# THE PATIENT REPORTED OUTCOMES, BURDENS AND EXPERIENCES (PROBE) STUDY

# THE PATIENT REPORTED OUTCOMES, BURDENS AND EXPERIENCES (PROBE) STUDY

BY

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## ABSTRACT

Outcomes measurement is an important component of routine hemophilia care, clinical trials and economic evaluations. Assessing outcomes in patients living with hemophilia is challenging due to a lack of validated outcome measures. Conventional clinical outcomes, for instance, bleeding rate, structural changes of joints or functional joint scores may be less relevant for the decision-making process. Patient reported outcomes measures has been increasingly interested in routine medical care and clinical research. However, the available validated patients reported outcome measures for patients with hemophilia are not generally implemented in routine care or clinical trials.

The Patent Reported Outcomes, Burdens, and Experiences (PROBE) study aims to develop a validated patient reported outcome measure for patients living with hemophilia. The PROBE questionnaire is organized in 4 sections, comprising 29 questions. Section I contains questions pertaining to demographic data. Section II contains questions pertaining to patient reported outcomes. Section III contains questions pertaining to hemophilia specific problems and treatments. Section IV contains the EuroQol five dimension 5-level instrument (EQ-5D-5L).

The psychometric analysis of revealed that the PROBE questionnaire has a good internal consistency (Cronbach's alpha coefficient=0.84). PROBE items showed moderate to strong correlations with corresponding EQ-5D-5L domains. The PROBE Score has a known group validity among known groups. The psychometric properties of

the PROBE questionnaire demonstrated the validity of the instrument in both patients living with hemophilia and control population (participants without bleeding disorder).

The test-retest reliability analysis demonstrated that the PROBE questionnaire has a substantial agreement when the questionnaire was repeatedly administrated. There were acceptable reliability properties between the paper-based and web-based questionnaires. The reliability properties of the PROBE questionnaire were established in both patients living with hemophilia and control population.

The PROBE questionnaire was cross-cultural implemented in 21 countries. The results showed that the regions of participant contributed a trivial variability of the PROBE score, indicating that the PROBE questionnaire is valid for assessing the health status among hemophilia patients and participants without bleeding disorder across regions.

Sexual health of patients living with hemophilia was evaluated using the PROBE questionnaire. The results showed that sexual difficulty was more prevalent in patients with hemophilia and associated with markers of disease severity. This finding warrants the sexual health assessment in routine hemophilia care.

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Lastly, I would like to thank all patients and participants who joined the PROBE study. Their inputs will help us develop the outcome measurement tool for hemophilia patients around the world.

## DEDICATION

This thesis is dedicated to my parents for their love and endless support.

# PREFACE

This thesis has been conducted as a sandwich thesis and consists of four individual manuscripts. At the time of writing, two of four individual manuscripts have been submitted to the journals. The remaining manuscripts will be submitted to the journals soon.

Dr. Chai-Adisaksopha was the principle contributor to the design and conception of the studies under the guidance from Dr. Alfonso Iorio and Mark Skinner. Dr. Chai-Adisaksopha generate the algorithm to calculate the PROBE score. Dr. Chai-Adisaksopha performed data cleaning, data analysis, manuscript writing and manuscript submitting.

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# LIST OF ILLUSTATIONS

## LIST OF ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome

ANCOVA: analysis of co-variance

ANOVA: analysis of variance

CHO-KLAT: Canadian Hemophilia Outcomes-Kids Life Assessment Tool

CI: confidence interval

EQ-5D-5L: EuroQol five dimension 5-level instrument

EQ-VAS: EuroQol visual analog scale

F: factor

FDA: Food and Drug Administration

HAL: Hemophilia activity list

HCV: hepatitis C virus

HIV: Human immunodeficiency virus

HRQoL: health-related quality of life

ICF: International Classification of Functioning, Disability and Health

ISPOR: International Society for Pharmacoeconomic and Outcomes Research

NHF: National Hemophilia foundation

NGO: non-governmental organization

OR: odds ratio

PRO: Patient reported outcome

PROBE: Psychometric properties of the Patient Reported Outcomes, Burdens and Experiences

PWH: people with hemophilia

SD: standard deviation

SF-36: 36-Item Short Form Survey

T: time

# CHAPTER 1

# INTRODUCTION

## GENERAL INTRODUCTION

Hemophilia is an inherited bleeding disorder caused by mutations in the gene encoding factor VIII (FVIII)-hemophilia A or factor IX (FIX)-hemophilia B. Prevalence is about 1 in 5,000 male live birth for hemophilia A and 1 in 40,000 for hemophilia B [1, 2]. The deficiency of coagulation protein results in defects in the clot formation. Consequently, patients with hemophilia are prone to have spontaneous bleeds in soft tissues, joints and muscles. The frequency and severity of bleeding correlate with the residual plasma level of coagulation factor. The disease severity is classified as severe when plasma level< 1 IU/dL, moderate when plasma levels are between 1 and 5 IU/dL and mild when plasma level> 5 but <40 IU/dL [3]. The diagnosis of hemophilia can be made by measuring plasma levels of FVIII or FIX. Genetic testing can be performed to confirm the diagnosis in de novo patients or patients with known family mutation.

The current standard of care in patients with severe hemophilia is a prophylaxis with factor concentrates. The goal of a prophylaxis is to maintain plasma level of coagulation factor around 1-2%. This rational was derived from the observation that mild to moderate hemophilia that patients had many fewer bleeding events as compared to those with severe hemophilia [4]. Data from a clinical trial supported that regular prophylaxis reduces frequency of hemarthrosis and other bleeding events when compared to on-demand treatment. Moreover, prophylaxis prevents further joint damage [5]. As a result, patients receiving regular prophylaxis tend to have an improvement of health related quality of life [6].

The advancement of the management in hemophilia, particularly with regards to the availability of factor concentrates and the provision of a high standard of care increases life expectancy of patients living with hemophilia [7]. However, hemophilia patients still experience long-term complications, including chronic joint pain, limitations of range of motion and limitations in daily activities [8, 9], hepatitis C virus (HCV) and Human Immunodeficiency Virus (HIV) infection in patients treated with plasma-derived factor prior to mid-1980s [10-12] and development of alloantibodies to FVIII or FIX [13].

Aging patients with hemophilia have become an emerging issue since the life expectancy of these patients is approaching that of the general population [14]. Studies report that the prevalence of atherosclerosis in patients with hemophilia is similar to the general population [15, 16]. In addition, patients with hemophilia who have cardiovascular risk factors, e.g. hypertension or hyperlipidemia, are at increased risk of atherosclerotic events [17]. Patients with hemophilia may also develop malignancies. Consequently, malignancies are considered as important causes of mortality in aging hemophilia patients [18, 19].

**Outcomes measurement in hemophilia**

Assessing outcomes in hemophilia is challenging. Outcome data allow treating physicians to determine the efficacy of treatment regimens [20]. In addition, from the funders' point of view, outcome data justify resource utilization for patients. The International Symposium on Outcome Measures in Hemophilic Arthropathy proposed recommendations for choosing outcome measures for assessing musculoskeletal health in

patients with hemophilia [21]. These recommendations were developed based on the International Classification of Functioning, Disability and Health (ICF) framework [22]. The expert committee recommended measuring bleeding, physical examination and imaging for assessing joint function and structure. Activities should be assessed by self-reported activities or observed activities. Participation should be assessed by days lost from school/work or paid employment. Lastly, economic evaluation should be assessed by clotting factor consumption, hemophilia-related surgeries and hospital visits.

**Patient reported outcomes instrument in hemophilia**

One of the major challenges of assessing outcomes in patients with hemophilia is a lack of validated outcome measurements [20]. The use of conventional outcomes, for example bleeding or bleeding rate, may be less important from patients' perspective. The recent National Hemophilia foundation (NHF)-McMaster Guideline on Care Models for Haemophilia Management has identified important outcomes which included mortality, missed days of school or work, number of emergency room visits, length of hospital stays, quality of life, joint damage or disease, educational attainment, patient adherence and patient knowledge [23]. Moreover, patients' perspectives on treatment outcome may differ from those of clinicians [24]. Therefore, using patient-centric approaches for outcome assessment has been become common in the clinical management of chronic diseases including hemophilia [25].

Patient reported outcomes (PRO) are defined as any report of the status of a patient's health condition that comes directly from a patient without interpretation by

clinician or anyone else [26]. PRO may contain type, frequency and severity of symptoms, disability, impact of disease on daily activities or perception of a patient towards a disease or a treatment [27]. Data directly obtained from patients are essential for improvement of hemophilia care [28]. Self-reported assessment allows clinicians, funders and stakeholders better understand patients' health conditions.

The available PRO in hemophilia are mainly focusing on health-related quality of life, physical functioning and treatment satisfaction [29]. Table 1 demonstrates the PRO instruments used in the assessment of patients with hemophilia. All these instruments were developed and validated specifically for hemophilia patients. Most of them have been translated to other languages. The psychometric properties were evaluated for each instrument. The following is a summary of the characteristics, target population(s) and psychometric properties of available PRO measures.

*Health related quality of life*

1. **Canadian Hemophilia Outcomes-Kids Life Assessment Tool (CHO-KLAT)**

   CHO-KLAT has been developed for children age 4-18 years [30]. The revised version of the CHO-KLAT (version 2.0) comprises 35 items [31]. This tool measures physical health, feeling, sense of self, perceived support, sports and school, dealing with hemophilia, treatment, future, global health and relationships. Potential scores range from 0-100 (worst-best). The psychometric properties of CHO-KLAT have been assessed. The tool's content validity was excellent [30, 31]. Test-retest reliability was good (intraclass correlation 0.74 for children and

0.83 for parent) [32]. Construct validity was fair to excellent [32-34]. The tool was originally developed in English language and has been translated to 20 languages. The French and Chinese version of CHO-KLAT were assessed for psychometric properties and found to be valid for content validity and hypothesis testing [35, 36].

2. **Haemo-QoL**

   Haemo-QoL was developed for children in 3 age groups (4-7, 8-12 and 13-16 years) [37]. There were 6 languages available in the original version of Haemo-QoL (English, Dutch, French, German, Italian and Spanish). The tool comprises 21 to 77 items depending on the age specific version, covering the following domains: physical health, feeling, view, friends, family, others, sport and school, treatment, perceived support, dealing with hemophilia, future and relationships. The internal consistency was acceptable, ranging from 0.85-0.91 for the different age groups [37]. The score ranged from 0-100 (best-worst). The test-retest reliability was acceptable, ranging from 0.90-0.92 [37]. The construct validity was acceptable; the correlation ranged from -033 to -0.63 [38].

3. **Disease-specific quality of life in young children**

   The disease-specific quality of life in young children questionnaire was developed for children age 2-6 years. The questionnaire is administered by patients' parents [39]. The questionnaire comprises 39 questions, covering the following domains: somatic symptoms, physical function, sleep disturbance, stigma, social, fear, mood and behavior, restriction, treatment, concern and energy level. The original

version was developed in English. A version translated to other languages is not available. The internal consistency was acceptable, ranging from 0.73 to 0.94. The results correlated with two general pediatric quality of life tools, which indicated acceptable construct validity and content validity [39].

4. **Haem-A-QoL**

   Haem-A-QoL is a questionnaire developed for adults who have hemophilia. The questionnaire comprises 46 items, assessing the following domains: physical health, feelings, view of patients' self, sports and leisure, work and school, dealing with hemophilia, treatment, future, family, relationship and sexuality [40]. Internal consistency analysis revealed acceptable results with Cronbach's alpha>0.70 for all but one dimension [41]. Test-retest reliability was high. Haem-A-QoL$_{\text{Elderly}}$ was evaluated in elderly patients (age 65 years or older) [40]. Psychometric properties demonstrated good to excellent values for validity and reliability. The Greek and Turkish versions of Haem-A-QoL were assessed for psychometric properties and found to have acceptable values for test-retest reliability and construct validity [41, 42].

5. **Hemofilia-QoL**

   Hemofilia-QoL was developed in Spanish for adult hemophilia patients; it contains the following domains: physical health, physical and emotional role, damage, pain, treatment satisfaction, metal health and social support [43]. Internal consistency was acceptable with Cronbach's alpha of 0.94. The test-retest reliability test yielded an intraclass correlation coefficient greater than 0.80 (with

0.92 for the total score) [44]. Convergent validity assessment showed correlations with the SF-36 subscale ranging from 0.17-0.77. Discrimination between groups was demonstrated.

6. **HAEMO-QoL-A**

HAEMO-QoL-A was developed for adult hemophilia patients. The questionnaire comprises of 41 items in 4 domains (daily activities, mood and feelings, social and family life (including work and school life) and hemophilia treatment [45]. The internal consistency was good to excellent with the Cronbach's alpha of 0.75-0.95 [45]. Test-retest reliability was good with an intraclass correlation greater than 0.80 for most of the items. Convergent validity with HAEMO-QoL-A and SF-36 was good with correlations ranging from 0.13-0.87. The translated version of HAEMO-QoL-A in the French language was assessed and found to have a good correlation ($r$ =0.78) with the generic health related quality of life measure (SF-36) [34].

7. **Hemophilia Well-being Index**

The hemophilia Well-being Index was developed for adult hemophilia patients. The original version of the questionnaire was in Spanish [46]. The questionnaire contains 8 items (family, employment, well-being, school, leisure and free time, friends and relationships, partnership, religion, social activism, economic status and emotions). Internal consistency was excellent with Cronbach's alpha>0.90 in all items. Test-retest reliability revealed high reliability (0.82). Scores moderately

correlated with the SF-36 and the European Quality of Life-5 Dimensions (EQ-5D).

*Physical functioning*

1. **HEP-Test-Q**

   HEP-Test-Q is a validated questionnaire for assessing physical functioning in adult hemophilia patients [47]. The questionnaire comprises of 25 items pertaining to the following domains: mobility, strength and coordination, endurance and body perception. The score ranges from 0-100 (worst-best). Internal consistency was good with Cronbach's alpha of 0.96. Test-retest reliability shows good correlation with $r$=0.90. The convergent validity was evaluated by correlating with Haem-A-QoL, HAL and SF-36. Discriminant validity was also demonstrated.

2. **Hemophilia Activity List (HAL)**

   HAL is a questionnaire originally developed for adult hemophilia patients [48]. The questionnaire consists of 57 items pertaining to 8 domains (lying down/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks, leisure activities and sports and others). Internal consistency was high with a Cronbach's alpha of 0.93-0.95 [49]. The convergent validity was good ($r$=0.47–0.84) when compared to the Dutch-Arthritis Impact Measurement Scales and the Impact on Participation and Autonomy questionnaire [48]. PedHAL was developed to assess physical functioning in pediatric patients with hemophilia (age 4-18 years) [50]. The items

in PedHaL were adjusted and evaluated by a focus group which consisted of health professionals, patients and parents. Test-retest reliability was good. Construct validity was moderate when compared with joint examination and moderate to good when compare with the physical function subscale of the Child Health Questionnaire-50 (CHQ-50).

*Treatment satisfaction*

1. **Hemo-Sat$_A$**

   Hemo-Sat$_A$ was the first validated tool for assessing treatment satisfaction in adult patients with hemophilia [51]. The questionnaire was developed in Italian and it was linguistically validated in 24 languages. The Hemo-SatA contains 34 items assessing 6 domains (ease and convenience, efficacy, burden, specialist, center and general satisfaction). The Cronbach's alpha ranged between 0.71 to 0.95. The construct validity showed correlation with a life satisfaction scale.

**Limitations of existing patient reported outcome instruments**

There are limitations of the existing PRO instruments using in hemophilia patients. First, patient engagement for the instrument development was insufficient [24]. According to the US Food and Drug Administration (FDA) Guidance for Patient-Reported Outcome Measures, all PRO instruments have to be developed using direct input from patients the instruments intend to [26]. Hemophilia-QoL was developed and had input from patients only at the initial phase [43]. The later phases of the instrument development (item constructions and relevance of items) were carried out by the expert

opinion only. Second, the existing instruments were developed to assess either health-related quality of life, physical functioning or treatment satisfaction. There is no instruments that assess all aspects of patients' outcomes as recommended by the ICF framework [22]. Third, most instruments do not incorporate co-morbid disease assessment. As mentioned above, aged hemophilia patients may be affected by other co-morbid disease, for example, cardiovascular disease or cancers. Co-morbid diseases will have an impact on the patients' outcomes and treatment that current scales may fail to account for. Fourth, none of instruments provided data on responsiveness to changes in health status and minimal clinically important difference. Fifth, the validity analyses of the instruments were conducted using small numbers of participants. More importantly, the instruments were translated into several languages. However, cross-cultural validity studies were only performed in one instrument. Lastly, the instruments were developed and validated in patients with hemophilia. It is almost impossible to use the instruments to assess the general population or patients who had other chronic diseases for comparison.

