PROTOCOL

World Bleeding Disorders Registry (WBDR)

WFH
WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

Authors:
Donna Coffin, MSc, Director of Research & Public Policy, WFH
Glenn Pierce, MD, PhD, Board of Directors, WFH
Alain Baumann, CEO, WFH

Introduction and Rationale

Hemophilia is a rare genetic bleeding disorder, which affects one in 5,000 births, almost exclusively males, and an estimated 400,000 people worldwide.(1) Despite great advances made in hemophilia care in the past 50 years, marked differences in treatment practices and access to therapies exist in much of the world. Patients around the world continue to suffer from increased morbidity and mortality due to bleeding into joints, muscles, the brain, and other sites.(2)

The advancement of evidence-based care of hemophilia and other rare bleeding disorders is limited by factors inherent to research in rare diseases: small samples sizes, geographical dispersion of patients, and heterogeneity in the clinical course observed in patients.(3) Combined, these factors diminish a study's statistical power, making the generation of high quality evidence in clinical and treatment outcomes in rare diseases challenging. This has given rise to a call for global rare-disease registries.(4)

Registries, with international collaboration between centres and countries, are an effective way to pool data in order to achieve a sufficient sample size to enable epidemiological and clinical research for rare disorders.(5, 6) Patient registries provide a real-world setting in which clinical therapies, drug safety, and quality of care can be monitored.(7) The observational component of a prospective, longitudinal clinical registry can facilitate multiple epidemiological, clinical, and intervention studies.(8) They also provide a cohort of patients from which subsequent clinical trials can rely upon for patient recruitment.(7) Increasingly, regulatory bodies around the globe (9-12) are relying on supplemental real world data, including patient registry data, to inform their regulatory and reimbursement decisions, health technology assessments, and treatment guidelines.

As part of the WFH's vision of treatment for all, the WFH has established that collecting data and generating evidence is an essential activity in achieving this goal. In 2000, the WFH began collecting country level data on the epidemiology of hemophilia and care around the world in the Annual Global Survey (AGS). Since then, the number of identified patients has increased from 78,629 to 187,183 and has shed light on the discrepancies of adequate care around the world.(13) Several studies have been published utilizing AGS data, which have pointed to large disparities in both patient identification and treatment based upon a country's socioeconomic status.(14-17) These results have formed the basis for WFH resource allocation and humanitarian aid efforts.

To meet the challenge of increasing the amount and type of data available on patients with bleeding disorders, the WFH is developing a World Bleeding Disorders Registry (WBDR), which will complement the AGS data by providing patient level data from individual treatment centers. This registry is intended to collect real world data on the patient clinical experience around the globe, allowing researchers to use country specific data and country comparative data to generate evidence and build advocacy initiatives aimed at health policy decision makers.

With reach to a network of over 1,000 Hemophilia Treatment Centres (HTCs) and 134 National Member Organizations, and with access to patients in countries with varying levels of quality of care, the WFH is uniquely positioned to effectively conduct such a global registry. Importantly, unlike many country specific registries which aim to capture all patients within a given country, the WBDR intends to sample a sufficient number of patients in a large number of different countries to permit adequate analyses to be performed.

2018

Objectives

Significant and numerous evidence gaps supporting optimal care of bleeding disorders still exist, which are difficult to address with conventional clinical study designs, such as randomized controlled trials.

The WBDR is intended to fill this gap by generating an unprecedented amount of real-world data, which will be tremendously useful for generating evidence to improve the quality of care worldwide. As data accumulates, the WBDR will be able to address gaps in evidence, such as assessing optimal timing, duration, and dosage of prophylaxis for different populations.(18)

More specifically, the WBDR will aim to address the following:

1. Identified gaps in evidence related to diagnosis, access to care, treatment, and outcomes in patients, such as:
    - Comparative evaluation of preventative treatment regimens (e.g., prophylaxis)
    - Identification of high risk populations
    - Inhibitors and other complications of BD
    - Trends in treatment patterns over time
    - Discrepancies in quality of care
    - Data on factor utilization
2. Collection of data to support advocacy initiatives aimed at improving diagnosis and access to care around the world, such as:
    - Burden of disease data:
        - Annual bleeding rate
        - Functional assessment
        - Hospitalization
        - Lost days of school / work
        - Educational / employment attainment
    - Between country discrepancies in factor usage

3

Methods

Study Design

The WBDR is a prospective, observational, and longitudinal registry of patients diagnosed with hemophilia.

