry by patients is voluntary and could be incomplete. Mandatory data entry are kept to a minimum, to balance the goal of ensuring accurate data completeness and maintaining usability of the system.

A series of mechanisms with continued and targeted engagement of end users in the clinical community are in place to ensure that data are error free and as complete as possible. First and foremost, several training sessions on data structure and entry are offered to users during the year. The sessions are kept short, topics are rotated, and session recordings are made available. These are valuable to train new users, and serve as continuing education for all users. Second, quarterly motivational campaigns geared to complete and clean-up specific segments of the database (e.g., checking accuracy of records for patients above a given age, or with a specific complication, or results of specific tests) are introduced quarterly. Third, reports from the registry by centre, including tables highlighting inconsistent or missing data to be fixed, are produced quarterly for each centre director. Every centre director is requested to sign off on these quarterly reports before merging the registry data into a national report. This method has proven effective to capture data outliers, omissions, and entry errors. Fourth, the AHCDC has adopted an incentive mechanism by which a yearly amount of funding is made available to centres to support data entry in the registry. These funds are dispersed based on a centre's performance in producing data quantity and quality, according to a specific algorithm accounting for 10 key data points selected as key performance indicators. Development funds are available on a limited term to support poor performing centres willing to implement quality improvement processes and presenting a documented action plan. CBDR-C and CBDR-SAG issues a quarterly newsletter highlighting best practices for data entry and seamless best practices to merge registry functions into a clinic's routine workflow. Finally, a user support centre with a dedicated portal of educational content and a trackable ticketing system is available to assist individual users with their questions in a responsive manner.

Canadian Bleeding Disorders Registry: Value of Data

Analysis and Reporting Activity

The CBDR offers a series of reporting, searching, and analysis functions meant to support the clinical workflow. Standardized reporting (on a quarterly and yearly basis) information is generated centrally with HTC and national-level detail. Overall data summaries are posted yearly on the web. The most recent report accounts for 10,061 records, which includes 3,213 patients for hemophilia A, 697 for hemophilia B, 4,653 for von Willebrand disease, and 1,498 for other rare congenital bleeding disorders. This provides epidemiological data on hemophilia A and B in Canada. A reporting interface with preset queries is available to the CBS partner for ad hoc reporting. Ad hoc reports and datasets are generated centrally to answer specific research questions by SQL querying of the database. A process is in place and overseen by the CBDR-C for third parties to submit requests for data extractions and analyses at an additional cost. Depending on the nature of the requesting agency (institutional, not-for-profit, commercial), a different level of contribution to the cost of the analyses can be requested. In all cases, reports are provided after complete patient de-identification and respecting of appropriate grouping rules to avoid privacy breaches. No individual patient data are provided under any circumstance. When appropriate, the core statistical support team develops and runs the analysis plan with input from the requesting organization. All reports are vetted by the CBDR-C or their delegates before being released.

Evidence Application Opportunities

More broadly related to disease, the CBDR could be used as a resource to inform burden of disease studies, including those designed to evaluate disease changes over time and disease variation with the availability of different treatment modalities.

Specifically related to treatment patterns and as indicated earlier in this document, some plasma clotting factor utilization information is used as part of the procurement process between CBS, Héma-Québec (the division within the MSSS responsible for procurement of blood products) and the manufacturers of plasma clotting factors. An improved understanding of the demographics of the patient population helps determine current factor utilization and future requirements, which is considered when evaluating different products during the procurement process.

There is the potential to further expand the use of the information and data collected within the CBDR. The clinical outcome data could be used for outcome-based performance agreements for certain therapies, especially novel options like gene therapies and monoclonal antibodies. These therapies have the potential for life-changing results, but only if they are able to deliver on the clinical outcomes for patients that were demonstrated in formal clinical studies. Many of these therapies also come with a much higher cost of treatment, which may be justified, though only if the desired clinical outcomes can be achieved. To be able to include outcome-based performance agreements in any procurement contract, there is a need for an accurate and comprehensive tool to capture these outcomes and the CBDR is well positioned to be that tool.

Discussion

The CBDR is a mature disease-specific registry, built and evolved by a partnership of treaters and patients. It is owned by a scientific not-for-profit organization, hosted and administered by an academic institution and financially supported by the Canadian provinces and territories, via CBS and the MSSS. Aggregate-level data and reports can be generated to support information needs for health care decision-making. The multistakeholder partnership, which has been successful and ongoing for several decades, is an exemplar model for commitment to a shared, sustainable, and effective organization. The CBDR is the comprehensive tool that is a product of this successful partnership; it collects information on virtually all patients affected by bleeding disorders in the country, using a standardized dataset, data quality control processes, and incentivizing mechanisms for HTCs.