**The Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire**

The PROBE study project is an international collaboration that aims to develop a standardized questionnaire for patients living with hemophilia [52]. In brief, the project was initiated by researchers who are mainly patients with hemophilia. The draft questionnaire was prepared by the investigators after a workshop, held in June 2013 in the Netherlands. The domains and items were derived from the Haemophilia Experiences, Results and Opportunities Summit (HERO Summit), literature review and opinions from patients, physicians and stakeholders. The draft version of the PROBE questionnaire was

evaluated by focus groups, comprised of patients with hemophilia, hemophilia experts, nurses and physiotherapist. Then the PROBE questionnaire was revised and reassessed for relevance, clarity and face validity by the investigators. After the PROBE questionnaire was finalized, an official translation was performed for 18 languages.

## STATEMENT OF PURPOSE

The purposes of this thesis were:

1. To determine the psychometric properties of the PROBE questionnaire, which included internal consistency reliability, convergent validity and known group validity.
2. To determine the test-retest reliability of the PROBE questionnaire in two platforms (paper-based and web-based).
3. To determine the regional variation when using the PROBE questionnaire in multiple countries.
4. To determine the prevalence of sexual difficulties among patients living with hemophilia in comparison with control population and to determine the variables that have an impact on sexual difficulties.

## HYPOTHESES

The main hypotheses of this thesis were that:

1. The PROBE questionnaire is a valid instrument for assessing health status of patients living with hemophilia and control populations.
2. The PROBE questionnaire is a reliable instrument for assessing health status of patients living with hemophilia and control populations.
3. Both paper-based and web-based questionnaire can be used interchangeably.
4. There is a trivial variation in results due to geographic region of participants. We hypothesized that the PROBE questionnaire can be used for cross-cultural data collection in multiple countries.
5. Patients with hemophilia have a high prevalence of sexual difficulties when compared to control population.
6. Patients who concurrently have health problems or hemophilia related problems are more likely to have sexual difficulties as compared to those who do not.

## CONTENT OF THESIS

This thesis has several components which form the assessment of validity and reliability of the PROBE questionnaire. **Chapter 1** was the introduction with regards to the existing of PRO instruments and their limitations. The statement of purpose and research hypothesis were listed. **In Chapter 2**, the psychometric properties of the PROBE questionnaire were investigated. We evaluated the descriptive analysis of the responded subitems and the PROBE score. Psychometric properties were assessed for factor analysis, internal consistency, convergent validity and known group validity. **In Chapter 3**, the test-retest reliability of the PROBE questionnaire was examined. Participants were asked to respond to the questionnaire 3 times (T1, T2 and T3). T1 and T2 were paper-based questionnaires. T3 was a web-based platform of an identical questionnaire. **In Chapter 4**, we explored the regional variation of the PROBE questionnaire. We performed the analysis on patients with hemophilia and participants without bleeding disorders from 21 countries, 4 regions. **In Chapter 5**, We performed the analyses on the sexual health of participants. The primary outcome of this study was the prevalence of sexual difficulties in patients with hemophilia compared with participants without bleeding disorders. The secondary outcomes were the variables that were associated with sexual difficulties. **Chapter 6** were summary of the results, strengths and limitation of the PROBE questionnaire, implications and conclusions.

## REFERENCES


1. Mannucci PM, Tuddenham EG: **The hemophilias--from royal genes to gene therapy**. *N Engl J Med* 2001, **344**(23):1773-1779.
2. Berntorp E, Shapiro AD: **Modern haemophilia care**. *Lancet* 2012, **379**(9824):1447-1456.
3. White GC, 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, Factor V, Factor IXS: **Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis**. *Thromb Haemost* 2001, **85**(3):560.
4. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC *et al*: **Guidelines for the management of hemophilia**. *Haemophilia* 2013, **19**(1):e1-47.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L *et al*: **Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia**. *N Engl J Med* 2007, **357**(6):535-544.
6. Oladapo AO, Epstein JD, Williams E, Ito D, Gringeri A, Valentino LA: **Health-related quality of life assessment in haemophilia patients on prophylaxis therapy: a systematic review of results from prospective clinical trials**. *Haemophilia* 2015, **21**(5):e344-358.

7. Tagliaferri A, Rivolta GF, Iorio A, Oliovecchio E, Mancuso ME, Morfini M, Rocino A, Mazzucconi MG, Franchini M, Italian Association of Hemophilia C *et al*: **Mortality and causes of death in Italian persons with haemophilia, 1990-2007**. *Haemophilia* 2010, **16**(3):437-446.

8. Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE: **Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy**. *Haemophilia* 2009, **15**(4):853-863.

9. van Genderen FR, Fischer K, Heijnen L, de Kleijn P, van den Berg HM, Helders PJ, van Meeteren NL: **Pain and functional limitations in patients with severe haemophilia**. *Haemophilia* 2006, **12**(2):147-153.

10. Franchini M: **Hepatitis C in haemophiliacs**. *Thromb Haemost* 2004, **92**(6):1259-1268.

11. Kroner BL, Rosenberg PS, Aledort LM, Alvord WG, Goedert JJ: **HIV-1 infection incidence among persons with hemophilia in the United States and western Europe, 1978-1990. Multicenter Hemophilia Cohort Study**. *J Acquir Immune Defic Syndr* 1994, **7**(3):279-286.

12. Rumi MG, De Filippi F, Santagostino E, Colombo M: **Hepatitis C in haemophilia: lights and shadows**. *Haemophilia* 2004, **10 Suppl 4**:211-215.

13. Astermark J: **Overview of inhibitors**. *Semin Hematol* 2006, **43**(2 Suppl 4):S3-7.

14. Franchini M, Mannucci PM: **Management of Hemophilia in Older Patients**. *Drugs Aging* 2017.

15. Sramek A, Reiber JH, Gerrits WB, Rosendaal FR: **Decreased coagulability has no clinically relevant effect on atherogenesis: observations in individuals with a hereditary bleeding tendency**. *Circulation* 2001, **104**(7):762-767.

16. Biere-Rafi S, Tuinenburg A, Haak BW, Peters M, Huijgen R, De Groot E, Verhamme P, Peerlinck K, Visseren FL, Kruip MJ *et al*: **Factor VIII deficiency does not protect against atherosclerosis**. *J Thromb Haemost* 2012, **10**(1):30-37.

17. Wang JD, Chan WC, Fu YC, Tong KM, Chang ST, Hwang WL, Lin CH, Tsan YT: **Prevalence and risk factors of atherothrombotic events among 1054 hemophilia patients: a population-based analysis**. *Thromb Res* 2015, **135**(3):502-507.

18. Dunn AL: **Malignancy in patients with haemophilia: a review of the literature**. *Haemophilia* 2010, **16**(3):427-436.

19. Tagliaferri A, Di Perna C, Santoro C, Schinco P, Santoro R, Rossetti G, Coppola A, Morfini M, Franchini M, Italian Association of Hemophilia C: **Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers**. *J Thromb Haemost* 2012, **10**(1):90-95.

20. Blanchette VS, O'Mahony B, McJames L, Mahlangu JN: **Assessment of outcomes**. *Haemophilia* 2014, **20 Suppl 4**:114-120.

21. Fischer K, Poonnoose P, Dunn AL, Babyn P, Manco-Johnson MJ, David JA, van der Net J, Feldman B, Berger K, Carcao M *et al*: **Choosing outcome assessment tools in haemophilia care and research: a multidisciplinary perspective**. *Haemophilia* 2017, **23**(1):11-24.

22. WHO: **The International Classification of Functioning, Disability and Health**. *World Heal Organ* 2001, **18**:237.

23. Pai M, Key NS, Skinner M, Curtis R, Feinstein M, Kessler C, Lane SJ, Makris M, Riker E, Santesso N *et al*: **NHF-McMaster Guideline on Care Models for Haemophilia Management**. *Haemophilia* 2016, **22 Suppl 3**:6-16.

24. Pocoski J, Benjamin K, Michaels LA, Flood E, Sasane R: **An overview of current trends and gaps in patient-reported outcome measures used in haemophilia**. *Eur J Haematol* 2014, **93 Suppl 75**:1-8.

25. Recht M, Konkle BA, Jackson S, Neufeld EJ, Rockwood K, Pipe S: **Recognizing the need for personalization of haemophilia patient-reported outcomes in the prophylaxis era**. *Haemophilia* 2016, **22**(6):825-832.

26. US Food and Drug Aministration. **Guidance for Industry, Patient-Reported Outcome Measure: Use in Medical Product Development to Support Labeling Claims** [http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf]

27. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP: **Patient-reported outcomes: A new era in clinical research**. *Perspect Clin Res* 2011, **2**(4):137-144.

28. O'Mahony B, Skinner MW, Noone D, Page D, O'Hara J: **Assessments of outcome in haemophilia - a patient perspective**. *Haemophilia* 2016, **22**(3):e208-209.

29. Riva S, Bullinger M, Amann E, von Mackensen S: **Content comparison of haemophilia specific patient-rated outcome measures with the international classification of functioning, disability and health (ICF, ICF-CY)**. *Health Qual Life Outcomes* 2010, **8**:139.

30. Young NL, Bradley CS, Blanchette V, Wakefield CD, Barnard D, Wu JK, McCusker PJ: **Development of a health-related quality of life measure for boys with haemophilia: the Canadian Haemophilia Outcomes--Kids Life Assessment Tool (CHO-KLAT)**. *Haemophilia* 2004, **10 Suppl 1**:34-43.

31. Young NL, Wakefield C, Burke TA, Ray R, McCusker PJ, Blanchette V: **Updating the Canadian hemophilia outcomes-kids life assessment tool (CHO-KLAT Version2.0)**. *Value Health* 2013, **16**(5):837-841.

32. Young NL, Bradley CS, Wakefield CD, Barnard D, Blanchette VS, McCusker PJ: **How well does the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) measure the quality of life of boys with haemophilia?** *Pediatr Blood Cancer* 2006, **47**(3):305-311.

33. Bradley CS, Bullinger M, McCusker PJ, Wakefield CD, Blanchette VS, Young NL: **Comparing two measures of quality of life for children with haemophilia: the CHO-KLAT and the Haemo-QoL**. *Haemophilia* 2006, **12**(6):643-653.

34. Young NL, St-Louis J, Burke T, Hershon L, Blanchette V: **Cross-cultural validation of the CHO-KLAT and HAEMO-QoL-A in Canadian French**. *Haemophilia* 2012, **18**(3):353-357.

35. McCusker PJ, Fischer K, Holzhauer S, Meunier S, Altisent C, Grainger JD, Blanchette VS, Burke TA, Wakefield C, Young NL: **International cross-cultural validation study of the Canadian haemophilia outcomes: kids' life assessment tool**. *Haemophilia* 2015, **21**(3):351-357.

36. Wu R, Zhang J, Luke KH, Wu X, Burke T, Tang L, Poon MC, Li X, Zhou M, Sun J *et al*: **Cross-cultural adaptation of the CHO-KLAT for boys with hemophilia in rural and urban China**. *Health Qual Life Outcomes* 2012, **10**:112.

37. von Mackensen S, Bullinger M, Haemo-Qo LG: **Development and testing of an instrument to assess the Quality of Life of Children with Haemophilia in Europe (Haemo-QoL)**. *Haemophilia* 2004, **10 Suppl 1**:17-25.

38. Bullinger M, von Mackensen S, Fischer K, Khair K, Petersen C, Ravens-Sieberer U, Rocino A, Sagnier P, Tusell JM, van den Berg M *et al*: **Pilot testing of the 'Haemo-QoL' quality of life questionnaire for haemophiliac children in six European countries**. *Haemophilia* 2002, **8 Suppl 2**:47-54.

39. Manco-Johnson M, Morrissey-Harding G, Edelman-Lewis B, Oster G, Larson P: **Development and validation of a measure of disease-specific quality of life in young children with haemophilia**. *Haemophilia* 2004, **10**(1):34-41.

40. von Mackensen S, Gringeri A, Siboni SM, Mannucci PM, Italian Association Of Haemophilia C: **Health-related quality of life and psychological well-being in elderly patients with haemophilia**. *Haemophilia* 2012, **18**(3):345-352.

41. Varaklioti A, Kontodimopoulos N, Katsarou O, Niakas D: **Psychometric properties of the Greek Haem-A-QoL for measuring quality of life in Greek haemophilia patients**. *Biomed Res Int* 2014, **2014**:968081.

42. Mercan A, Sarper N, Inanir M, Mercan HI, Zengin E, Kilic SC, Gokalp AS: **Hemophilia-Specific Quality of Life Index (Haemo-QoL and Haem-A-QoL questionnaires) of children and adults: result of a single center from Turkey**. *Pediatr Hematol Oncol* 2010, **27**(6):449-461.

43. Arranz P, Remor E, Quintana M, Villar A, Diaz JL, Moreno M, Monteagudo J, Ugarriza A, Soto I, Perez R *et al*: **Development of a new disease-specific quality-of-life questionnaire to adults living with haemophilia**. *Haemophilia* 2004, **10**(4):376-382.

44. Remor E, Arranz P, Quintana M, Villar A, Jimenez-Yuste V, Diaz JL, Rincon C, Marrero C, Moreno M, Lucia JF *et al*: **Psychometric field study of the new haemophilia quality of life questionnaire for adults: the 'Hemofilia-QoL'**. *Haemophilia* 2005, **11**(6):603-610.

45. Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, Garrido RP, Scharrer I, Schramm W, Gorina E, Members of the H-Q-ASC: **Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia**. *Haemophilia* 2008, **14**(5):1023-1034.

46. Remor E: **Development and psychometric testing of the Hemophilia Well-being Index**. *Int J Behav Med* 2013, **20**(4):609-617.

47. von Mackensen S, Czepa D, Herbsleb M, Hilberg T: **Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with haemophilia--the HEP-Test-Q**. *Haemophilia* 2010, **16**(1):170-178.

48. van Genderen FR, van Meeteren NL, van der Bom JG, Heijnen L, de Kleijn P, van den Berg HM, Helders PJ: **Functional consequences of haemophilia in adults: the development of the Haemophilia Activities List**. *Haemophilia* 2004, **10**(5):565-571.

49. van Genderen FR, Westers P, Heijnen L, de Kleijn P, van den Berg HM, Helders PJ, van Meeteren NL: **Measuring patients' perceptions on their functional abilities: validation of the Haemophilia Activities List**. *Haemophilia* 2006, **12**(1):36-46.

50. Groen WG, van der Net J, Helders PJ, Fischer K: **Development and preliminary testing of a Paediatric Version of the Haemophilia Activities List (pedhal)**. *Haemophilia* 2010, **16**(2):281-289.

51. S vM, A G, Mantovani: **Development and validation of the first treatment satisfaction scale for adult haemophiliacs (Hemo-SatA)**. *Haemophilia* 2004, **10(Suppl. 3)**(126).

52. Skinner MW, Driessens M, Curtis R, Frick N, Iorio A, Nichol M, Noone D, O'Mahony B, Page D, Stonebraker J: **The Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Phase 1 Methodology and Feasibility**. *Haemophilia* 2016, **22 (Suppl. 4)**:118.

Table 1 Patient reported outcome measures for assessing health-related quality of life, physical functioning and treatment satisfaction

| Tool | Target-population | (items) | Original language | Translation | Response options | Score range | Psychometric properties assessment |
|---|---|---|---|---|---|---|---|
| **Health-related quality of life** | | | | | | | |
| CHO-KLAT | 4-18 years | 35 | English | 20 languages | Likert scale | 0-100 | Internal consistency, test-retest reliability, content validity, construct validity, and translation validity |
| Haemo-QoL | i. 4-7 years ii.8-12 years iii.13-16 years | 27-77 | 6 languages | 28 languages | Likert scale | 0-100 | Internal consistency, test-retest reliability, content validity, construct validity and translation validity |
| Disease-specific QoL in young children | 2-6 years | 39 | English | N/A | Likert scale | N/A | Internal consistency, content validity and construct validity |
| Hemo-A-QoL | >18 years | 46 | English and Italian | 57 languages | Likert scale | 0-100 | Internal consistency, test-retest reliability, content validity and construct validity |
| Hemofilia-QoL | >18 years | 36 | Spanish | 9 languages | Likert scale | N/A | Internal consistency, test-retest reliability, content validity and construct validity |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| HAEMO-QoL-A | >18 years | 41 | English | 4 languages | Likert scale | 0-100 | Internal consistency, test-retest reliability, content validity and construct validity |
| Hemophilia Well-being Index | >18 years | 8 | Spanish | 3 languages | Likert scale | 0-100 | Internal consistency, test-retest reliability, content validity and construct validity |
| **Physical functioning** | | | | | | | |
| HEP-Test-Q | >18 years | 25 | German | 7 languages | Likert scale | 0-100 | Internal consistency, test-retest validity and construct validity |
| HAL | >18 years<br>4-18 (PedHAL) | 57 | Dutch | N/A | Likert scale | 0-100 | Internal consistency, test-retest reliability (PedHAL) and construct validity |
| **Treatment satisfaction** | | | | | | | |
| Hemo-Sat$_A$ | >18 year | 34 | Italian | 24 languages | | N/A | Internal consistency and construct validity |

# CHAPTER 2

# PSYCHOMETRIC PROPERTIES OF THE PATIENT REPORTED OUTCOMES, BURDENS AND EXPERIENCES (PROBE) QUESTIONNAIRE

Psychometric properties of the Patient Reported Outcomes, Burdens and Experiences (PROBE) Questionnaire

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## ABSTRACT

**Background:** The Patient Reported Outcomes, Burdens and Experiences (PROBE) study aims to develop the standardized questionnaire for assessing health status in patients with hemophilia and participants without bleeding disorders.