Study Population

Patients will be recruited through participating hemophilia treatment centers (HTCs). Hemophilia treatment centers from all levels of economic development, based on the World Bank Gross National Income classification, will be invited to join the WBDR starting in late-2017, and patient recruitment will begin at HTCs upon ethics approval. Over the first 5-year period, from 2018-2023, the WBDR seeks to include HTCs from > 50 countries, representing > 200 of all HTCs worldwide, and > 10,000 individuals with hemophilia.

The inclusion criteria for the registry are patients with hemophilia A, hemophilia B, and hemophilia type unknown who are registered at one of the participating HTCs. The inclusion of patients with von Willebrand disease (VWD) and other rare bleeding disorders (RBD) will be considered in the future. There are no exclusions based on age or severity of disease.

Variables and Outcomes

The variables included in the data collection forms in the WBDR were established by a Steering Committee represented by clinicians, patients, researchers, and methodologists, from countries around the world, including Canada, India, Netherlands, Senegal, UK, and USA. The outcomes of interest are evidence based, selected based on published recommendations and definitions by consensus of internationally recognized experts. They include demographic characteristics, clinical and treatment related outcomes, burden of disease outcomes, and patient reported outcomes. Many of the outcomes have been identified as patient important outcomes in hemophilia.(19)

The variables and outcomes included in the WBDR are:

Minimal Data Set (minimal details on the following variables)

- Demographics
- Baseline characteristics
- Diagnostic data
- Inhibitor status
- Bleeding events
- Joint disease
- Treatment
- Hospitalization
- Mortality

Extended Data Set (expanded details on the following variables)

- Demographics *(age, sex)*
- Baseline characteristics *(diagnosis, severity, clotting factor activity, weight, height, employment status, education attainment)*
- Diagnostic data *(date, age, primary bleeding disorder, lab tests, factor assay, inhibitor status)*
- Medical history *(data before diagnosis, family history)*
- Complications, comorbidities *(inhibitors, HIV, HCV, joint damage)*
- Bleeding events *(frequency and location, at every follow up)*
- Joint disease *(range of motion, mobility)*
- Treatment *(prophylaxis, episodic, first 50 exposures, product, regimen)*
- Hospitalization *(duration, reason)*
- Mortality *(cause)*

Additional Modules

- Quality of Life scale (EQ-5D-5L)
- Functional scales
    - Range of Motion
    - Joint Disease
    - WFH Score (aka Gilbert Score)
    - Hemophilia Joint Health Score (HJHS)
    - Functional Independence Score for Patients with Hemophilia (FISH)

Implementation Plan

Starting in 2017, invitations were sent to HTCs globally, aiming for participation of at least 200 HTCs in 50 countries, over 5 years. The WFH works closely with HTCs to ensure local ethics approval. At approved HTCs, consecutive patients who meet the inclusion criteria will be approached to participate in the WBDR by the principal investigator and/or medical staff at the HTCs. Patients will receive a copy of the consent form to read and have time to ask any questions before signing. Data will be collected at baseline visit (visit the patient signs the consent form) and prospectively thereafter. Patients will remain in the registry and continue to contribute data until either the registry is terminated or the patient no longer wishes to participate. Inclusion in the registry will not affect the patient's care or the clinical practice routine of the HTC. The registry will begin with collection of the minimal dataset in 2018. The extended dataset will be implemented in January 2019. A mobile application to record bleeding events and treatments will be added in 2019. Engagement of the HTCs will be facilitated by the long established relationships WFH has with the local HTCs, which are in turn closely aligned with the national member organizations within each country.