Though CBDR is technically a registry, it was also intentionally approved as a research protocol (long-term observational study of the determinants of health for patients with inherited bleeding disorders). The protocol is open by design to any treatment approved for the population, and it has been amended several times to add new data points as they have been introduced. Changes in the core data structure undergo a tightly controlled process, with multiple levels of approval, beta-testing of the new implementation, and training of the users, which generally takes 3 to 6 months to complete. Changes in the data handled via the CBDR-R module can be implemented in days to weeks, and are approved by the responsible study investigator only, who takes ownership of producing ethical clearance when required. This approach has allowed for the use of CBDR data to generate real-world evidence on the impact of extended half-life plasma clotting factor concentrates,[26,37,38] and on the comparative effectiveness of the first in class non-factor replacement treatment for hemophilia.[36,39,40] The CBDR is a dynamic data collection and information tool that allows for inclusion of new datapoints and the evaluation of evidence in real time.

On a global level, the CBDR has also contributed to a pooled data analysis of 7 international registries that reestablished the expected incidence of hemophilia at birth, adopting a novel statistical approach to the analysis of registry data.[36] The CBDR data were also used to derive and test quality of care indicators adopted by the World Federation of Hemophilia.[35] Finally, the CBDR has successfully provided a data and technology platform for several investigator-initiated retrospective and prospective observational studies, notably those focusing on hemophilia care in perinatal settings (CHIMPS study) and in adults living with a complication of hemophilia treatment where a patient's immune system may develop antibodies (or inhibitors) to treatment (ACHILLES study).

Among the strengths of the registry are its multistakeholder design, that it is embedded in clinical practice and flow of clinical work, and that it contributes additional value for institutional stakeholders, Canadian blood product providers, and funders. For clinicians, who have for decades been engaged in registry development, it provides complementary support to the provision of optimal care and supports ongoing research efforts. For the patient community, it allows for focused and individualized care and follow-up, clinical evidence generation, and ongoing educational opportunities all with the goal of care optimization. For HTCs, there is the capacity to query the database for centre-specific information for audit and planning purposes. Finally, the CBDR data have been successfully used by CBS and Héma-Québec to inform product procurement processes, monitor product use patterns and variability, forecast future product volume and utilization requirements, and measure the value of treatments provided.

Lessons Learned and Opportunities

Finalizing DTAs between each of the health care institutions hosting a hemophilia treatment centre and McMaster University was anticipated to be a complex task; indeed, it took approximately 2 years to achieve. The same amount of time was required for successful research ethics board approvals at each institution. The main challenges are time constraints and the inertia with collecting data. Unlike other jurisdictions (e.g., several European countries, Japan, and several South American countries), the registration of individuals and full accountability for the dispensed drug is not required in Canada (outside of Quebec) to entitle the physician to prescribe and the patient to continue to receive treatments from the blood product providers. Therefore, participating in the registry and data entry is a voluntary activity, and it is always at risk when health care resources are or become scarce. The registry budget covers core staffing at the hosting site (McMaster University) with 3 dedicated staff, and some peripheral data entry cost is subsidized on occasions, but covering the cost for staffing of the participating HTCs is beyond the capacity of the organization. A practical solution has been to link participation and data entry into the CBDR with the ordering of plasma clotting factor concentrates directly from CBS and Héma-Québec. For example, ordering from CBS directly via the CBDR (as opposed to using paper order forms) has resulted in fewer errors, quicker processing, reconciliation of the treatment plan, and recording of the dispensed amount into the CBDR. As well, inputting this and other critical clinical data into the CBDR allows clinicians to print a patient summary sheet that is very useful and increases the effectiveness of the yearly individual patient assessment.

It has to be acknowledged, and previously mentioned, the CBDR is not (yet) integrated with the EMRs of the health care institution hosting the HTC. Therefore, while facilitating hemophilia care, it is inevitable that use of the CBDR introduces a small amount of duplicate data entry in the overall documenting of patient care. The development of certain technical enhancements and dissemination of best practices have helped with reducing this particular burden but not to the extent that would be provided by a seamless integration with local EMR tools.

One additional challenge is presented by the common practice of using proprietary case report form modules for patients enrolled in phase II and III clinical trials. This practice, aimed at ensuring the collection of good clinical practice–grade data that is acceptable for submission to regulatory authorities (like Health Canada), creates a challenging situation for a disease-oriented database like CBDR, as data for patients enrolled in studies will be missing, which compromises the integrity and completeness of the data collection. As a result, double data entry become necessary, causing an obvious additional strain on resources. A more comprehensive solution would be to enhance the CBDR-R module to meet regulatory authority requirements and to develop data sharing agreements that protect the intellectual properties right to the data of the drugs under development. Other countries have gone further by integrating disease-specific and trial-specific data collections systems to overcome this challenge (e.g., the American Thrombosis and Hemostasis Network in the US).