**Objective:** To assess the psychometric properties of questionnaire.

**Methods:** This was a cross-sectional, multi-national study. Participants were enrolled if they were 10 years or older and were patients with hemophilia A or B or people without a bleeding disorder. Participants were invited through non-governmental patient organizations in 21 countries between 04/08/2015 and 12/28/2015.The following psychometric properties: missing data; floor and ceiling effects; exploratory factor analysis; and internal consistency reliability were examined. A PROBE Score was derived and assessed for its convergent and known groups validity.

**Results:** The study analyzed the data on 916 participants with median age of 37.0 (interquartile range 27.0 to 48.0) years, 74.8% male. In the domain assessing patient reported outcomes more than 15% of participants presented a ceiling effect for all items but two, and a floor effect for one item. Factor analysis identified two factors explaining the majority of the variance. Cronbach's alpha coefficient indicated good internal consistency reliability (0.84). PROBE items showed moderate to strong correlations with corresponding EQ-5D-5L domains. We found the PROBE Score had strong correlation (r=0.67) with EQ-5D-5L utility index score. The PROBE Score has a known validity among predefined known groups.

**Conclusions:** The results of this study suggest that PROBE is a valid questionnaire for evaluating PROs in people with hemophilia, as well as control populations. The known group validity property of PROBE will allow its use in future clinical trials, longitudinal studies, health technology assessment studies, routine clinical care or registries.

Trial registration: NCT02439710

## BACKGROUND

Hemophilia is an inherited X-linked recessive bleeding disorder characterized by the reduction or absence of blood coagulation factor (F) VIII (hemophilia A) or FIX (hemophilia B). Severity of hemophilia is categorized by the baseline factor level (mild; factor level >0.05 to <0.40 IU/ml, moderate; factor level 0.01-0.05 IU/ml and severe; factor level<0.01 IU/ml) [1]. Coagulation factor deficiency renders patients prone to abnormal bleeding. Symptoms of hemophilia vary depending on the severity of hemophilia, mechanism and severity of injury and affected organs. People with hemophilia (PWH) commonly present with hemarthrosis, gastrointestinal or genitourinary tract bleeding, intramuscular bleeding or intracranial bleeding [2-6].

Life expectancy of PWH substantially improved with factor replacement therapy [7]. However, PWH who live longer encounter more chronic complications from both hemophilia-related conditions and degenerative diseases that occur in normal population. Chronic degenerative joint diseases are found in 90% of PWH by the second or third decade of life [8]. PWH with recurrent joint bleeding suffer from chronic pain, limitation of range of motion and disability [9]. Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections became prevalent among PWH prior to the implementation of intensive viral screening and inactivation steps in plasma-derived factor concentrates and the use of recombinant factor concentrates [10]. One of the major consequences of chronic HCV infection is cirrhosis, resulting in end-stage liver disease which is the most common cause of death in PWH [10]. Moreover, 43% of cancers diagnosed in PWH were related to HCV infection [11]. Aged PWH are also affected by cardiovascular diseases. A

retrospective study using an administrative database of 3,422 males with hemophilia reported a prevalence of ischemic heart disease of 15% in PWH older than 60 years [12]. When compared to general population, PWH are at lower risk for ischemic heart disease [13]. Risk factors of cardiovascular disease in PWH are equivalent to patients without hemophilia [14]. These long-term complications of hemophilia directly impact on health-related quality of life (HRQoL) in PWH [15].

Patient reported outcomes (PROs) are defined as any reports of status of patients' health conditions that come directly from the patients without interpretation by clinicians or anyone else [16]. PROs provide data that obtained from patients including symptoms, frequency of symptoms, severity of symptoms, impact of disease on daily life, disability and perfection of patients toward diseases and treatments [17]. Thus, PROs have been increasingly valued by researchers, stakeholders, policy makers and health technology assessment agencies [18-21]. Recently, the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) Clinical Outcome Assessment Emerging Good Practices Task Force published the Patient-reported outcome and observer-reported outcome assessment in rare disease clinical trials [22]. This report demonstrated the challenges of assessing patient-reported outcome in rare diseases, for instance, heterogeneity of disease severity and patient experience or understanding treatment benefit from patients' perspective. Hemophilia, which is a rare bleeding disorder, exhibits various disease severity. Moreover, patients' perspective on their symptom may be dissimilarly influenced by age, co-morbid disease, inhibitor status, current treatment or

progression of symptoms. Therefore, a hemophilia-specific PRO measure is essential for assessing outcomes in this patient population.

The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project is a patient-lead research initiative. The main objectives of the PROBE Project are to develop a standardised PRO questionnaire and to develop a dedicated research network to generate and continuously update PROBE reference data. The rationale, research group establishment and PRO questionnaire development [23] has been previously reported. The feasibility study of the PROBE questionnaire was conducted in collaborations with non-governmental hemophilia patient organizations (NGOs) in 18 countries. Previously reported results demonstrated that the burden of the PROBE questionnaire implementation was minimal and the time required to complete the questionnaire was less than 15 minutes for over 75% of participants [23]. The objective of the current study is to assess the psychometric properties of the PROBE questionnaire.

## METHODS

### Participant enrollment and study procedure

This study was designed as a cross-sectional assessment. Participants were enrolled through NGOs from 1/27/2016 to 2/23/2017. Participants were recruited if they were more than 10 years old and they were either PWH (hemophilia A or hemophilia B) or controls (participants without bleeding disorders). Controls were unaffected family members or volunteers. Participants were instructed to complete the questionnaire for themselves, and parents or caregivers not to answer for their child. Although collected as part of the study, participants who identified themselves as carriers of hemophilia were excluded from the analysis. Patients with other bleeding disorders or an unknown bleeding disorder were also excluded.

The participating NGOs distributed the PROBE questionnaires through mail, e-mail, in-person meetings or a combination of methods. The PROBE questionnaire was available in 18 languages with localized language versions in both paper- and web-based format.

### Ethical approval

Patients' identifier or personal information were not collected as part of the study. Data were collected as anonymous individuals, and study data were transferred and stored at McMaster University. Ethical approval was obtained from the Hamilton Integrated Research Ethics Boards. Additional local review ethical board approval was obtained when requested by the local regulation.

**PROBE questionnaire**

The detail of questionnaire development and feasibility study was described elsewhere [23]. The PROBE questionnaire is organized in 4 sections, comprising 29 questions. Sections are numbered following the order of presentation in the questionnaire. PROBE PRO domains are covered in Section II. The questions in Section I and III do not cover PRO domains. Only PWH are expected to complete Section III, whereas every participant completes Sections I, II and IV. Section I contains 7 questions pertaining to demographic data (country, gender, diagnosis of hemophilia or absence of a bleeding disorder, year of birth, body weight, age first started and finished school, marital status and children). Section II contains 9 questions pertaining to PROs, including general health issues, use of mobility aids or assistive devices, pain (including acute, chronic, and pain medications), daily activities, current work or student status, surgeries or procedures, and co-morbid diseases. Section III contains 12 questions pertaining to clinical aspects of hemophilia (severity of hemophilia, inhibitor status, bleeding history, hemophilia care, treatment regimen, target joints, joint bleeding, range of motion and life- or limb-threatening bleeds). Section IV contains the EuroQol five dimension 5-level instrument (EQ-5D-5L) [24], consisting of questions regarding mobility, self-care, usual activities, pain or discomfort and anxiety or depression, and the EuroQol visual analog scale (EQ-VAS) of global health [24] were incorporated in the PROBE questionnaire with permission.

### Item scaling and PROBE score calculation

PROs were evaluated only in Section II. The calculation of the PROBE score was based on multiattribute value functions [25, 26]. The assessed scores (Xi) were converted to returns-to-scale score (ViXi ), given that $0 \leq Vi(Xi) \leq 1$. Q.8 which had a dichotomous response (0 = no, 1 = yes) produce dichotomous score of 0 and 1. Two questions (Q.10 and Q.15) asked for frequency of the use of pain medication(s) and number of surgeries or invasive procedures. The 6- and 7-level Likert scales from these two questions were converted to a returns-to-scale score, ranging from 0 to 1. The number of days absent from work or school (Q.14) was converted to returns-to-scale score by dividing by 366. Questions regarding mobility aids, acute pain, chronic pain and co-morbid diseases (Q.9, Q.11, Q.12, Q.13 and Q.16) had multiple choices. The scales for these items were calculated based on the cumulative number of choices checked. We apply weight for subitems in each question (if needed). The final score was calculated by summing all of the 11 items scores from the 9 questions using additive value function and then scaled so the PROBE Score ranged from 0 to 1 (higher value indicates better health status).

### Data analyses

### Descriptive statistics

Demographic data of study participants were summarized using mean with corresponding standard deviation (SD) or median and quartile range as appropriate. Categorical data were summarized using numbers and percentages. Participants who did not respond in Q.3 (disease status; hemophilia A, hemophilia B, hemophilia carrier, other

bleeding disorders or no bleeding disorder) were excluded from the analysis. An item distribution analysis to evaluate the proportion of missing data was performed. Floor and ceiling effects were evaluated by the proportion of respondents with scores at floor (minimum score) and ceiling (maximum score), respectively.

**Psychometric analyses**

Face and content validity were assessed and reported previously [23]. Test-retest reliability analyses of the PROBE questionnaire were reported elsewhere [27]. In the current study, the following psychometric analyses were carried out.

**Factor analysis**

An exploratory factor analysis of 9 questions, pertaining to the PROs (Section II). Principal component factor analysis was conducted with oblique rotation method was performed. Investigators made a priori decision to retain all factors that had eigenvalues of 1.0 or greater, according to Kaiser criterion [28]. A scree plot was generated [29]. The percentage of variance on the items that were explained by the factors was evaluated. A higher percentage indicated strong influence of the factors. The regression coefficients (factor loadings) of the item responses on the retaining factors after factor rotation was calculated.

**Internal consistency reliability**

An analysis to confirm the precision of the scale based on the intercorrelations of the items evaluating the same construct was conducted. We hypothesized that the

questions asking about pain and the use of medications (Q.10-Q.13) were correlated. Cronbach's alpha was used to determine the correlation between items. Cronbach's alpha coefficient greater than 0.7 was considered to indicate acceptable reliability [30].

**Convergent validity**

The convergent validity of the items in the same construct with the existing, standardised questionnaire were assessed. Specifically, we hypothesized that the items asking about the use of mobility aids and assistive devices correlated with the mobility domain of EQ-5D-5L; the items asking about the use of pain medication, acute and chronic pain (Q.10, Q.11 and Q.12) correlated with pain and discomfort domain of EQ-5D-5L; the items asking about activities of daily living (Q.13) correlated with the self-care and usual activity domains of EQ-5D-5L. The correlation between EQ-5D-5L utility index score and the PROBE Score was assessed. The correlation coefficient (r) was interpreted as the followings, r 0.20-0.39; weak correlation; r 0.40-0.59, moderate correlation; r 0.60-0.79, strong correlation; and r 0.80-1.00, very strong correlation [31].

**Known group validity**

The ability of the PROBE questionnaire to determine the differences between known subgroups was assessed. Participants were classified into groups according to information collected in Section III, as diagnosis (hemophilia or non-hemophilia), severity of hemophilia (mild, moderate or severe), current inhibitor status (yes or no), number of bleeds in the past year (categorical variable), bleed in the past two weeks (yes, no), presence of target joint (yes, no), limitation of range of motion of the joints (yes, no)

and life- or limb-threatening bleeding in the past year (yes, no). The PROBE Scores were compared between subgroups using t-test or one-way ANOVA for the univariate analysis, as appropriate. A priori hypotheses included PWH (as compared to participants without bleeding disorders), patients with severe hemophilia (as compared to mild and moderate hemophilia), patients with current inhibitor (as compared to those without an inhibitor), patients with greater numbers of bleeding, patients who had recent bleeding within the past 2 weeks (as compared to those without), patients with presence of target joint(s) (as compared to those without), patients who had reduced range of motion of any joints (as compared to those without) and patients who had life- or limb- threatening bleeding in the past year (as compared to those without) had worse PROBE scores. The multivariable analysis of the known group validity was conducted using a linear regression. The regression model included age and gender of participants in the analysis. Regression coefficients with corresponding 95% CI were reported. P-value less than 0.05 was considered statistically significant.

**Sample size**

With regards to the sample size. In order to evaluate the measurement properties of health status questionnaire, sample size was suggested to exceed 50 participants for assessing floor and ceiling effects, internal consistency, known group validity and internal consistency [32]. Moreover, sample size was suggested to exceed 100 participants for assessing factor analysis [32].

## RESULTS

### Participants' demographic data

Since inception, NGOs from 21 countries have participated in the PROBE project. Figure 1 demonstrates the flow of participant selection who participated in this phase of research. There were 1287 participants who responded to the questionnaire. After excluding hemophilia carriers, other bleeding disorders and missing value, the analysis included 916 participants. Demographic data is shown in Table 1. Median age of PWHs was lower than that of controls, 33 (1$^{st}$ quartile, 3$^{rd}$ quartile of 24, 46) vs 43 (1$^{st}$ quartile, 3$^{rd}$ quartile of 34, 54) years. The proportion of male participants in hemophilia group was greater than those in control group (93.7% vs 6.4%). Among hemophilia patients, most had severe hemophilia. Seventeen participants (2.6%) of PWH had an inhibitor during the study period.

### Descriptive analysis

Table 2 demonstrates item distribution and missing data. A ceiling effect greater than 15% was observed in all but one item (the use of pain medications) in Section II. Similarly, a ceiling effect greater than 15% was observed in all domains of the EQ-5D-5L. A floor effect greater than 15% was found in four items (problems related to health, bleeding in the past 12 months, limitation of range of motion and life- or limb-threatening bleeding). Missing data was 0% to 21.8% in Section II, 18.2% to 49.4% in Section III and 21.6% to 22.9% in Section IV. The median PROBE Score across all participants was 0.78 (mean=0.76, SD=0.16, minimum=0.26 and maximum=0.99).

## Psychometric analyses

### Exploratory factor analysis

The principal component factor analysis of the 9 questions (11 items) pertaining to the PROs was carried out. The scree plot demonstrated two factors with eigenvalue greater than 1.0 (Figure 2). These two factors were retained for the following analyses. Cumulatively, the combination of two factors explained 50.6% of the variance. Table 3 demonstrates factor loadings based on two factors. The items were grouped per factor with their maximum loading (bold).

Factor 1 appears to be the most influential, explaining 40.8% of the variance. There were 8 items contained in this factor (problems related to health, mobility aids or assistive devices, use of pain medications, activities and interference related to acute pain, activities and interference related to chronic pain, activities of daily living, and work/school life). Factor 2 explained 9.8% of the variance, and contained two items (joint surgery or procedure and comorbid disease). All items in the each factor had acceptable factor loadings ($r \geq 0.3$) [33].

### Internal consistency reliability

The internal consistency reliability was carried out using Cronbach's alpha. An analysis on pain-related items was performed. The Cronbach's alpha coefficient was acceptable at 0.84.

**Convergent validity**

Table 4 shows the correlation coefficients between PROBE items and EQ-5D-5L. The results showed that Q. 3 (the use of mobility aids and assistive devices) had a moderate correlation with mobility domain of EQ-5D-5L (r=0.42). The pain and discomfort domain of EQ-5D-5L had a moderate to strong correlation with most of the pain related items of the PROBE questionnaire (r=0.55 for pain medication, 0.42 for acute pain occurrence, 0.39 for acute pain interference, 0.56 for chronic pain occurrence and 0.57 for chronic pain interference). Items related to activities of daily living had a strong correlation with the self care and usual activities domain (r=0.65 and 0.71, respectively). The PROBE score had a strong correlation with the EQ-5D-5L utility index score (r=0.67).