Patient Withdrawal

A patient may withdraw from the registry at any time for any reason, or they may be withdrawn by the principal investigator. If a patient withdraws from the registry, no additional data will be collected. The registry data for that patient will be retained and analyses will continue to use any data collected before with withdrawal of consent.

Data Governance

Using data from registries is a powerful clinical research tool. It is anticipated that the WBDR will hold data on > 10,000 patients with hemophilia A and B, within 5 years. This large amount of data on patients will facilitate multiple epidemiological and clinical studies, including prevalence and incidence, define the clinical manifestations and sequelae associated with hemophilia and comparative effectiveness studies for existing and new treatments. These data will also be used for advocacy purposes for under developed areas. On a case by case basis, reports and documents using the WBDR data can be tailored to assist countries in need, to advocate for policy change and improved quality of care.

Through an approval process, participating researchers will be able to use the WBDR data for many purposes: to conduct research studies; to advance the clinical science; to supplement RCT data in regulatory applications; to support policy change; and to inform HTAs and treatment guidelines. Researchers will have the opportunity to submit questions to the WBDR Research Committee overseeing the data usage. Patients will also have an opportunity to submit research questions that they have, based on their personal experiences.

A Research Committee overseeing the research studies using the real world data stemming from the registry will be established by the WFH. The Research Committee's main functions will be to encourage use of data, evaluate data requests and study proposals for scientific merit, support researchers with the development and implementation of their research studies, encourage researchers to meet publication and presentation timelines, create awareness of the WBDR and involvement by the scientific community, and encourage researchers to publish and disseminate their findings.

