PROTOCOL

World Bleeding Disorders Registry (WBDR)

Version History and Date

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Introduction and Rationale

Hemophilia is a rare genetic bleeding disorder that has a prevalence of 17.1 cases for Hemophilia A and 3.8 for Hemophilia B per 100,000 males.(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)

Inherited von Willebrand disease (VWD) is the most common bleeding disorder, with an approximated 1% prevalence in the general population.(3) Current classification of VWD include 3 types: types 1 and 3, which are distinguished by quantitative deficiencies of von Willebrand factor (VWF), as well as types 2A, 2B, 2M, and 2N, which are qualitative variants.(4) Achieving an accurate and timely diagnosis remains a major challenge for patients and clinicians. Barriers to diagnosis include a lack of understanding of the difference between normal and abnormal bleeding symptoms, difficulty in identifying the appropriate diagnostic approach, and limited availability and expertise of laboratory testing.(5-8)

The advancement of evidence-based care of hemophilia, VWD, 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.(9) 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.(10)

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.(11, 12) Patient registries provide a real-world setting in which clinical therapies, drug safety, and quality of care can be monitored.(13) The observational component of a prospective, longitudinal clinical registry can facilitate multiple epidemiological, clinical, and interventional studies.(14) They also provide a cohort of patients from which subsequent clinical trials can rely upon for patient recruitment.(13) Increasingly, regulatory bodies around the globe are relying on supplemental real world data, including patient registry data, to inform their regulatory and reimbursement decisions, health technology assessments, and treatment guidelines. (15-18)

As part of the World Federation of Hemophilia (WFH) 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 people with hemophilia has increased from 78,629 to 256,840 and from 24,619 to 98,298 for people with VWD. AGS data continue to shed light on the discrepancies of adequate care around the world.(19) 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.(20-23) 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 has developed the World Bleeding Disorders Registry (WBDR), which complements the AGS data by providing patient-level data from individual treatment centres. 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 large network of Hemophilia Treatment Centres (HTCs) around the world and 147 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.

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.(24)

More specifically, the WBDR aims to address the following:

1. Identify 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 bleeding disorders
    - 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 / marital status

- Discrepancies in factor usage between countries

Methods

Study Design

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

Study Population

Patients are recruited through participating hemophilia treatment centres (HTCs). HTCs from all levels of economic development, based on the World Bank Gross National Income classification, were invited to join the WBDR in 2017, and patient recruitment can begin at HTCs upon ethics approval. Over the first 5-year period, from 2018-2022, the WBDR sought to include HTCs from over 50 countries, representing over 200 of all HTCs worldwide, and > 10,000 individuals with hemophilia.

The inclusion criteria for the registry are patients, males and females, who are registered at one of the participating HTCs and who are diagnosed with hemophilia or with VWD, regardless of the type and severity of the disease. Patients for whom the type of hemophilia or VWD is unknown can also be enrolled. 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 and VWD.(25, 26)

The variables and outcomes for **hemophilia** included in the WBDR are:

Demographics	**Diagnostics**	**Clinical**
Date of birth	Date of diagnosis	Bleeding events
Gender	Hemophilia type	Target joints
Country of residence	Hemophilia severity	Treatments
Employment	Hemophilia factor level	Inhibitor status
Education	Inhibitor history	Hospitalization
Marital status	Treatment history	Mortality
	Bleeding history	Adverse events

	Genetic testing	Comorbidities
	Blood type	Pregnancy
	Family history	

The variables and outcomes for **VWD** included in the WBDR are:

Demographics	**Diagnostics**	**Clinical**
Date of birth	BAT Score	Bleeding events
Gender	VWD type	Target joints
Country of residence	VWD diagnostic tests	Treatments
Employment	Inhibitor history	Inhibitor status
Education	Treatment history	Hospitalization
Marital status	Bleeding history	Mortality
	Genetic testing	Adverse events
	Blood type	Comorbidities
	Family history	Pregnancy

Additional Modules

- Patient-Reported Outcomes (PRO) through the myWBDR patient mobile app
    - Treatment
    - Bleeds
    - Burden of disease (PROBE) and quality of life (EQ-5D-5L)
- Quality of life questionnaire
    - EQ-5D-5L completed at the HTC
- Functional scales
    - Range of Motion
    - Joint Disease
    - WFH Score (Gilbert Score)
    - Hemophilia Joint Health Score (HJHS)
    - Functional Independence Score for Patients with Hemophilia (FISH)
- COVID-19