**Known group validity**

The regression coefficients of each a priori variable and the PROBE Score were demonstrated in Table 5. Participants without a bleeding disorder had a significantly higher PROBE Score when compared with PWH (mean score (SD), 0.87 (0.11) vs 0.71 (0.16), P<0.001). PWH with mild to moderate hemophilia had a slightly higher PROBE Score (mean 0.71, SD 0.16) than severe PWH (mean 0.70, SD 0.16), PWH who had a greater number of bleeding episodes had a significantly lower PROBE Score when compared to those who had less frequent bleeding (P<0.001). Patients who reported bleeding in the past two weeks had a significantly lower PROBE score (mean 0.67, SD 0.15) than those without (mean 0.76, SD 0.15). Patients who reported the presence of any

target joints had a significantly lower PROBE score (mean 0.68, SD 0.15) when compared to those who did not (mean 0.78, SD 0.16). Patients who reported three or more spontaneous joint bleeds in the past 6 months had significantly lower PROBE score (mean 0.66, SD 0.14) than those who did not report (mean 0.73, SD 0.14). Patients with reduced range of motion of any joints had a significantly lower PROBE score (mean 0.68, SD 0.14) as compared to those without (mean 0.73, SD 0.15). Patients who previously had life- or limb-threatening bleeding in the past year had a significantly lower PROBE Score (mean 0.62, SD 0.16) when compared to those who did not (mean 0.72, SD 0.15).

## DISCUSSION

The psychometric properties of the PROBE questionnaire have been assessed, and it was found that the PROBE questionnaire has strong internal consistency, robust convergent validity and excellent differentiation properties between known groups. We believe these characteristics, jointly with the availability of country specific reference ranges and low impact on NGO resources and time required by the patients, make the PROBE questionnaire a tool with great potential for efficient PROs collection in clinical and comparative effectiveness research, and for advocacy purposes.

As demonstrated by factor analysis, the core of PROBE revolves around two factors, explaining the majority of the variance in responses. The most influential factor was pain, followed by use of mobility aids or assistive device (complemented by work or school absent days), and comorbidity. It is no surprise these three elements explain 50% of the variance among different participants: the novelty of PROBE is summarizing the assessment of these 3 domains in a lightweight set of questions for which excellent internal consistency was demonstrated.

The convergent validity analysis showed moderate to strong correlation between PROBE and EQ-5D-5L items, with lower correlations for items concerning pain (r ranged from 0.39 to 0.57). The overall convergence with EQ-5D-5L was confirmed. This finding was intentionally sought to ensure maximizing external validity and efficiency for cross-disease comparisons. The pain related questions in the PROBE questionnaire are related to different aspects (when the pain occurred..., if the pain interfered with any of

following…) than EQ-5D-5L [34]. From this perspective, PROBE might be seen as a new hybrid PRO tool, sharing some properties of a generic and some of a disease specific tool. The total PROBE score has a strong correlation with the utility index score of the EQ-5D-5L, both in patients (r=0.57), and controls (r=0.53), but explores a more specific set of subdomains.

The most important result of this analysis is the demonstration of the known group validity property of the PROBE questionnaire and score. In known group validity analysis, PWH had significantly lower PROBE Score when compared to the control population (participants without hemophilia). Patients with more frequent bleed, target joint, reduced range of motion and previous life- or limb-threatening bleed were demonstrated to have a lower PROBE score (indicating worse health status).

The investigators did not observe a significant difference of the total PROBE scores among severity of disease as well as current inhibitor status. This outcome may be confounded by bleeding phenotype and joint status. It has been shown that the presence of inhibitor has negative impact on health-related quality of life in PWH [35]. The regression analysis in this present study revealed that number of bleeds, presence of target joint(s) and limitation of range of motion of any joints, not inhibitor status, were associated with worse health status. These findings are in contrast to prior studies that reported the negative health-related quality of life in hemophilia patients with inhibitor who had poor orthopedic joint score, who had acute bleeding and who had more frequent bleeding [36-38]. It is important to note that there are relatively a small number of patients with mild-moderate diseases (8.8% and 14.3%, respectively) and those with

current inhibitors (4.1%) in this study. The association between inhibitor status and health status of PWH warrant further studies with adequate power.

The PROBE Project has several strengths. First, participants were recruited from 21 countries involving 6 regions of the world. The findings of this study are therefore internationally generalizable regardless of languages and cultures. Second, both PWH and participants without bleeding disorders were recruited, asked PRO questions meaningful to both, and derived a PROBE score applicable to both. Therefore, we were able to compare the health status across health-specific conditions (hemophilia vs non-hemophilia in this study). There is a potential role for the use of the PROBE questionnaire to compare health status between PWH with any other diseases that share common features, e.g. von Willebrand disease, rheumatoid arthritis or osteoarthritis. Third, both school-aged and adult participants were included. The work or school life was assessed in the same manner. As a result, the PROBE questionnaire is valid to implement in participants in all age groups (starting at the not-yet defined age when one is able to comprehend the questionnaire). Third, the questions in the PROBE questionnaire included a standardized observation period in each question stem, generally the past 12 months. This is helpful for participants to respond to each item closest to their actual health condition in a specific time frame.

This PROBE Project also has some limitations, the first being that responsiveness of the PROBE Score has not yet been validated. This study was conducted with a cross-sectional study design. This means participants responded to the questionnaire at a single time. Assessing responsiveness requires a more complicated and demanding study design,

which will be addressed in the future. Second, the observation period in the items was up to 12 months. Whereas this was chosen to maximize capturing the impact of rare events, it might introduce recall bias in some participants. Third, a ceiling effect was observed for all except one item concerning PRO, as well as, all EQ-5D-5L items. The recent study regarding floor and ceiling effects of the EQ-5D-5L in 996 English general population showed that 47.6% of respondents reported the best possible heath state (ceiling effect) [39]. In addition, the ceiling effects ranged from 58.4% to 90.8% in the subdomains [39]. The floor effects in the study were relatively lower than the previous reports [39], probably because sicker participants (PWH) were included

## CONCLUSIONS

The properties of the PROBE questionnaire are well suited for differentiating PWH with better or worse health status. The immediate use of the PROBE score based on these results would be in cross-sectional comparisons in different settings, e.g. those defined by different levels of access to care. Future applications, as assessing treatment effect in clinical trials, or monitoring patients' health status over time in longitudinal observational studies will enable us to define the responsiveness properties of PROBE to meaningful treatment and disease changes over time.

## List of abbreviations

PROBE: Psychometric properties of the Patient Reported Outcomes, Burdens and Experiences; EQ-5D-5L: EuroQol five dimension 5-level instrument; F:factor; EQ-VAS: EuroQol visual analog scale; PWH: people with hemophilia; HIV: Human immunodeficiency virus; HCV: hepatitis C virus; HRQoL: health-related quality of life; PRO: Patient reported outcome; ISPOR: International Society for Pharmacoeconomic and Outcomes Research; NGO: non-governmental organization; SD: standard deviation; ANOVA; analysis of variance

## Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Hamilton Integrated Research Ethics Boards. Additional local review ethical board approval was obtained when requested by the local regulation.

## Consent for publication

Not Applicable.

## Availability of data and material

Not Applicable.

## Competing interests

CC have no potential conflict of interest. Investigators received grants from Baxalta, now part of Shire; Bayer; Bioverativ; CSL Behring, Novo Nordisk; Roche; and Sobi and non-financial support from the US National Hemophilia Foundation.

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## Authors' contributions

MS, AI, RC, NF, MN, DN, BOM, DP, MAC and JS conceptualized the study. CC and LT performed data collection and statistical analysis. CC, AI, MAC and MS drafted the manuscript. All authors critically reviewed the manuscript. All authors approved the final manuscript.

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## REFERENCES

1. White GC, 2nd, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J, Factor V, Factor IXS: **Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis**. *Thromb Haemost* 2001, **85**(3):560.
2. Avina-Zubieta JA, Galindo-Rodriguez G, Lavalle C: **Rheumatic manifestations of hematologic disorders**. *Curr Opin Rheumatol* 1998, **10**(1):86-90.
3. McCoy HE, 3rd, Kitchens CS: **Small bowel hematoma in a hemophiliac as a cause of pseudoappendicitis: diagnosis by CT imaging**. *Am J Hematol* 1991, **38**(2):138-139.
4. Fernandez-Palazzi F, Hernandez SR, De Bosch NB, De Saez AR: **Hematomas within the iliopsoas muscles in hemophilic patients: the Latin American experience**. *Clin Orthop Relat Res* 1996(328):19-24.
5. Small S, Rose PE, McMillan N, Belch JJ, Rolfe EB, Forbes CD, Stuart J: **Haemophilia and the kidney: assessment after 11-year follow-up**. *Br Med J (Clin Res Ed)* 1982, **285**(6355):1609-1611.
6. Ljung RC: **Intracranial haemorrhage in haemophilia A and B**. *Br J Haematol* 2008, **140**(4):378-384.
7. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Hill FG, Hay CR, Lee CA, Ludlam CA, Williams M: **Mortality rates, life expectancy, and causes of death in**

**people with hemophilia A or B in the United Kingdom who were not infected with HIV**. *Blood* 2007, **110**(3):815-825.

8. Rodriguez-Merchan EC: **Musculoskeletal complications of hemophilia**. *HSS J* 2010, **6**(1):37-42.
9. Lobet S, Hermans C, Lambert C: **Optimal management of hemophilic arthropathy and hematomas**. *J Blood Med* 2014, **5**:207-218.
10. Mazepa MA, Monahan PE, Baker JR, Riske BK, Soucie JM, Network USHTC: **Men with severe hemophilia in the United States: birth cohort analysis of a large national database**. *Blood* 2016, **127**(24):3073-3081.
11. Tagliaferri A, Di Perna C, Santoro C, Schinco P, Santoro R, Rossetti G, Coppola A, Morfini M, Franchini M, Italian Association of Hemophilia C: **Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers**. *J Thromb Haemost* 2012, **10**(1):90-95.
12. Kulkarni R, Soucie JM, Evatt BL, Hemophilia Surveillance System Project I: **Prevalence and risk factors for heart disease among males with hemophilia**. *Am J Hematol* 2005, **79**(1):36-42.
13. Tuinenburg A, Mauser-Bunschoten EP, Verhaar MC, Biesma DH, Schutgens RE: **Cardiovascular disease in patients with hemophilia**. *J Thromb Haemost* 2009, **7**(2):247-254.
14. Sharathkumar AA, Soucie JM, Trawinski B, Greist A, Shapiro AD: **Prevalence and risk factors of cardiovascular disease (CVD) events among patients with**

**haemophilia: experience of a single haemophilia treatment centre in the United States (US)**. *Haemophilia* 2011, **17**(4):597-604.

15. Ferreira AA, Leite IC, Bustamante-Teixeira MT, Correa CS, da Cruz DT, Rodrigues Dde O, Ferreira MC: **Health-related quality of life in hemophilia: results of the Hemophilia-Specific Quality of Life Index (Haem-a-Qol) at a Brazilian blood center**. *Rev Bras Hematol Hemoter* 2013, **35**(5):314-318.
16. Health USDo, Human Services FDACfDE, Research, Health USDo, Human Services FDACfBE, Research, Health USDo, Human Services FDACfD, Radiological H: **Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance**. *Health Qual Life Outcomes* 2006, **4**:79.
17. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP: **Patient-reported outcomes: A new era in clinical research**. *Perspect Clin Res* 2011, **2**(4):137-144.
18. Lowe MM, Blaser DA, Cone L, Arcona S, Ko J, Sasane R, Wicks P: **Increasing Patient Involvement in Drug Development**. *Value Health* 2016, **19**(6):869-878.
19. Hoos A, Anderson J, Boutin M, Dewulf L, Geissler J, Johnston G, Joos A, Metcalf M, Regnante J, Sargeant I *et al*: **Partnering With Patients in the Development and Lifecycle of Medicines: A Call for Action**. *Ther Innov Regul Sci* 2015, **49**(6):929-939.
20. Skinner MW: **WFH: closing the global gap--achieving optimal care**. *Haemophilia* 2012, **18 Suppl 4**:1-12.

21. Noone D, O'Mahony B, van Dijk JP, Prihodova L: **A survey of the outcome of prophylaxis, on-demand treatment or combined treatment in 18-35-year old men with severe haemophilia in six countries**. *Haemophilia* 2013, **19**(1):44-50.

22. Benjamin K, Vernon MK, Patrick DL, Perfetto E, Nestler-Parr S, Burke L: **Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report**. *Value Health* 2017, **20**(7):838-855.

23. Skinner MW, Driessens M, Curtis R, Frick N, Iorio A, Nichol M, Noone D, O'Mahony B, Page D, Stonebraker J: **The Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Phase 1 Methodology and Feasibility**. *Haemophilia* 2016, **22 (Suppl. 4)**:118.

24. EuroQol G: **EuroQol--a new facility for the measurement of health-related quality of life**. *Health Policy* 1990, **16**(3):199-208.

25. Dyer JS, Rarin RK: **Measurable multiattribute value functions**. *Oper Res* 1979, **27**: 810 - 822.

26. Kirkwood CW: **Strategic Decision Making: Multiobjective Decision Analysis with Spreadsheets** Belmont, CA: Wadsworth Publ. Co

1996.

27. Chai-Adisaksopha C, Iorio A, Curtis R, Frick N, Nichol M, Noone D, O'Mahony B, Page D, Stonebrake J, Skinner MW: **Test-Retest Reliability Analysis of The Patient Reported Outcomes Burdens and Experiences (PROBE) Study**. *Haemophilia* 2017, **23 (Suppl.2)**:29-140. [abstract P037].

28. Larsen R, Warne RT: **Estimating confidence intervals for eigenvalues in exploratory factor analysis**. *Behav Res Methods* 2010, **42**(3):871-876.

29. Ledesma RD, Valero-Mora P, Macbeth G: **The Scree Test and the Number of Factors: a Dynamic Graphics Approach**. *Span J Psychol* 2015, **18**:E11.

30. Cronbach LJ, Warrington WG: **Time-limit tests: estimating their reliability and degree of speeding**. *Psychometrika* 1951, **16**(2):167-188.

31. Evans JD: **Straightforward statistics for the behavioral sciences**. Pacific Grove, CA: Brooks/Cole Publishing.; 1996.

32. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, Bouter LM, de Vet HC: **Quality criteria were proposed for measurement properties of health status questionnaires**. *J Clin Epidemiol* 2007, **60**(1):34-42.

33. Tabachnick BG, Fidell LS: **Using multivariate statistics**. Boston, MA: Allyn & Bacon; 2007.

34. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X: **Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)**. *Qual Life Res* 2011, **20**(10):1727-1736.

35. McLaughlin JM, Munn JE, Anderson TL, Lambing A, Tortella B, Witkop ML: **Predictors of quality of life among adolescents and young adults with a bleeding disorder**. *Health Qual Life Outcomes* 2017, **15**(1):67.

36. Brown TM, Lee WC, Joshi AV, Pashos CL: **Health-related quality of life and productivity impact in haemophilia patients with inhibitors**. *Haemophilia* 2009, **15**(4):911-917.

37. Recht M, Neufeld EJ, Sharma VR, Solem CT, Pickard AS, Gut RZ, Cooper DL: **Impact of acute bleeding on daily activities of patients with congenital hemophilia with inhibitors and their caregivers and families: observations from the Dosing Observational Study in Hemophilia (DOSE)**. *Value Health* 2014, **17**(6):744-748.

38. Scalone L, Mantovani LG, Mannucci PM, Gringeri A, Investigators CS: **Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors**. *Haemophilia* 2006, **12**(2):154-162.

39. Feng Y, Devlin N, Herdman M: **Assessing the health of the general population in England: how do the three- and five-level versions of EQ-5D compare?** *Health Qual Life Outcomes* 2015, **13**:171.