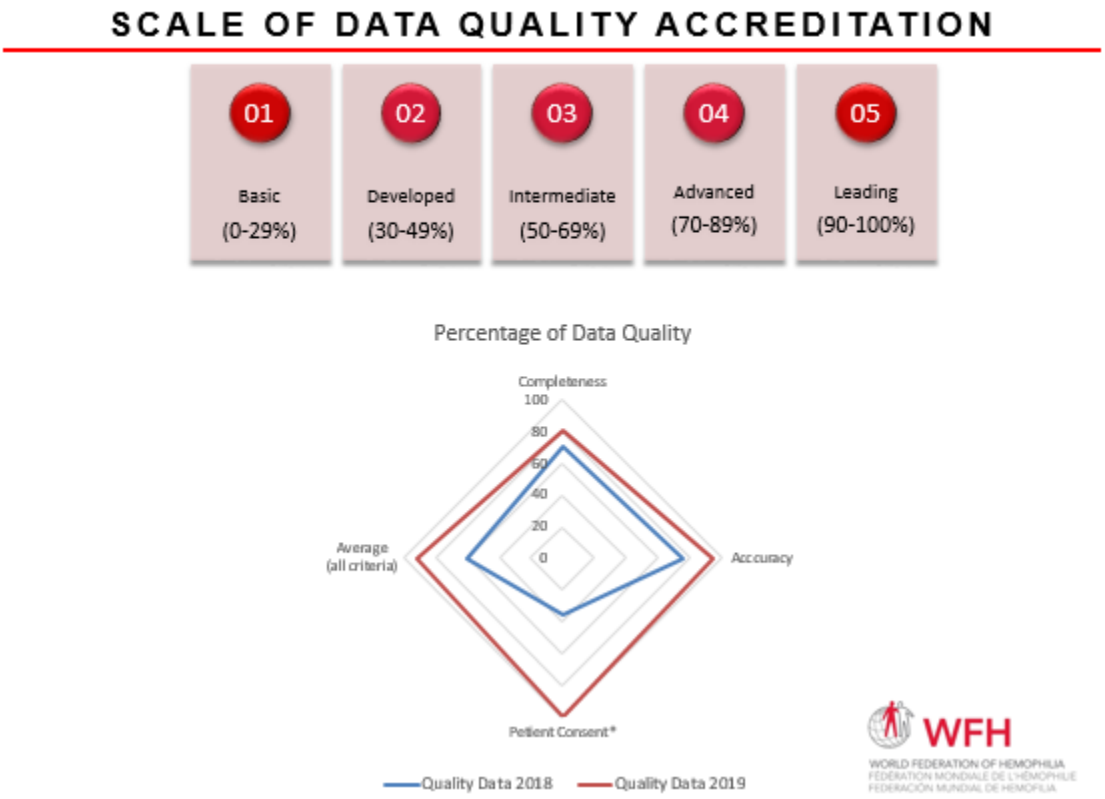
Data Quality

The Data Quality Program, aimed at ensuring data is accurate and complete, includes Data Collection Workshops, aimed at building capacity and knowledge in countries with little experience in the collection of high quality data. Regional and national workshops are held around the world. In 2017-2018, workshops were conducted in South Africa, Jordan, Costa Rica, Columbia, Kyrgyzstan, Myanmar and Sri Lanka. The series will continue in 2019 with the first workshop planned for January 2019 in Kuala Lumpur. Investigators meeting and in-person training will occur at international conferences, and regional managers will be available to answer questions.

The WBDR has implemented a Data Quality Accreditation Program, where each HTC providing data to the WBDR is rated against WFH's data quality standards on. All data (100% of patient data, on 100% of

patients at each HTC) are assessed on the 3 criteria of data quality: completeness, accuracy and patient consent. Each HTC is attributed to a level on the scale of data quality (Figure 1). All HTCs reaching the Leading level (90-100% of data is complete and accurate), will be recognized as such in the WFH WBDR Annual Report.

2018



Data Dissemination

Data and knowledge will be shared via an Annual Report of the WBDR, periodic newsletters updating contributors and researchers on events and accomplishments with the WBDR, and presented at an annual meeting. Publications and presentations will be managed through the Research Committee.

Data Harmonization & Linkage

To facilitate the scientific evaluation of clinical and treatment outcomes, the sharing and pooling of data between registries are critical and only possible if data are collected using similar operational definitions of outcomes and measurement scales. Linking registries at the patient level will allow us to maximize the quantity of data on patients with hemophilia from around the world and make the best use of our data in a limited environment. As a first step towards data integration, the WFH is conducting a Proof of Concept study, with the Czech Republic National Hemophilia Program registry, to establish a methodology to enable data integration into the WBDR from other hemophilia registries. Our objective is to develop a

7

simple, cost-effective methodology of data transfer between the Czech Republic's national registry and the WBDR, integrating an optimal set of important core data fields, based on the minimal data set. The end goal is to create a standard process to accept de-identified patient data from existing patient registries, while ensuring patient privacy and data security as well as compliance with relevant legislation. The Proof on Concept study is being conducted in collaboration with the WFH, the Czech Republic national registry and Health Solutions.

Database Hosting

The web-based data entry system is being be developed, maintained and hosted by the Karolinska Institute and Health Solutions, both based in Sweden.

Privacy and Confidentiality

The database will be hosted in a secure data center with appropriate physical, administrative and technical safeguards in place. These procedures are aimed to protect information from misuse, unauthorized access, interference, alteration, loss and/or disclosure, which will meet or exceed the privacy and security regulation requirements in Canada. Data policy guidelines of Health Solutions adhere to both the CE-mark (Conformité Européenne) and the UK standard IGSoc (Information Governance Standard of Compliance). The WBDR database is compliant with the new General Data Protection Regulation which went into effect as of 25 May 2018.

Steering Committee

A global WBDR Steering Committee of clinicians, patients, researchers, and methodologists has been assembled to develop and implement the World Bleeding Disorder Registry.