Future Perspectives and Conclusions

The CBDR has the potential to continue to be a conduit to real-world evidence generation related to patient health outcomes as a result of treatments. To assess its readiness for this scope, the CBDR has been assessed against the Registry Evaluation and Quality Standards Tool (REQueST) standards.[41] For most of the requirements, the CBDR is compliant, which provides reassurance that the database is robust. The main aspect where additional work is

required is in the production and maintenance of detailed documentation on structure and governance. As is the case for International Organization for Standardization certification; good clinical practice standards or other more general, explicit quality standards, developing and maintaining the registry documentation layer certainly improves the quality of the final product. However, this also adds a significant financial and human resource burden to the process and, as mentioned, given the voluntary nature of participating in the registry and data entry, current health care resources for this activity are at risk. As compliance with standards is essential for regulatory agency purposes, there is no immediate plan to develop such documentation unless specific agreements and dedicated resources become available.

The CBDR could be adopted to collect data for other rare diseases. Modifying the research protocol to include other populations would certainly be possible; it remains to be assessed whether it is more feasible to amend the existing protocol or submit a new one. The hardware infrastructure could certainly host data on a different population or another disease, or additional registry segments. Adding new treatments for patients living with bleeding disorders is possible with the current software, and there is a set of administrative functionalities to efficiently and quickly allow this. Defining new patient populations (e.g., a subpopulation of patients with bleeding disorders) can be achieved using the CBDR-R module, where an entire set of new data collection fields can be defined. However, the CBDR and CBDR-R would share the same demographic set, to ensure the coherence of the dataset. Developing new registry segments to support unrelated diseases (for example, sickle cell disease and other blood pathologies), has been explored. Technically, one could define a new diagnosis in the CBDR, use the main module only for handling the demographic information, and use CBDR-R to develop the disease-specific forms. The advantage would be leveraging the CBDR infrastructure; specifically its privacy and ethical framework. The successful multistakeholder coordination and alignment achieved with the development and function of the CBDR is an exemplar that could be extended to these other disease areas with specific customizations to ensure utility and effectiveness.

In terms of long-term sustainability, the most appropriate business model remains to be evaluated. As previously mentioned, the direct cost of the CBDR is approximately CA$700,000 per year, or 0.002% of the overall yearly cost of hemophilia treatment in Canada. Worldwide, the most successful longstanding registries are supported by public funding, and the cost is often incorporated into the cost for treatment. In the UK, the national database is managed by the UK Hemophilia Centres Doctors' Organization and the operational costs are supported by the National Health Service (which procures blood products) via a yearly registration fee paid by each HTC. In Australia, the cost for hemophilia registries is incorporated into the acquisition cost for plasma clotting factor concentrates, as are the handling, stocking, and distribution costs through the National Blood Authority (the blood product procurement agency). Similar models are in place in Ireland and New Zealand. Embedding the cost for registry data collection into the treatment acquisition cost for inherited bleeding disorders seems to be an effective way of supporting the critical activity of generating real-world evidence on treatment for inherited bleeding disorders. This also serves to minimize the need (and associated conflict of interest) to receive funding from pharmaceutical manufacturers or other third-party agencies. It would be interesting to explore in further detail such an approach for Canada and estimate the associated return on investment. Considering the volume of the market, the cost of the registry, and the savings introduced by having an effective tendering and procurement system implemented by the Canadian blood product providers, it is very likely that the net balance would lean toward significant savings, and improved patient health and satisfaction in most settings implementing various levels of universal care provision.

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Conflicts of Interest

All authors reported their conflicts of interest as follows:

Alfonso Iorio received research grants from Roche and payments for academic appointments from Bayer, and he held senior committee positions with the Association of Hemophilia Clinic Directors of Canada and the World Federation of Hemophilia.

David Matino received funding for travel and speaking engagements from Bayer and other companies and research grants from Bayer, Sanofi, and Pfizer.

Jayson Stoffman had speaking engagements and consultations with Bayer and Hoffmann-LaRoche Ltd.

Jean-Eric Tarride received research grants from Assurex/Myriad, Edwards, and Boehringer Ingelheim; and consultant payments from Amgen, Bayer, Evidera, Analytica Laser International, Lilly, Merck, and Novartis.

Jerry Teitel consulted for Roche and received payments for serving on advisory boards, data monitoring committees, and steering committees for other companies.

Lorraine Boyle, Sylvian Grenier, Emma Iserman, Arun Keepanasseril, and David Page completed conflict-of-interest forms and had no conflicts to declare.

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