## FIGURE LEGENDS AND TABLES

Figure 1 Flow diagram of participant selection

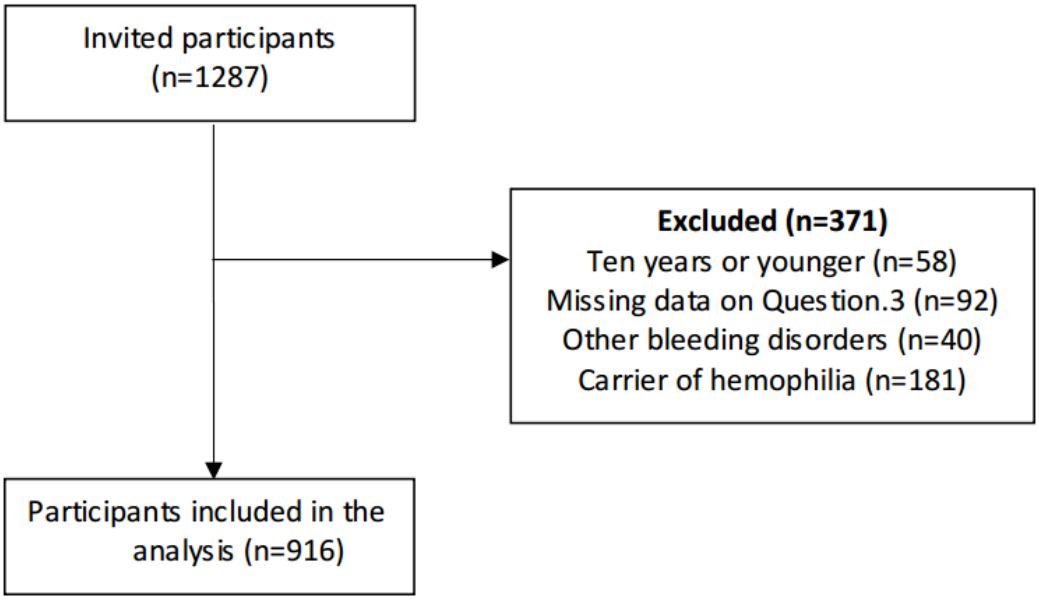

Figure 2. Scree plot of exploratory principal-component factors analysis

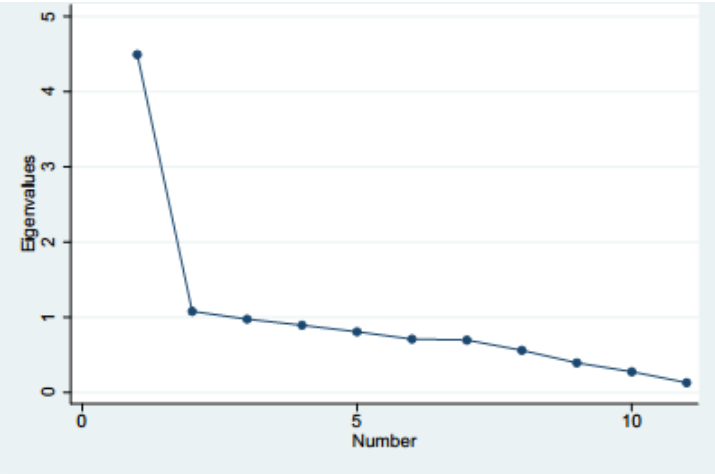

Table 1. Participants' characteristics

| Characteristics | Participants (n=916) |
|---|---|
| Age, median (Q1, Q3) | 37 (27, 48) |
| Diagnosis, n (%)<br>• Hemophilia A<br>• Hemophilia B<br>• Non-hemophilia | <br>532 (58.1)<br>82 (8.9)<br>302 (33.0) |
| Severity of hemophilia*, n (%)<br>• Normal<br>• Mild<br>• Moderate<br>• Severe<br>• Do not know | <br>3 (0.6)<br>54 (10.6)<br>88 (17.3)<br>352 (69.3)<br>11 (2.2) |
| Ever been diagnosed with inhibitor*, n (%)<br>• Yes<br>• No<br>• Do not know | <br>70 (14.1)<br>384 (77.2)<br>43 (8.7) |
| Currently have an clinically significant inhibitor, n (%) | 24 (2.6) |
| Sex, n (%)<br>• Male<br>• Female | <br>685 (74.8)<br>231 (25.2) |
| Age when started school, median (Q1, Q3) | 6 (5, 6) |
| Year of school or education, median (Q1, Q3) | 15 (12, 18) |
| Married or long-term relationship, n (%) | 581 (69.0) |
| Having Children, n (%) | 462 (55.3) |
| Region, n (%) | |
| Africa | 8 (0.9) |
| Western Pacific | 216 (23.6) |
| South America | 343 (37.4) |
| North America | 138 (15.1) |
| Europe | 211 (23.0) |

*only hemophilia population

Abbreviations: Q1; interquartile 1, Q3; interquartile 3

Table 2. Item distribution and missing data

| Item | Floor (%) | Ceiling (%) | Missing (%) |
|---|---|---|---|
| Patient reported outcome | | | |
| Q.8 Problem related to health* | 59.1 | 32.3 | 8.6 |
| Q.9 Mobility aids or assistive devices | 0.1 | 0 | 11.5 |
| Q.10 Pain medications | 3.0 | 14.6 | 12.3 |
| Q.11.1 Acute pain (activities) | 0.7 | 33.1 | 12.8 |
| Q.11.2 Acute pain (interference) | 0.3 | 33.2 | 12.8 |
| Q.12.1 Chronic pain (activities) | 1.4 | 32.6 | 13.5 |
| Q.12.2 Chronic pain (interference) | 0.1 | 33.6 | 13.5 |
| Q.13 Daily activities | 0.1 | 42.4 | 14.3 |
| Q.14 Work/school life | 0.1 | 27.8 | 21.8 |
| Q.15 Joint surgery or procedure | 1.3 | 52.4 | 17.0 |
| Q.16 Comorbid diseases | 0 | 56.1 | 0 |
| Hemophilia related health | | | |
| Q.17 Severity | N/A | N/A | 17.3 |
| Q.18 Inhibitor status | N/A | N/A | 19.1 |
| Q.19 Bleeding in the past 12 months | 16.6 | 8.5 | 18.2 |
| Q.20 Bleeding in the past 2 weeks | N/A | N/A | 18.9 |
| Q.21 Hemophilia treatment center | N/A | N/A | 19.4 |
| Q.25 Target joints | N/A | N/A | 22.6 |
| Q. 26 spontaneous bleeding | N/A | N/A | 49.4 |
| Q.27 Limitation of range of motion* | 66.6 | 11.4 | 22.0 |
| Q.28 Life- or limb-threatening bleeding* | 15.2 | 62.1 | 22.8 |
| EQ-5D-5L and EQ-VAS | | | |
| Mobility | 1.1 | 32.4 | 21.6 |
| Self-care | 0.7 | 55.0 | 22.3 |
| Usual activities | 0.7 | 37.9 | 22.4 |
| Pain/discomfort | 1.1 | 23.9 | 22.9 |
| Anxiety/depression | 1.6 | 37.3 | 22.8 |
| VAS | 0 | 3.1 | 22.8 |

*dichotomous outcome

N/A: not applicable

Table 3. Principal-component factors analysis, non-orthogonal rotated structure matrix loadings

| Items | Factor1 | Factor2 | Uniqueness |
|---|---|---|---|
| Q.8 Problem related to health | **0.5648** | 0.1011 | 0.6707 |
| Q.9 Mobility aids or assistive devices | **0.4653** | -0.1721 | 0.7539 |
| Q.10 Pain medications | **0.6571** | -0.0856 | 0.5609 |
| Q.11.1 Acute pain (activities) | **0.7273** | -0.2825 | 0.3913 |
| Q.11.2 Acute pain (interference) | **0.7275** | -0.3425 | 0.3535 |
| Q.12.1 Chronic pain (activities) | **0.7853** | 0.1408 | 0.3635 |
| Q.12.2 Chronic pain (interference) | **0.8061** | 0.1257 | 0.3344 |
| Q.13 Daily activities | **0.7868** | 0.0102 | 0.3808 |
| Q.14 Work/school life | **0.5562** | -0.2130\| | 0.6453 |
| Q.15 Joint surgery or procedure | 0.3142 | **0.6981** | 0.4139 |
| Q.16 Comorbid diseases | 0.4140 | **0.5146** | 0.5638 |

Table 4. Correlations between PROBE and EQ-5D-5L items (convergent validity)

| EQ-5D-5L | PROBE | Correlation | 95% confidence interval |
|---|---|---|---|
| Mobility | Q.9 Mobility aids | 0.42 | 0.35 to 0.47 |
| Pain and discomfort | Q.10 Pain medications | 0.55 | 0.50-0.60 |
| | Q.11.1 Acute pain (activities) | 0.42 | 0.36 to 0.48 |
| | Q.11.2 Acute pain (interference) | 0.39 | 0.32 to 0.45 |
| | Q.12.1 Chronic pain (activities) | 0.56 | 0.51 to 0.61 |
| | Q.12.2 Chronic pain (interference) | 0.57 | 0.52 to 0.62 |
| Self care | Q.13 Activities of daily living | 0.65 | 0.61 to 0.69 |
| Usual activities | Q.13 Activities of daily living | 0.71 | 0.67 to 0.74 |
| Anxiety | N/A | N/A | N/A |
| Utility index score | Total score | 0.67 | 0.62 to 0.71 |

Table 5. Known group validity analyses, univariate analysis

| Subgroup | Total PROBE score, mean (SD) | p-value |
|---|---|---|
| Q.2 Diagnosis | | |
| • Non-hemophilia | 0.87 (0.11) | <0.001 |
| • Hemophilia | 0.71 (0.16) | |
| Q.17 Severity of hemophilia | | |
| • Mild-moderate | 0.71 (0.16) | 0.45 |
| • Severe | 0.70 (0.16) | |
| Q.18 Current inhibitor | | |
| • No | 0.71 (0.19) | 0.35 |
| • Yes | 0.67 (0.12) | |
| Q.19 Number of bleeds in past year | | |
| • 0 bleed | 0.80 (0.14) | <0.001 |
| • 1 bleed | 0.85 (0.11) | |
| • 2-3 bleeds | 0.75 (0.15) | |
| • 4-7 bleeds | 0.74 (0.14) | |
| • 8-10 bleeds | 0.70 (0.13) | |
| • 11-15 bleeds | 0.68 (0.12) | |
| • 16-30 bleeds | 0.65 (0.15) | |
| • >30 bleeds | 0.61 (0.15) | |
| Q.20 Bleed in the past two weeks | | |
| • No | 0.76 (0.15) | <0.001 |
| • Yes | 0.67 (0.15) | |
| Q.25 Target joint | | |
| • No | 0.78 (0.16) | <0.001 |
| • Yes | 0.68 (0.15) | |
| Q.26 Spontaneous joint bleeding | | |
| • No | 0.73 (0.15) | 0.0004 |
| • Yes | 0.66 (0.14) | |
| Q.27 having reduced range of motion | | |
| • No | 0.86 (0.13) | <0.001 |
| • Yes | 0.68 (0.14) | |
| Q.28 Life threatening bleed | | |
| • No | 0.72 (0.15) | <0.001 |
| • Yes | 0.62 (0.16) | |

Table 6. Coefficients derived from multivariable linear regression analysis

| | Coefficient* | 95% confidence interval | p-value |
|---|---|---|---|
| Q.2 Diagnosis | | | |
| • Non-hemophilia | Control | N/A | N/A |
| • hemophilia | -0.22 | -0.25 to -0.18 | <0.001 |
| Q.17 Severity of hemophilia | | | |
| • Mild-Moderate | Control | N/A | N/A |
| • Severe | -0.003 | -0.03 to 0.03 | 0.83 |
| Q.18 Current inhibitor | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.04 | -0.14 to 0.05 | 0.34 |
| Q.19 Number of bleeds in past year | | | |
| • 0 bleed | Control | N/A | N/A |
| • 1 bleed | 0.04 | -0.03 to 0.10 | 0.29 |
| • 2-3 bleeds | -0.06 | -0.11 to 0.001 | 0.06 |
| • 4-7 bleeds | -0.07 | -0.12 to -0.01 | 0.02 |
| • 8-10 bleeds | -0.10 | -0.16 to -0.03 | 0.002 |
| • 11-15 bleeds | -0.14 | -0.20 to 0.08 | <0.001 |
| • 16-30 bleeds | -0.15 | -0.21 to -0.09 | <0.001 |
| • >30 bleeds | -0.19 | -0.24 to -0.13 | <0.001 |
| Q.20 Bleed in the past two weeks | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.09 | -0.12 to -0.07 | <0.001 |
| Q.25 Target joint | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.09 | -0.13 to -0.06 | <0.001 |
| Q.26 Spontaneous joint bleeding | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.09 | -0.12 to -0.05 | <0.001 |
| Q.27 having reduced range of motion | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.14 | -0.19 to -0.11 | <0.001 |
| Q.28 Life threatening bleed | | | |
| • No | Control | N/A | N/A |
| • Yes | -0.10 | -0.13 to -0.06 | <0.001 |

*Adjusted from age and gender

Abbreviation: N/A; not applicable

# CHAPTER 3

# TEST-RETEST PROPERTIES OF THE PATIENT REPORTED OUTCOMES, BURDENS AND EXPERIENCES (PROBE) QUESTIONNAIRE AND ITS CONSTITUENT DOMAINS AND QUESTIONS

Test-retest properties of the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire and its constituent domains and questions

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**Running title:** PROBE test-retest reliability analysis

**Keywords:** reliability, hemophilia, patient reported outcome, quality of life

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## ABSTRACT

**Background:** The Patient Reported Outcomes, Burdens and Experiences (PROBE) study aims to develop and validate questionnaire for assessing health status in patients with hemophilia and participants without bleeding disorders.

**Objective:** To investigate the test-retest properties of the PROBE questionnaire.

**Methods:** The PROBE questionnaire covers four domains (pain, mobility and function, school and work, health conditions or comorbidities) and is comprised of 31 questions, of which 20 are common to people with and without hemophilia. People with hemophilia (PWH) and participants without bleeding disorder were invited to participate in this study. All participants were asked to complete the PROBE questionnaire three times (paper-based survey on two consecutive days: T1 and T2 and then a web-based version: T3). Test-retest properties and percentages agreement were analyzed.

**Results:** A total of 63 participants were enrolled in this study with a median age of 50 (range 17-76) years. Of these, 30 (47.6%) were PWH. On the questions common to PWH and participants without bleeding disorder, Kappa coefficients ranged from 0.69 to 0.90, indicating substantial to almost perfect agreement (T1 vs T2). For hemophilia-related questions, Kappa coefficients ranged from 0.5-1.0. Of these, 5 of 11 items were in perfect agreement (Kappa=1.0), T1 vs T2. The web-based questionnaire (T3) showed substantial to almost perfect agreement with the paper version (T1). Correlation coefficient between the total PROBE score between T1 vs T2 was 0.95 (95% CI; 0.85-0.98) and T1 vs T3 was

0.95 (95% CI; 0.86-0.99), indicating acceptable reliability properties. Test-retest properties were comparable between PWH and individuals without a bleeding disorder.

**Conclusions:** The results suggest that PROBE is a reliable tool to assess patient reported outcomes for PWH and benchmark data in participants without bleeding disorder. The web-based questionnaire and the standard paper-based version can be used interchangeably.

## INTRODUCTION

Hemophilia is a rare bleeding disorder characterized by a congenital deficiency of factor VIII (hemophilia A) or IX (hemophilia B). The most common manifestation of hemophilia is bleeding into joints or soft tissues, either spontaneously or following trauma or invasive procedure. Management of hemophilia is hinged upon replacement therapy with plasma-derived or recombinant factor concentrates [1]. Hemophilia itself and its treatment are associated with burden of acute and chronic diseases, including, pain, difficulties of mobility, hepatitis B, C or HIV infection or chronic liver disease [2]. With the improvement in hemophilia treatment availability and safety, the life expectancy of people with hemophilia (PWH) has increased to 67-71 years [3, 4]. The aging hemophilia patients are not spared by the conditions associated with aging in the normal population, for example, obesity, osteopenia, cardiovascular disease and cancer [5, 6].

Focusing on aspects critical for a test-retest experiment, hemophilia is a chronic disease, characterized by a progressive deterioration of joint functions which develops over many years which is (partially) slowed down by replacement therapy. Superimposed on this baseline, persons living with hemophilia experience recurrent bleeds, provoking acute pain and various degrees of transient functional limitation. Bleeds can happen with any frequency, and related symptoms potentially lasting from several hours to several days.

Patient reported outcomes are defined as relevant health outcome parameters describing patients' perception of their health status or other aspects of their life

experience without interpretation by a clinician or anyone else [7]. The Patient Reported Outcomes, Burdens, and Experiences (PROBE) Project was developed to directly assess health status using outcomes PWH identified as important to their care. This questionnaire comprises two sections. The core section covers patient reported outcomes, including general health problems and disease impact on the life experience of the participants. The detail of questionnaire development and pilot testing was described before by Skinner et al [8]. In brief, the development phase of the PROBE Project was conducted to develop and test the questionnaire for relevance, content, clarity and completeness. This phase enrolled 704 participants (PWH and individuals without a bleeding disorder) from 17 countries. Most (>70%) of the participants completed the questionnaire within 15 minutes. In summary, the PROBE questionnaire comprises 31 items and 4 parts. Part I (7 questions) collect participant demographic data, primary language of participants and time to complete the questionnaire; Part II (9 questions) is the core section collecting patient reported outcomes (general health problems, including presence of acute and chronic pain and the use of pain medication, limitations in mobility, absence from work or school, health conditions), Part III (12 questions) collects hemophilia-related information, including severity of hemophilia, treatment regimes, number of bleeds, presence of target joint (these two sections are not part of the tool, and data are collected only to help with result interpretation) and Part IV is the EuroQol 5-dimensions 5-level instrument (EQ-5D-5L), a standardized measure of health status developed by the EuroQol Group and the EuroQol visual analog scale (EQ VAS) of global health [9]. PWH respond to all of the items, whereas participants without a

bleeding disorder respond to all parts except hemophilia-related questions. The responses are a combination of yes/no answer, unidirectional 5-level and 7-level Likert scale, multiple choices, open answer and visual analog scale. Inspecting the data collected during earlier phases of the questionnaire development, there was evidence of a strong correlation between the PROBE questions belonging to part II and III, suggesting a good potential for assessing the most important characteristic of a questionnaire useful for clinical research and quality improvement or audit purposes, i.e. discrimination and responsiveness [8].