Implementation Plan

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 (the visit during which 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 began with the collection of the minimal dataset in 2018. The extended dataset was implemented in January 2019. myWBDR patient mobile application was launched progressively in 2021 (Appendix 1). It is available for enrolled VWD and hemophilia patients who wish to use it to record bleeding events and treatments, and to answer quality of life questionnaires including PROBE (hemophilia only) and EQ-5D-5L. Engagement of the HTCs will be facilitated by the long-established relationships the WFH has with 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 and 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 analysis will continue to use any data collected before the 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 more than 10,000 patients with hemophilia and VWD. This large amount of data on patients will facilitate multiple epidemiological and clinical studies, including prevalence, define the clinical manifestations and sequelae associated with these bleeding disorders and comparative effectiveness studies for existing and new treatments. These data will also be used for advocacy purposes for underdeveloped areas. On a case by case basis, reports and documents using the WBDR aggregated 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 randomized controlled trials data in regulatory applications; to support policy change; and to inform health technology assessments (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.

The WBDR Research Committee oversees the research studies using the real-world data stemming from the registry. The Research Committee's main functions is to encourage use of data, evaluate data requests, 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 and Accreditation Program was developed to ensure the data is accurate and complete. The Program offers Data Collection Workshops aimed at building capacity and knowledge. Regional and national workshops are held around the world. Since 2017, virtual and in-person workshops were conducted in over 16 countries.

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. All data (100% of patient data, on 100% of patients at each HTC) are assessed on the 2 criteria of data quality: completeness and accuracy. Each HTC is attributed to a level on the scale of data quality (Figure 1).

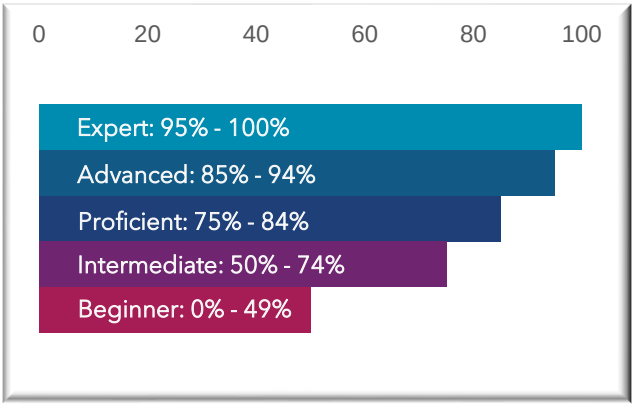

Figure 1. Rating scale of the WBDR Data Quality Accreditation Program

Data Dissemination

Aggregated data are shared via an Annual WBDR Data Report, periodic newsletters updating contributors and researchers on events and accomplishments, and presentations during annual meetings. Publications and presentations are 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 and VWD 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 conducted a Proof-of-Concept study with Czechia National Hemophilia Program registry, to establish a methodology to enable data integration into the WBDR from other hemophilia registries. We have successfully developed a simple, cost-effective methodology of data transfer between a national registry and the WBDR, integrating an optimal set of important core data fields. We created a standard process to accept de-identified patient data and aggregated data from existing patient registries, while ensuring patient privacy and data security as

well as compliance with relevant legislation. Up-to-date data are imported annually from participating national registries.

Database Hosting

The web-based data entry system is maintained and hosted by BCB Medical, based in Sweden.

Privacy and Confidentiality

The database is hosted in a secure data centre with appropriate physical, administrative and technical safeguards in place. These procedures ensure the protection of information from misuse, unauthorized access, interference, alteration, loss and/or disclosure, which will meet or exceed the privacy and security regulation requirements worldwide. Data policy guidelines of BCB Medical 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 General Data Protection Regulation.