Committee Members

- Barbara Konkle, MD, USA, Co-chair
- Alfonso Iorio, MD, Canada, Co-chair
- Vanessa Byams, PhD, CDC, USA
- Saliou Diop, MD, Senegal
- Cedric Hermans, MD, Belgium
- Declan Noone*, Ireland
- Jamie O'Hara*, M.Sc., UK
- Marijke van den Berg, MD, Netherlands,
- Glenn Pierce*, MD, PhD, USA, WFH VP Medical, Ex-officio
- Alain Weill*, France, WFH President
- Donna Coffin, MSc, WFH
- Mayss Naccache, MSc, WFH

2018

*patient representatives

Timeline

	Start Date	End Date
Pilot project	April 2016	December 2016
Assessment of pilot project	January 2017	March 2017
Identification of collaborating academic institution	January 2017	July 2017
Implement WBDR	August 2017	ongoing

References

1. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Hematol. 1998;Dec;59(4):288-94.
2. Mazepa M, Monahan P, Baker J, Riske B, Soucie J. US Hemophilia Treatment Center Network. Men with severe hemophilia in the United States: birth cohort analysis of a large national database. Blood. 2016;127(24):3073-81.
3. Augustine E, Adams H, Mink J. Clinical Trials in Rare Disease: Challenges and Opportunities. J Child Neurol. 2013;Sep;28(9):1142-50.
4. Forrest C, Bartek R, Rubinstein Y, Groft S. The case for a global rare-diseases registry. Lancet. 2011;377(9771):1057-9.
5. Berntorp E. Future of haemophilia outcome assessment: registries are key to optimized treatment. J Intern Med. 2016;279(6):498-501.
6. Keipert C, Hesse J, Haschberger B, Heiden M, Seitz R, van den Berg H, et al. The growing number of hemophilia registries: Quantity vs. quality. Clin Pharmacol Ther. 2015;May;97(5):492-501.
7. Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm.
8. Potter B, Khangura S, Tingley K, Chakraborty P, Little J. Translating rare-disease therapies into improved care for patients and families: what are the right outcomes, designs, and engagement approaches in health-systems research? Genet Med. 2016;18(2):117-23.
9. Bate A, Juniper J, Lawton A, Thwaites R. Designing and incorporating a real world data approach to international drug development and use: what the UK offers. Drug Discov Today. 2016;Mar;21(3):400-5.
10. Garrison L, Neumann P, Erickson P, Marshall D, Mullins C. Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health. 2007;10(5):326-35.
11. Parker S. The pooling of manpower and resources through the establishment of European reference networks and rare disease patient registries is a necessary area of collaboration for rare renal disorders. Nephrol Dial Transplant. 2014;Sep;29(Suppl 4):iv9-14.
12. Nason E, Husereau D. Roundtable on Real World Evidence. System Readiness - Are we ready to use routinely collected data to improve health system performance? Summary Report. Institute of Health Economics. September 2015;Available at: http://www.ihe.ca/research-programs/knowledge-transfer-dissemination/roundtables/real-world-evidence/rwe-docs (Accessed on 15September2016).
13. World Federation of Hemophilia. Report on the Annual Global Survey 2015.Available at: http://www1.wfh.org/publication/files/pdf-1669.pdf; Accessed on 20 December 2016. October 2016.
14. Stonebraker J, Bolton-Maggs P, Brooker M, Farrugia A, Srivastava A. A study of reported factor IX use around the world. Haemophilia. 2011;May;17(3):446-55.
15. Stonebraker J, Bolton-Maggs P, Soucie J, Walker I, Brooker M. A study of variations in the reported haemophilia A prevalence around the world. Haemophilia. 2010;Jan;16(1):20-32.
16. Stonebraker J, Bolton-Maggs P, Soucie M, Walker I, Brooker M. A study of variations in the reported haemophilia B prevalence around the world. Haemophilia. 2012;May;18(3):e91-4.
17. Stonebraker J, Brooker M, Amand R, Farrugia A, Srivastava A. A study of reported factor VIII use around the world. Haemophilia. 2010;Jan;16(1):33-46.
18. Windyga J. Is Continuous Low-Dose Prophylaxis Superior to On-Demand Treatment for Patients with Hemophilia? Semin Thromb Hemost. 2016;Jul;42(5):533-40.
19. Pai M, Key N, Skinner M, Curits R, Feinstein M, Kessler C, et al. NHF-McMaster guideline on care models for haemophilia management. Haemophilia. 2016;22 (Suppl 3): 6–16.