Before proceeding with testing those properties in a larger study, we decided to formally assess the test-retest property of the individual questions of the PROBE and of a candidate version of the PROBE score. A test-retest experiment is most informative when the time interval chosen between the test and retest is long enough in stable patients to minimize memory effects [7]. However, the choice of the time interval has to take into account the variability of the disease or experience being evaluated (e.g. the potential for change in the condition over time). In other words, the test-retest experiment is intended to explore the variability in stable patients, and is therefore biased by actual changes in the condition. The FDA guidance acknowledges that "for remitting and relapsing or episodic diseases, test-retest properties may be difficult or impossible to establish." As a consequence, the test-retest properties can be explored over a variety of intervals to satisfy different study protocols. Examples in the musculoskeletal field span from intervals between the two tests of minutes to several months [10-13]. Given its

characteristics, hemophilia qualifies among the diseases for which the optimal test-retest interval is difficult to define. Here we report the results of the test-retest assessment.

## METHODS

### Participants

PWH (including hemophilia carriers) and individuals without a bleeding disorder who attended a hemophilia-related workshop in Lisbon, Portugal, January 2016 were invited to participate in this study, but were not informed of the test-retest design until after the second filled questionnaire were collected, to minimize any effort to memorize the answers provided. Participants without a bleeding disorder were enrolled as controls. We hypothesized the PROBE questionnaire is robust in measuring the general health status and its determinants in a normal population. Therefore, the test-retest properties should not be different among PWH compared to those without bleeding disorders. Participation was voluntary, and data was collected anonymously.

### Test-retest interval

We balanced the consideration of the recurrent nature of bleeding events with the need of avoiding easy recall of the answers given on the previous test. We selected a short primary test-retest interval (one day), to minimize the chance of background noise introduced by the occurrence of any bleeds. However, we also included a third repeat after a 4-6 week interval, to minimize recall. The first and second repeats were done on paper, the third using a web-based version. Since the intended use of the PROBE is to interchangeably use the paper or online version, we decided to simplify the study and

accept not discriminating the variability linked to use of the paper or online version of the questionnaire.

**Study procedure**

Sets of adhesive labels with alpha-numeric codes were used to pair up replicates, avoiding use of any subject identifier. Identical and non-identifiable envelopes were prepared, each containing 4 copies of a sticky label with the same 6-digit code, and a paper card with the PROBE website address. On Time 1 (T1), each participant received an envelope, was invited to apply one of the stickers on the card, wrote his/her name on the paper card (in case the envelope was lost), and was asked to keep the envelope with them for the entire meeting and to take it home. Each participant was asked to fill out a paper copy of the PROBE questionnaire, and stick one label on it. On time 2 (T2), they did the same, and attached a second label. For time 3 (T3), participants were instructed to log into the PROBE website, using the same 6-digit code, and complete the questionnaire. T3 web-based responses were collected over 50 days beginning one week after T1. Participants were asked to fill out the questionnaire objectively, answering the questions for themselves. The questionnaires were collected immediately after being filled out on T1 and T2, so that participants could not access the questionnaire filled the previous days. Participants were allowed to select either an English or Spanish version of the PROBE tool.

**Calculation of the PROBE score**

A summary PROBE score was calculated from section II. Each item had a value score ranged from 0 (assigned to the answer indicating normal health/absence of disease) to 1 (the worst health status). The dichotomous response was scored 1 (have any problems) or 0 (do not have problem in the past). The 6- and 7-level Likert scales were converted to a standardized score, ranging from 0 (indicating normal health) to 1 (the worst health status). The numbers of days absent from work or school were converted to standardized score by dividing by 365 (minimum score=0 and maximum score=1). Multiple choice items were converted to a standardized score by dividing by their denominators. Each item was weighted equally. Final PROBE score was calculated by summing 11 items then converting to a scale from 0 to 1. The minimum PROBE Score was 0 (indicating the worst health status) and maximum PROBE score was 1 (indicating normal health status). No pre-specified cut offs were used for classification of results.

**Statistical Analysis**

Descriptive statistics were used to describe patients' demographic and clinical data. Test-retest agreement for binary data was analyzed using percentages agreement and Cohen's Kappa (κ) statistic [14]. For data collected on a Likert scale, a weighted Kappa was calculated for each item [15]. In terms of interpretation, we followed the level of agreement according to Landis and Koch (0.81-1.00 indicates almost perfect agreement, 0.61-0.80, substantial agreement; 0.41-0.60, moderate agreement; 0.21-0.40, fair agreement; 0.00-0.20, slight agreement; and <0.00, poor agreement) [16]. For the items

for which participants could select more than one answer, we used non-parametric two-way analysis of variance and Kendall's coefficient of concordance [17]. We further explored the test-retest reliability of continuous outcome by calculating Lin's correlation coefficient for both the complete questionnaire and its items separately [18]. Correlation coefficient ≥0.75 was considered acceptable [19, 20]. We used Bland and Altman plots to compare the two replicates and calculated mean difference with corresponding limits of agreement [21-23]. Mean differences of EQ VAS scale (spanning from 0 –death - to 100 - full health). Test-retest agreement was calculated for the T1 vs T2 (paper-based) and T1 vs T3 (paper- vs web-based), as a primary analysis. A secondary analysis was carried out for the agreement between T2 vs T3 and T1 vs T2 vs T3, respectively (the results are shown in supplementary material only). As a sensitivity analysis, participants were stratified into PWH and participants without a bleeding disorder.

The sample size for the test-retest study is defined, when the measurement properties of the instrument under study are known, by calculating the number of subjects needed to exclude a pre-specified variability. This is almost invariably the case when the test-retest experiment involves a pre-validated instrument used in a different setting or modified or translated. The sample size was calculated based on an expected correlation coefficient value of 0.6, number of replicates of 3, alpha level of 0.05 and power of 0.8 [24, 25], as well as an expected kappa of 0.6, proportion of positive rating of 0.5, alpha level of 0.05 and power of 0.8. Since at least 52 participants were needed for the test-retest analysis we planned to enroll 15% more to allow for drop-outs [26].

All of the analyses were performed using STATA version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

## RESULTS

A total of 63 participants were enrolled in this study. Median age was 50 (range 17-76) years. Thirty (47.6%) were PWH and 33 (52.4%) were participants without a bleeding disorder. Forty-five participants (71.4%) were male. Table 1 shows participant demographic data and clinical characteristics.

### Patient reported outcomes-General health problems (Part II)

Table 2 demonstrates test-retest reliability of this domain. For T1 vs T2, Kappa coefficients ranged from 0.69 to 0.92. Five items were almost in perfect agreement, whereas 4 items showed substantial agreement. The lowest Kappa coefficients was found in the item measuring "acute pain" ($\kappa$=0.69). Percentages agreement ranged from 85% to 97% indicating almost perfect agreement for all items.

Kappa coefficients for the web- versus paper-based questionnaire ranged from 0.29 to 0.76 and percentages agreement ranged from 65% to 95%. Kappa indicated moderate to substantial agreement for all except one item (acute pain). However, percentages agreement indicated substantial agreement and almost perfect agreement for all items.

### Hemophilia-related problems (Part III)

Only PWH completed this part. Table 3 demonstrates test-retest reliability for hemophilia-related problems. Kappa coefficients ranged from 0.50 to 1.0 and percentages agreement ranged from 87% to 100%. All but one of the items were in almost perfect

agreement. Of these, 5 out of 11 items were in perfect agreement (κ=1.0). Percentages agreement indicated almost perfect agreement for all items.

Test-retest reliability of the web-based questionnaire compared with the paper-based version had Kappa coefficients of 0.57 to 1.0 and percentages agreement of 80 to 100%. All but one of the items (Item 20 - bleed within the past 2 weeks) were in substantial to perfect agreement.

**Health-related quality of life (Part IV)**

HRQOL was evaluated in both PWH and participants without a bleeding disorder. Table 4 demonstrates test-retest reliability results for HRQOL. Kappa coefficients for each item of EQ-5D-5L ranged from 0.63 to 0.85 and percentages agreement ranged from 90% to 95%. Lowest Kappa coefficient was found in the item measuring "pain and discomfort" (κ=0.63). Correlation coefficient of EQ VAS was 0.90 (95% CI; 0.83-0.94). Mean difference of EQ VAS (T1 vs T2) was -0.45. Limits of agreement were -10.35 and 9.43 (data not shown).

Test-retest reliability of the web-based compared with paper-based questionnaire showed that kappa coefficients ranged from 0.36-0.91. Better agreement was demonstrated from percentages agreement, ranging from 88%-98%. The worst agreement was found in items measuring "pain and discomfort" and "anxiety". Correlation coefficient of EQ VAS was 0.71 (0.53 to 0.83). Mean difference of EQ VAS (T1 vs T3) was 1.46. Limits of agreement were -16.36 and 19.30 (data not shown).

**Total PROBE score**

Table 5 reports the total score of PWH and participants without bleeding disorder over the three repetitions. Mean and median total score were consistently higher among PWH than participants without bleeding disorder for general health problems. Correlation coefficient between total PROBE Score between T1 vs T2 was 0.95 (95% CI; 0.85-0.98) and T1 vs T3 was 0.95 (95% CI; 0.86-0.99), indicating acceptable reliability properties. Mean difference of the total PROBE Score (T1 and T2) was 0.07. Limits of agreement (95%) were -0.54 and 0.67 (Figure 1). Mean difference of the total PROBE Score (T1 and T3) was 0.06 and limits of agreement (95%) were -0.56 and 0.68 (Figure 2).

**Secondary analysis and sensitivity analysis**

Test-retest reliability analysis for T2 vs T3 and T1 vs T2 vs T3 are reported in the supplemental material. Overall, the results did not substantially change from the primary analysis. The sensitivity analysis was carried out when participants were stratified into PWH and participants without a bleeding disorder. For general health problems, all items showed substantial to perfect agreement in both groups (supplementary material). With respect to HRQOL, PWH had substantial to almost perfect agreement with EQ-5D-5L items, whereas participants without bleeding disorder had fair, moderate, or almost perfect agreement. Intraclass correlation of EQ VAS was 0.86 in PWH and 0.91 in participants without a bleeding disorder.

## DISCUSSION

This study investigated the test-retest reliability of the PROBE questionnaire in PWH, administered on paper over two consecutive days and subsequently via a dedicated web-version. The results demonstrate an excellent overall agreement. The PROBE tool incorporates EQ-5D-5L, which has been widely translated and validated in multinational studies [9, 27] and is broadly used for assessing health outcomes in economic evaluations and technology assessments. The test-retest properties analysis in the EQ-5D-5L original study demonstrated Kappa coefficients of 0.00-0.66 and percentages of agreement of 69.8% to 99.7% [27], which were replicated in our study, confirming the appropriateness of its design. The total scores were well correlated comparing between three-time points. The lowest agreement was found in the item measuring acute pain (moderate agreement for paper-based and fair agreement for web-based questionnaire), which is not surprising, considering the specific transient nature of acute pain in most of the cases. Possibly, the time interval to assess test-retest properties for acute pain should be measured in hours if not minutes. Therefore, this finding reflected the nature of the item determining acute pain which was more vulnerable to change during the study period when compared to the others.

We decided to analyze both kappa coefficients and agreement because both provided different information. Percentages agreement measures absolute degree of measurement error of the tool. On the other hand, kappa coefficient takes the variability between the subjects in to the account [28, 29]. Most of the items had concordant values between percentages agreement and Kappa coefficients. Lower Kappa coefficients as

compared to percentages agreement in each item reflected variability of the subjects in addition to measurement error. One interesting finding was the discrepancy between Kappa coefficient and unadjusted percentages agreement in some items. For example, item 4, part II (acute pain) had a Kappa coefficient of 0.69 but percentage agreement of 85%; similarly, item 8, part II (invasive procedure) had a Kappa coefficient of 0.57 but percentage agreement of 78%. A simulation study by Feinstein et al. (24) demonstrated that the paradox of discordant Kappa coefficients and percentages agreement might be due to substantial imbalance in the prevalence of the levels of the health status investigated. In our study, the discrepancies between Kappa and percentages agreement were mostly detected in the items for which most of the participants selected preferentially one of the answers over the others. For this circumstance, low Kappa coefficients may not refer to low rate of agreement, and should be disregarded.

An objective of this study was to assess the test-retest characteristics of the PROBE when data are obtained with the paper and web-based versions of the questionnaire. We did not include a randomization of the order of administration of the two forms of the questionnaire for practical reasons. Therefore, we cannot discriminate whether the slightly lower agreement observed when comparing the web-based questionnaire (T3) with the paper version (T1) is due to the modality or the lag time. Indeed, the difference could be entirely explained by the elapsed time between the two replicas of the test rather than the platform of the tests. However, the observed difference is more of scientific than practical interest: the results of our study suggest that the web-

based PROBE questionnaire may be used in as an alternative to the paper-based questionnaire.

There are some limitations in this study that need to be addressed. First, the participant selection was based on a convenience sample of participants in a specific hemophilia-related workshop. These participants may be more knowledgeable about their health status than those who did not attend the workshops, limiting generalizability to patients within the broader hemophilia community. Second, the participants were reminded to submit their response via web-based questionnaire beginning 1 month after the workshop. The differences of the time interval from T1 to completion of the web survey T3 (up to 8 weeks) may contribute to the variance of agreement in our study. Third, 8 and 23 participants failed to return the questionnaire at T2 and T3 of the study, respectively. We performed the analysis based on complete case analysis. Therefore, the test-retest analysis may lead to overestimating the agreement reliability, even if with a low margin. Fourth, although we enrolled participants from 21 countries, most of them are from North America and Europe. The results of this study may not reflect the broad spectrum of patients with differing hemophilia care. Finally, we have not yet developed a definitive summary PROBE score; specifically, we plan to further explore how to optimally differentiate the impact of acute bleed and chronic arthropathy on pain and function; however, the provisional summary score we have tested performed already more than satisfactorily, and allow to consistently obtain different scores in patients and controls.

## CONCLUSION

The PROBE tool is designed to be used for assessing the health status of PWH, comparing cross-sectionally among different settings, longitudinally over time and across changes in care availability and modality of provision, and comparing people with hemophilia with a reference population. The test-retest properties reported in this study support PROBE's use, both as a paper- and web-based questionnaire. Additional studies are planned to investigate the test retest properties of the PROBE questionnaire across random samples of people from different countries, and to test the discrimination and responsiveness of the tool.

**List of abbreviations**

PROBE: Psychometric properties of the Patient Reported Outcomes, Burdens and Experiences; EQ-5D-5L: EuroQol five dimension 5-level instrument; F:factor; EQ-VAS: EuroQol visual analog scale; PWH: people with hemophilia; HIV: Human immunodeficiency virus; HCV: hepatitis C virus; HRQoL: health-related quality of life; PRO: Patient reported outcome; ISPOR: International Society for Pharmacoeconomic and Outcomes Research; NGO: non-governmental organization; SD: standard deviation; ANOVA; analysis of variance

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**Competing interests**

CC and DM have no potential conflict of interest. Investigators received grants from Baxalta, now part of Shire; Bayer; Bioverativ; CSL Behring, Novo Nordisk; Roche; and Sobi and non-financial support from the US National Hemophilia Foundation.

**Authors' contributions**

MS, AI, RC, NF, MN, DN, BOM, DP, LT, MAC and JS conceptualized the study. CC performed data collection and statistical analysis. CC, AI and MS drafted the manuscript. All authors critically reviewed the manuscript. All authors approved the final manuscript.

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## REFERENCES

1. Franchini M: **The modern treatment of haemophilia: a narrative review**. *Blood Transfus* 2013, **11**(2):178-182.
2. Barr RD, Saleh M, Furlong W, Horsman J, Sek J, Pai M, Walker I: **Health status and health-related quality of life associated with hemophilia**. *Am J Hematol* 2002, **71**(3):152-160.
3. Plug I, Van Der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L, Smit C, Willemse J, Rosendaal FR: **Mortality and causes of death in patients with hemophilia, 1992-2001: a prospective cohort study**. *J Thromb Haemost* 2006, **4**(3):510-516.
4. Tagliaferri A, Rivolta GF, Iorio A, Oliovecchio E, Mancuso ME, Morfini M, Rocino A, Mazzucconi MG, Franchini M, Italian Association of Hemophilia C *et al*: **Mortality and causes of death in Italian persons with haemophilia, 1990-2007**. *Haemophilia* 2010, **16**(3):437-446.
5. Philipp C: **The aging patient with hemophilia: complications, comorbidities, and management issues**. *Hematology Am Soc Hematol Educ Program* 2010, **2010**:191-196.
6. Young G: **New challenges in hemophilia: long-term outcomes and complications**. *Hematology Am Soc Hematol Educ Program* 2012, **2012**:362-368.
7. U.S Food and Drugs Administration. **Guidance for Industry, Patient-Reported Outcome Measure: Use in Medical Product Development to Support Labeling Claims** available at

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf (last acessed August 2017).