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

- Alfonso Iorio, MD, Canada, Co-chair
- Emna Gouider, MD, Tunisia, Co-chair
- Catherine Lambert, MD, PhD, Belgium
- Barbara Konkle, MD, USA
- Saliou Diop, MD, Senegal
- Cedric Hermans, MD, Belgium
- Jamie O'Hara*, M.Sc., UK
- Glenn Pierce*, MD, PhD, USA, WFH VP Medical, Ex-officio
- Cesar Garrido, WFH President
- Donna Coffin, MSc, WFH
- Emily Ayoub, PhD, WFH

*patient representatives

Protocol Amendment History

Original WBDR Protocol: version 4.4 (February 2019)

Amendment 1, protocol version 4.5 (October 2023)

Summary of changes include:

- The WBDR dataset were amended to reflect the latest addition of data fields and modules.
- Details on the myWBDR mobile app were added in Appendix I, with the WBDR Steering Committee approval.
- The addition of VWD to the WBDR required a minor update to the protocol, including additions in the introduction and inclusion of VWD dataset.

Appendix I – myWBDR Patient Mobile Application

The myWBDR patient mobile app was developed and launched by the WFH in June 2021 to serve two main objectives: 1) provide patients with a tool to record and monitor their bleeds, treatment, and quality of life; 2) collect Patient-Reported Outcomes (PRO) to complement the WBDR real-world data collected by healthcare providers at the HTC.

myWBDR allows the patient to enter data on the following:

- Bleeding events (date, location, pain level, treatment)
- Treatment (date, indication, dose, drug,)
- EQ-5D-5L quality of life questionnaire
- PROBE questionnaire

A collaboration with the PROBE team facilitates the use of the EQ-5D-5L and PROBE questionnaires through myWBDR. Other features include a calendar and a dashboard where patients can visualize their treatment and bleed history.

Importantly, the data collected through the App are stored in the WBDR database and can be viewed by healthcare providers at the patient's own HTC.

Patient participation and consent

The App is available to all hemophilia and VWD patients enrolled in the WBDR. Using the App is optional and does not affect the patient's status in the WBDR. Patients can sign-up to use myWBDR by themselves via the app store or they can sign-up through the WBDR online platform with the help of their healthcare provider at the HTC.

The HTC is not required to facilitate patient consent to use the App. Patients give their consent through the App directly after reading the myWBDR Terms of Use and myWBDR Privacy Policy.

Data Privacy and confidentiality

All myWBDR patient data are stored in the WBDR database. These data are de-identified and confidential and follow the same data privacy and protection guidelines that apply to the WBDR data collected through the online data entry system at the HTC level. More information can be found in myWBDR Privacy Policy and myWBDR Terms of Use documents.

References

1. Iorio A, Stonebraker JS, Chambost H, Makris M, Coffin D, Herr C, et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-6.
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. Rodeghiero F, Castaman G, Dini E. Epidemiological investigation of the prevalence of von Willebrand's disease. Blood. 1987;69(2):454-9.
4. James PD, Connell NT, Ameer B, Di Paola J, Eikenboom J, Giraud N, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Adv. 2021;5(1):280-300.
5. Sidonio RF, Jr., Zia A, Fallaize D. Potential Undiagnosed VWD Or Other Mucocutaneous Bleeding Disorder Cases Estimated From Private Medical Insurance Claims. J Blood Med. 2020;11:1-11.
6. James AH. Von Willebrand disease in women: awareness and diagnosis. Thromb Res. 2009;124 Suppl 1:S7-10.
7. Favaloro EJ, Pasalic L, Curnow J. Laboratory tests used to help diagnose von Willebrand disease: an update. Pathology. 2016;48(4):303-18.
8. De Jong A, Eikenboom J. Developments in the diagnostic procedures for von Willebrand disease. J Thromb Haemost. 2016;14(3):449-60.
9. Augustine E, Adams H, Mink J. Clinical Trials in Rare Disease: Challenges and Opportunities. J Child Neurol. 2013;Sep;28(9):1142-50.
10. Forrest C, Bartek R, Rubinstein Y, Groft S. The case for a global rare-diseases registry. Lancet. 2011;377(9771):1057-9.
11. Berntorp E. Future of haemophilia outcome assessment: registries are key to optimized treatment. J Intern Med. 2016;279(6):498-501.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.
17. 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.

18. 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).
19. World Federation of Hemophilia. Report on the Annual Global Survey 2021.Available at: https://www1.wfh.org/publications/files/pdf-2324.pdf; Accessed on 19 October 2023. October 2022.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. Connell NT, Flood VH, Brignardello-Petersen R, Abdul-Kadir R, Arapshian A, Couper S, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Blood Adv. 2021;5(1):301-25.