8. Skinner MW, Driessens M, Curtis R, Frick N, Iorio A, Nichol M, Noone D, O'Mahony B, Page D, Stonebraker J: **The Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Phase 1 Methodology and Feasibility**. *Haemophilia* 2016, **22 (Suppl. 4)**:118.
9. EuroQol G: **EuroQol--a new facility for the measurement of health-related quality of life**. *Health Policy* 1990, **16**(3):199-208.
10. Streiner DL, Norman GR, Cairney J: **Health Measurement Scales: A Practical Guide to Their Development and Use Oxford University Press.**; 2014.
11. Theiler R, Spielberger J, Bischoff HA, Bellamy N, Huber J, Kroesen S: **Clinical evaluation of the WOMAC 3.0 OA Index in numeric rating scale format using a computerized touch screen version**. *Osteoarthritis Cartilage* 2002, **10**(6):479-481.
12. Whitehouse SL, Lingard EA, Katz JN, Learmonth ID: **Development and testing of a reduced WOMAC function scale**. *J Bone Joint Surg Br* 2003, **85**(5):706-711.
13. Yang KG, Raijmakers NJ, Verbout AJ, Dhert WJ, Saris DB: **Validation of the short-form WOMAC function scale for the evaluation of osteoarthritis of the knee**. *J Bone Joint Surg Br* 2007, **89**(1):50-56.
14. Cohen J: **A coefficient of agreement for nominal scales.** *Educ Psychol Meas* 1960, **20**:37-16.

15. Cohen J: **Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit**. *Psychol Bull* 1968, **70**(4):213-220.

16. Landis JR, Koch GG: **The measurement of observer agreement for categorical data**. *Biometrics* 1977, **33**(1):159-174.

17. Gibbons JD: **Nonparametric Statistical Inference.** New York: Marcel Dekker; 1985.

18. Lin LI: **A concordance correlation coefficient to evaluate reproducibility**. *Biometrics* 1989, **45**(1):255-268.

19. Shrout PE, Fleiss JL: **Intraclass correlations: uses in assessing rater reliability**. *Psychol Bull* 1979, **86**(2):420-428.

20. Cicchetti DV: **Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology**. *Psychol Assessment* 1994, **6**(4):284-290.

21. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement**. *Lancet* 1986, **1**(8476):307-310.

22. Bland JM, Altman DG: **Comparing methods of measurement: why plotting difference against standard method is misleading**. *Lancet* 1995, **346**(8982):1085-1087.

23. Bland JM, Altman DG: **Applying the right statistics: analyses of measurement studies**. *Ultrasound Obstet Gynecol* 2003, **22**(1):85-93.

24. Walter SD, Eliasziw M, Donner A: **Sample size and optimal designs for reliability studies**. *Stat Med* 1998, **17**(1):101-110.

25. Shoukri MM, Asyali MH, Donner A: **Sample size requirements for the design of reliability study: review and new results**. *Stat Methods Med Res* 2004, **13**(1):251-271.

26. Sim J, Wright CC: **The kappa statistic in reliability studies: use, interpretation, and sample size requirements**. *Phys Ther* 2005, **85**(3):257-268.

27. Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Gusi N, Herdman M *et al*: **Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study**. *Qual Life Res* 2010, **19**(6):887-897.

28. de Vet HC, Terwee CB, Knol DL, Bouter LM: **When to use agreement versus reliability measures**. *J Clin Epidemiol* 2006, **59**(10):1033-1039.

29. Kottner J, Streiner DL: **The difference between reliability and agreement**. *J Clin Epidemiol* 2011, **64**(6):701-702; author reply 702.

## FIGURE LEGENDS AND TABLES

Figure 1 Plot of differences between total PROBE Score time 1 and time 2 versus the mean of total the PROBE score of the two measurements, mean difference of -006 (95% confidence interval -0.022 to 0.010, limits of agreement of -0.061 to 0.049.

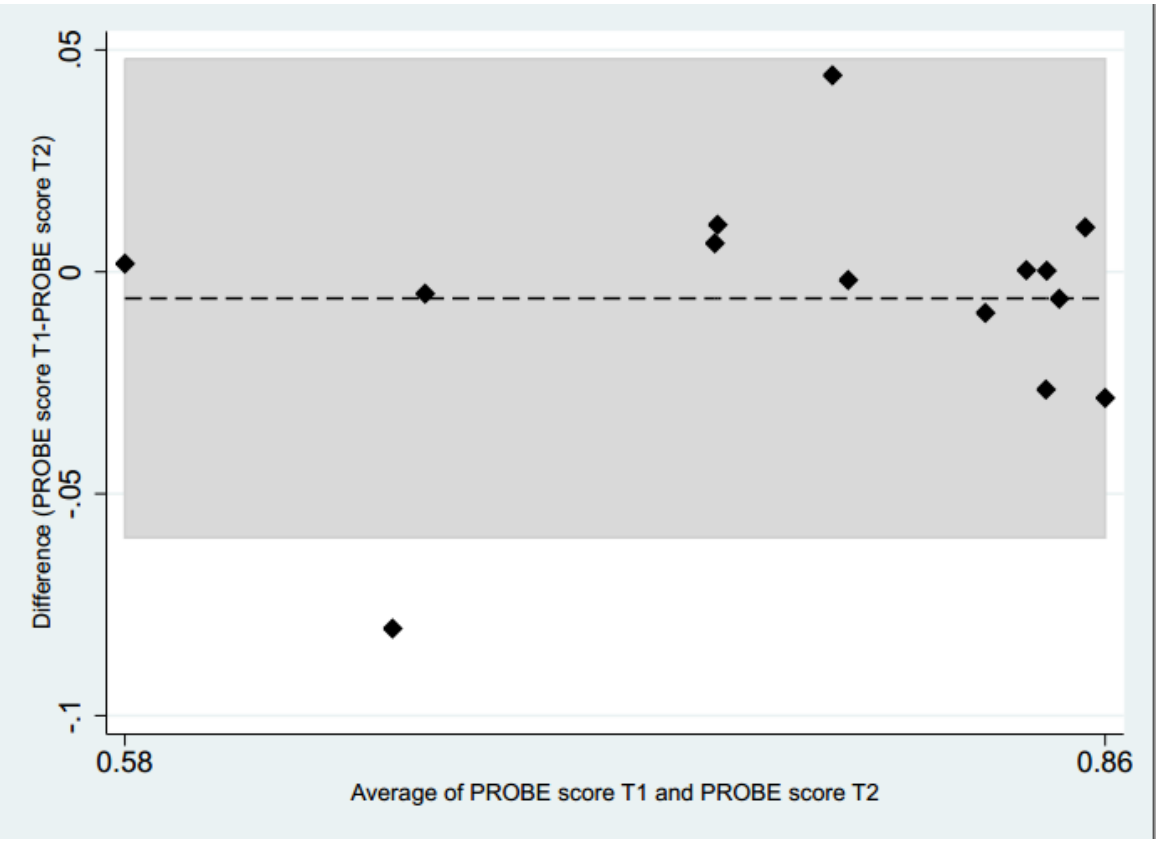

Figure 2 Plot of differences between total PROBE Score time 1 and time 3 versus the mean of the total PROBE Score of the two measurements, mean difference of -0.005 (95% confidence interval of -0.022 to 0.012), limits of agreement of -0.062 to 0.051

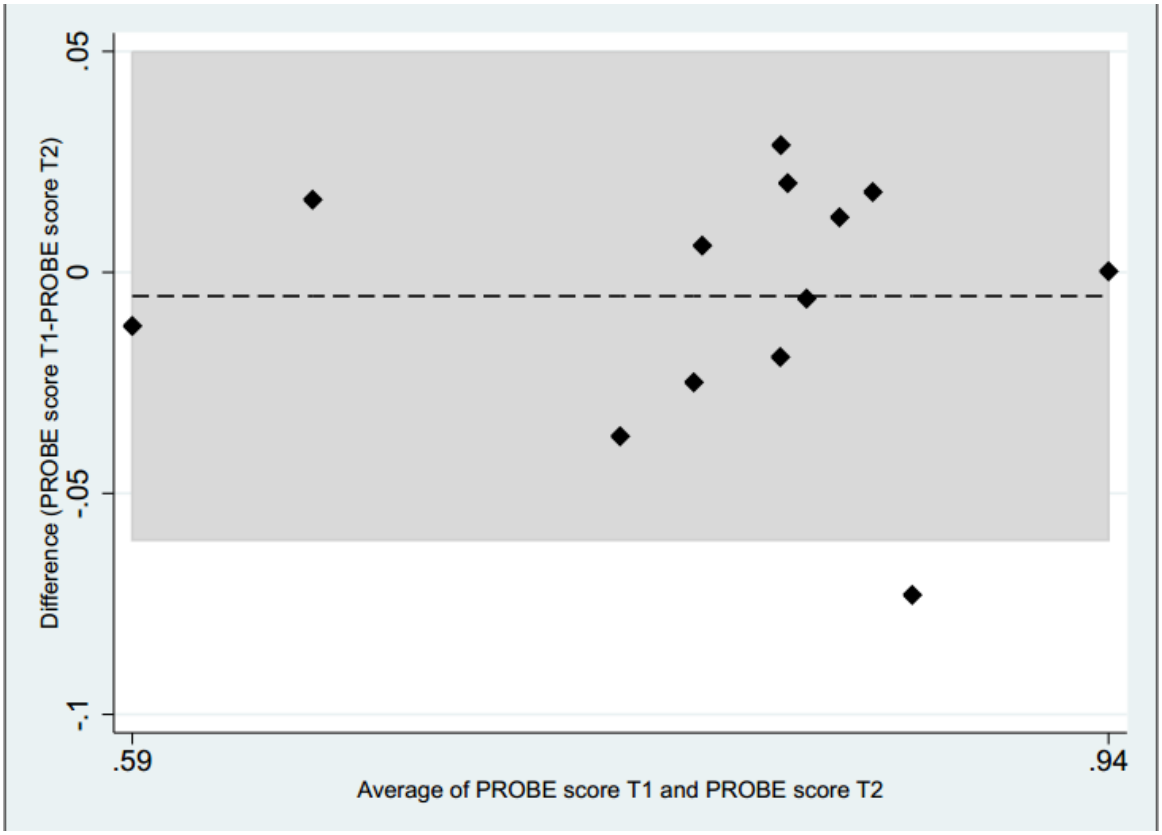

Table 1. Demographic and clinical characteristic data of participants

| | Total (n=63) | Patients with hemophilia (n=30) | Without bleeding disorder (n=33) | p-value |
|---|---|---|---|---|
| Sex, Male, (%) | 45 (71.4) | 24 (80.0) | 21 (63.6) | 0.151 |
| Age (years), median (min-max) | 50 (17-76) | 42 (17-76) | 51 (27-68) | 0.083 |
| Marital status, n (%)<br>Married | 47 (75.8) | 24 (80) | 23 (71.9) | 0.455 |
| Age at start school (years), median (min-max) | 5 (3-7) | 5 (4-7) | 5 (3-7) | 0.641 |
| Age at finish school (years), median (min-max) | 18 (14-26) | 18 (15-24) | 19 (14-26) | 0.082 |
| Diagnosis, n (%)<br>No bleeding disorder<br>Hemophilia A<br>Hemophilia B<br>Hemophilia A, B carrier | <br>33 (53.4%)<br>20 (31.8%)<br>5 (7.9%)<br>5 (7.9%) | <br>N/A<br>20 (66.6)<br>5 (16.7)<br>5 (16.7) | N/A | N/A |

Abbreviation: NA; not applicable

Table 2. Test-retest agreement for general health problems (Part II)

| Item | Question | Time 1-Time 2 (n=55) | | Time 1-Time 3 (n=40) | |
|---|---|---|---|---|---|
| | | Kappa (95%CI) | Agreement (%) | Kappa (95%CI) | Agreement (%) |
| 1 | In the past 12 months, have you experienced any problems related to your health? (y/n) | 0.83 (0.65 - 1.00) | 94.00 (93.72-94.28) | 0.66 (0.39 - 0.93) | 87.50 (87.20-87.80) |
| 2 | Please indicate the frequency you used each of the following mobility aids or assistive devices in the past 12 Months. (Likert scale)[#] | 0.79[$] (0.57 -0.84) | 97.37[$] (96.22-98.51) | 0.55[$] (0.36-0.75) | 95.79[$] (93.20-98.38) |
| 3 | During the past 12 months did you use any medication for pain? (y/n) | 0.76 (0.53 - 0.98) | 92.73 (92.47-92.99) | 0.63 (0.34 - 0.92) | 87.80 (87.51-88.09) |
| | If yes, please estimate the percent of the time you used pain medication. (Likert scale)[#] | 0.85[#] (0.83 - 0.86) | 96.30 (96.10-96.50) | 0.70[#] (0.57 - 0.87) | 90.97 (90.72-91.22) |
| 4 | During the past 12 months, have you experienced acute pain? (y/n) | 0.69 (0.50 - 0.89) | 85.45 (85.19-85.71) | 0.30 (0.00 - 0.59) | 65.85 (65.55-66.15) |
| 5 | During the past 12 months, have you experienced chronic pain? (y/n) | 0.86 (0.72 - 0.99) | 92.73 (92.47-92.99) | 0.76 (0.56 - 0.96) | 87.80 (87.49-88.10) |
| 6 | Do you currently have difficulty with any activities of daily living? (y/n) | 0.92 (0.82 - 1.00) | 96.36 (96.10-96.62) | 0.46 (0.24 - 0.69) | 78.95 (78.73-79.17) |

| | | | | | |
|---|---|---|---|---|---|
| 7 | Please select the best answer to describe your current work and/or school life?[#] | 0.89[#] (0.73 - 0.95) | 98.10 (97.94-98.26) | 0.45[#] (0.31 - 0.64) | 90.74 (90.60-90.88) |
| | If you are working part-time (Estimate percent of full-time) [Ω] | 1.00 [Ω] (1.00 - 1.00) | - [€] | 0.92 [Ω] (0.88 - 0.95) | - [€] |
| | How many days during the past 12 months were you not able to work or attend school due to health related reasons? [Ω] | 0.99 [Ω] (0.99 - 0.99) | - [€] | 0.68 [Ω] (0.53 - 0.83) | - [€] |
| 8 | Have you ever gone through joint surgery or another invasive procedure? (y/n) | 0.78 (0.61 - 0.95) | 88.89 (88.62-89.16) | 0.57 (0.36 - 0.78) | 78.18 (77.92-78.44) |
| 9 | In the past 12 months have you had any of the following conditions or problems? (hepatitis B, hepatitis C, stroke, high blood pressure, angina/chest pain, heart attack, heart failure or enlarged heart, asthma, liver cancer, cancer, diabetes, seizure, arthritis, gingivitis, HIV/AIDS, others) | 0.82[*] | - [€] | 0.67[*] | - [€] |

[#]Weighted kappa, *Kendall's coefficient, [€]Not applicable, [¥]Too few rating categories, [Ω]Correlation coefficient, [$]mean (95% confidence interval)

Abbreviations: CI, confidence interval; y, yes; n, no

Table 3. Test-retest agreement for hemophilia-related problems (Part III)

| Item | Question | Time 1-Time 2 (n=24) | | Time 1-Time 3 (n=18) | |
|---|---|---|---|---|---|
| | | Kappa (95%CI) | Agreement (%) | Kappa (95%CI) | Agreement (%) |
| 1 | How severe is your hemophilia? | 0.79 (0.48 - 0.88) | 91.67 (91.41-91.93) | 0.77 (0.43 - 1.00) | 94.44 (93.99-94.89) |
| 2 | Have you ever been diagnosed with a clinically significant inhibitor? | 0.78 (0.36 - 1.00) | 95.83 (95.44-96.22) | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) |
| | If yes, do you currently have a clinically significant inhibitor? | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) |
| 3 | How many bleeds did you have in the past 12 months?[#] | 0.90[#] (0.85 - 0.920) | 96.43 (96.17-96.69) | 0.70[#] (0.61 - 0.88) | 91.11 (90.79-91.43) |
| 4 | Within the past two weeks, have you had a bleed? | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 0.57 (0.15 - 0.99) | 80.00 |
| 5 | Where do you receive your regular treatment? [#] | 0.81[#] (0.00 - 1.00) | 96.97 (96.65-97.29) | 0.78[#] (0.00 - 1.00) | 96.43 (95.97-96.89) |
| 6 | What is your current treatment regimen? [#] | 0.96[#] (0.94 - 1.00) | 98.67 (98.34-99.00) | 0.64[#] (0.00 - 0.65) | 95.56 (95.19-95.93) |
| 7 | How do you currently treat? If you treat with a combination of | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | regimens, please indicate all that apply.<br>- Typical dose of Factor VIII/IX concentrate used for prophylaxis | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 0.79 (0.62 - 1.00) | 83.33 (83.05-83.55) |
| | - Typical prophylaxis frequency | 1.00[#] (1.00 - 1.00) | 100.0 (100.0-100.0) | 0.74 [#] (0.65 - 0.76) | 89.74 (89.38-90.10) |
| | - Typical dose of Factor VIII/IX concentrate used per infusion for on-demand treatment[#] | -[¥] | 93.33 (93.33-93.33) | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) |
| 9 | Do you currently have any "target joints"? | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 0.82 (0.47 - 1.00) | 93.33 (92.83-93.83) |
| 10 | Have you had 3 or more spontaneous bleeds (including those resulting from normal daily activity) into any one joint in the past 6 months? | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) |
| 11 | Is the range of motion of any joint currently reduced because of your having hemophilia? | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) | 1.00 (1.00 - 1.00) | 100.0 (100.0-100.0) |
| 12 | Other than joint bleeds, have you had any life- or limb-threatening bleeds in the past 12 months? | 0.50 (0.01 - 0.99) | 87.50 (87.11-87.89) | -[¥] | 85.71 (85.71-85.71) |

[#]Weighted kappa, *Kendall's coefficient, [€]Not applicable, [¥]Too few rating categories, [Ω]Correlation coefficient

Abbreviations: CI, confidence interval

Table 4. Test-retest reliability on health-related quality of life

| Question | Time 1-Time 2 (n=55) | | Time 1-Time 3 (n=40) | |
|---|---|---|---|---|
| | Kappa (95%CI) | Agreement (%) | Kappa (95%CI) | Agreement (%) |
| Mobility[#] | 0.85[#] (0.79 - 0.92) | 94.55 (94.33-94.77) | 0.90[#] (0.88 - 0.93) | 96.25 (96.00-96.50) |
| Self-care[#] | 0.67[#] (0.31 - 0.78) | 95.45 (95.23-95.67) | 0.91[#] (0.76 - 0.93) | 98.75 (98.48-99.02) |
| Usual activities[#] | 0.74[#] (0.62 - 0.83) | 93.64 (93.41-93.87) | 0.66[#] (0.48 - 0.91) | 92.50 (92.21-92.79 |
| Pain/discomfort[#] | 0.63[#] (0.56 - 0.67) | 90.30 (90.11-90.49) | 0.63[#] (0.58 - 0.82) | 87.50 (87.26-87.74) |
| Anxiety/depression[#] | 0.81[#] (0.63 - 1.00) | 95.45 (95.22-95.68) | 0.36[#] (0.21 - 0.38) | 88.33 (88.08-88.58) |
| Total EQ-5D-5L score | 0.89[Ω] (0.83 - 0.94) | - [€] | 0.83[Ω] (0.69 - 0.90) | - [€] |
| VAS | 0.90[Ω] (0.83 - 0.94) | - [€] | 0.71[Ω] (0.53 - 0.83) | - [€] |

[#]Weighted kappa, [€]Not applicable, [Ω]Correlation Coefficient

Abbreviations: CI, confidence interval

Table 5 Summary PROBE score, classified by hemophilia status of the respondent

| | Patient with hemophilia (n=30) | | Participants without bleeding disorders (n=33) | |
|---|---|---|---|---|
| | Median (range) | Mean (SD) | Median (range) | Mean (SD) |
| Time 1 | 0.77 (0.58-0.95) | 0.76 (0.10) | 0.90 (0.83-0.98) | 0.90 (0.06) |
| Time 2 | 0.76 (0.58-0.85) | 0.76 (0.09) | 0.85 (0.70-0.98) | 0.85 (0.08) |
| Time 3 | 0.79 (0.59-0.94) | 0.77 (0.10) | 0.84 (0.79-0.96) | 0.86 (0.06) |

Abbreviations: SD; standard deviation, N/A; not applicable

## Supplemental Appendix

**Table 1s.** Test-retest agreement for general health problems

| Item | Question | Day 2-Day 3 (n=40) | | Day1-2-3 (n=38) |
|---|---|---|---|---|
| | | Kappa (95%CI) | Agreement (%) | Kappa (95% CI) |
| 8 | In the past 12 months, have you experienced any problems related to your health? (y/n) | 0.73 (0.48 - 0.98) | 89.74 | 0.75 (0.49 - 0.89) |
| 9 | Please indicate the frequency you used each of the following mobility aids or assistive devices in the past 12 Months. (Likert scale)[#] | 0.560[$] (0.48-0.714 | 96.44[$] (94.29-98.60) | 0.44[$] (0.25-0.63) |
| 10 | During the past 12 months did you use any medication for pain? (y/n) | 0.76 (0.50 - 1.00) | 92.50 | 0.73 (0.68 - 0.81) |
| | If yes, please estimate the percent of the time you used pain medication. (Likert scale)[#] | 0.66[#] (0.60 - 0.78) | 91.11 | 0.61[#] (0.53 - 0.69) |
| 11 | During the past 12 months, have you experienced acute pain? (y/n) | 0.28 (-0.03 - 0.58) | 67.50 | 0.47 (0.33 - 0.58) |
| 12 | During the past 12 months, have you experienced chronic pain? (y/n) | 0.75 (0.55 - 0.95) | 87.50 | 0.79 (0.72 - 0.88) |
| 13 | Do you currently have difficulty with any activities of daily living? (y/n) | 0.46 (0.23 - 0.69) | 78.18 | 0.62 (0.61 - 0.63) |
| 14 | Please select the best answer to describe your current work and/or school life? (Working full-time, working part-time, student full-time, student part-time, on long-term sick or disability leave, early retirement, other)[#] | 0.46[#] (0.33 - 0.57) | 91.27 | 0.55[#] (0.45 - 0.63) |
| | If you are working part-time (Estimate percent of full-time) [Ω] | 0.92 [Ω] (0.88 - 0.95) | - [€] | - [€] |
| | How many days during the past 12 months were you not able to work or attend school due to health related reasons? [Ω] | 0.69 [Ω] (0.52 - 0.81) | - [€] | - [€] |
| 15 | Have you ever gone through joint surgery or another invasive procedure? (y/n) | 0.58 (0.36 - 0.80) | 78.85 | 0.65 (0.47 - 0.68) |

| | | | | |
|---|---|---|---|---|
| | If yes, how many joint surgeries or other invasive procedures have you ever gone through?[#] | 0.74[#] (0.52 - 0.92) | 94.00 | 0.76[#] (0.73 - 0.86) |
| 16 | In the past 12 months have you had any of the following conditions or problems? | 0.612[*] | - [€] | 0.65[*] |

[#]Weighted kappa, [*]Kendall's coefficient, [€]Not applicable, [¥]Too few rating categories, [Ω]Interclass Correlation Coefficient (ICC), [$]mean (95% confidence interval)

**Abbreviations:** CI, confidence interval; y, yes; n, no

**Table 2s.** Test-retest agreement for hemophilia-related problems

| Item | Question | Day 1-Day 2 (n=24) | | Day 1-Day 3 (n=18) | |
|---|---|---|---|---|---|
| | | **Kappa (95%CI)** | **Agreement (%)** | **Kappa (95%CI)** | **Agreement (%)** |
| 17 | How severe is your hemophilia? | 0.79 (0.48 - 0.88) | 91.67 | 0.77 (0.43 - 1.00) | 94.44 |
| 18 | Have you ever been diagnosed with a clinically significant inhibitor? | 0.78 (0.36 - 1.00) | 95.83 | 1.00 (1.00 - 1.00) | 100.00 |
| | If yes, do you currently have a clinically significant inhibitor? | 1.00 (1.00 - 1.00) | 100.00 | 1.00 (1.00 - 1.00) | 100.00 |
| 19 | How many bleeds did you have in the past 12 months?[#] | 0.90[#] (0.85 - 0.92) | 96.43 | 0.70[#] (0.61 - 0.88) | 91.11 |
| 20 | Within the past two weeks, have you had a bleed? | 1.00 (1.00 - 1.00) | 100.00 | 0.57 (0.15 - 0.99) | 80.00 |
| 21 | Where do you receive your regular treatment? [#] | 0.81[#] (0.00 - 1.00) | 96.97 | 0.78[#] (0.00 - 1.00) | 96.43 |
| 22 | What is your current treatment regimen? [#] | 0.96[#] (0.94 - 1.00) | 98.67 | 0.64[#] (0.00 - 0.65) | 95.56 |
| 23 | How do you currently treat? If you treat with a combination of regimens, please indicate all that apply.<br>- Typical dose of Factor VIII/IX concentrate used for prophylaxis | 1.00 (1.00 - 1.00) | 100.00 | 0.79 (0.62 - 1.00) | 83.33 |
| | - Typical prophylaxis frequency | 1.00[#] (1.00 - 1.00) | 100.00 | 0.74 [#] (0.65 - 0.76) | 89.74 |
| | - Typical dose of Factor VIII/IX concentrate used per infusion for on-demand treatment[#] | - [¥] | 93.33 | 1.00 (1.00 - 1.00) | 100.00 |
| 25 | Do you currently have any "target joints"? | 1.00 (1.00 - 1.00) | 100.00 | 0.82 (0.47 - 1.00) | 93.33 |
| 26 | Have you had 3 or more spontaneous bleeds (including those resulting from normal daily activity) into any one joint in the past 6 months? | 1.00 (1.00 - 1.00) | 100.00 | 1.00 (1.00 - 1.00) | 100.00 |
| 27 | Is the range of motion of any joint currently reduced because of your having hemophilia? | 1.00 (1.00 - 1.00) | 100.00 | 1.00 (1.00 - 1.00) | 100.00 |

| | | | | | |
|---|---|---|---|---|---|
| 28 | Other than joint bleeds, have you had any life- or limb-threatening bleeds in the past 12 months? | 0.50 (0.01 - 0.99) | 87.50 | -[¥] | 85.71 |

[#]Weighted kappa, *Kendall's coefficient, [€]Not applicable, [¥]Too few rating categories, [Ω]Interclass Correlation Coefficient (ICC)

**Abbreviations:** CI, confidence interval

**Table 3s.** Test-retest agreement for general health problems, stratified by participants

| Item | Question | Kappa or Weighted kappa (95%CI) | | Agreement (%) | |
|---|---|---|---|---|---|
| | | Patients with hemophilia (n=33) | Without bleeding disorder (n=30) | Patients with hemophilia (n=33) | Without bleeding disorder (n=30) |
| 8 | In the past 12 months, have you experienced any problems related to your health? (y/n) | 0.83 (0.52 - 1.00) | 0.82 (0.57 - 1.00) | 96.00 | 92.00 |
| 9 | Please indicate the frequency you used each of the following mobility aids or assistive devices in the past 12 Months. (Likert scale)[#] | 0.89 (0.85 - 0.93) | 0.75 (0.61 - 0.86) | 96.00 | 95.69 |
| 10 | During the past 12 months did you use any medication for pain? (y/n) | 1.00 (1.00-1.00) | 0.62 (0.29 - 0.96) | 100.00 | 86.21 |
| | If yes, please estimate the percent of the time you used pain medication. (Likert scale)[#] | 0.87 (0.85 - 0.88) | 0.73 (0.62 - 0.87) | 95.45 | 92.75 |
| 11 | During the past 12 months, have you experienced acute pain? (y/n) | 0.74 (0.48 - 1.00) | 0.65 (0.37 - 0.93) | 88.46 | 82.76 |
| 12 | During the past 12 months, have you experienced chronic pain? (y/n) | 1.00 (1.00-1.00) | 0.66 (0.37 - 0.92) | 100.00 | 86.21 |
| 13 | Do you currently have difficulty with any activities of daily living? (y/n) | 0.92 (0.77 - 1.00) | 0.87 (0.62 - 1.00) | 96.15 | 96.55 |
| 14 | Please select the best answer to describe your current work and/or school life? (Working full-time, working part-time, student full-time, student part-time, on long-term sick or disability leave, early retirement, other) | 0.94 (0.87- 1.00) | 0.76 (0.43 - 0.91) | 96.67 | 90.91 |
| | If you are working part-time (Estimate percent of full-time) | 0.98[Ω] (0.89 -0.99) | 0.80[Ω] (-0.58-0.99) | -[€] | -[€] |
| | How many days during the past 12 months were you not able to | 0.98[Ω] (0.89-1.00) | 0.80[Ω] (0.50 -0.93) | -[€] | -[€] |

| | | | | | |
|---|---|---|---|---|---|
| | work or attend school due to health related reasons? (y/n) | | | | |
| 15 | Have you ever gone through joint surgery or another invasive procedure? (y/n) | 0.82 (0.59 - 1.00) | 0.70 (0.43 - 0.97) | 92.31 | 85.71 |
| 16 | In the past 12 months have you had any of the following conditions or problems**?** | 0.86* | 0.72* | -€ | -€ |

#Weighted kappa, *Kendall's coefficient, €Not applicable, ΩInterclass Correlation Coefficient (ICC)

**Abbreviations:** CI, confidence interval

**Table 4s.** Test-retest reliability on EQ5D and VAS score, stratified by participants

| Item | Question | Weighted kappa (95%CI) | | Agreement (%) | |
|---|---|---|---|---|---|
| | | **Patients with hemophilia (n=31)** | **Without bleeding disorder (n=29)** | **Patients with hemophilia (n=31)** | **Without bleeding disorder (n=29)** |
| 29 | Mobility | 0.82 (0.61 - 0.91) | 0.63 (0.16 - 1.00) | 92.31 | 93.10 |
| | Self-care | 0.62 (0.60 - 0.70) | 1.00 (1.00-1.00) | 90.38 | 100.00 |
| | Usual activities | 0.66 (0.47 - 0.76) | 0.78 (0.37 - 1.00) | 88.46 | 96.55 |
| | Pain/discomfort | 0.73 (0.68 - 0.87) | 0.34 (0.10 - 0.39) | 92.31 | 82.76 |
| | Anxiety/depression | 1.00 (1.00-1.00) | 0.54 (0.27 - 1.00) | 100.00 | 91.38 |
| | Total EQ-5D score | 0.91 (0.81-0.96) | 0.53 (0.24-0.73) | -€ | -€ |
| | VAS score | 0.86 (0.71-0.93) | 0.91 (0.81-0.96) | -€ | -€ |

€Not applicable

# CHAPTER 4

# EXPLORING REGIONAL VARIATIONS IN THE CROSS-CULTURAL, INTERNATIONAL IMPLEMENTATION OF THE PATIENT REPORTED OUTCOMES BURDENS AND EXPERIENCE (PROBE) STUDY

Exploring regional variations in the cross-cultural, international implementation of the Patient Reported Outcomes Burdens and Experience (PROBE) study

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## ABSTRACT

**Background:** The Patient Reported Outcomes Burdens and Experience (PROBE) study has developed and validated the PROBE questionnaire for assessing patient reported outcomes in people living with hemophilia and participants without bleeding disorders. In this present study, we explored the regional variations in the international implementation of the PROBE questionnaire.

**Methods:** Data were collected from participants in four regions (Western Pacific, South America, North America and Europe). Participants were able to choose English or translated versions of the PROBE questionnaire into their first language. We used analysis of variance methods and multivariable regression to determine the relative contribution of the variance explained by region controlling for hemophilia diagnosis, age group and levels of educations. We also explored interactions between region and the other components.

**Results:** We used 862 questionnaires from 21 countries. Mean age of participants was 40.03 years (standard deviation 13.89) and 73.67% were male. After adjusting, region contributed 0.44% to 7.98% of the variance component in subitem scores and 0.26% in the PROBE score. Years of education contributed 0.34% in the PROBE score. Age and Hemophilia diagnosis contributed 3.42% and 22.42% of the PROBE score.

**Conclusions:** The results demonstrate that the PROBE questionnaire is valid to implement for assessing health status among patients with hemophilia and participants without bleeding disorders across regions.

## BACKGROUND

Hemophilia is a genetic bleeding disorder cause by defective or missing coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Consequently, patients with hemophilia exhibit bleeding symptoms corresponding to the severity of factor deficiency [1]. Hemophilia is classified into 3 categories according to residual coagulation factor activity: severe (<1 IU/ml), moderate (1-5 IU/ml) or mild (>5 to <40 IU/ml) [2]. Muscle and joint bleeding are clinical hallmarks of hemophilia [3]. Recurrent joint hemorrhage results in chronic joint destruction (hemophilia arthropathy). Patients with end-stage joint damage suffer from chronic pain, limitation of range of motion and disability [4].

Replacement therapy with coagulation factor concentrates is indicated when patients have acute bleeding episodes. Widespread availability of factor concentrates made it possible for patients to have prophylaxis at home. The aim of prophylaxis is to reduce spontaneous bleeding, especially hemarthrosis. Data from randomized controlled trials and observational studies demonstrates that prophylaxis reduces bleeding episodes, decreases joint damage and improves health-related quality of life [5-7]. This improvement in the quality of hemophilia management has resulted in an increased life expectancy in patients with hemophilia [8, 9].

Outcome measurement in hemophilia has been developed to capture clinically relevant outcomes like bleeding rates, pharmacokinetics, joint pain, joint function scores, radiologic changes, and mortality rates [10-13]. More recently, patient reported outcomes

(PROs) have gained prominent role in the assessment of interventions in routine clinical care, clinical trials, quality assessment and health care research [14-16]. The Patient Reported Outcomes Burdens and Experience (PROBE) study is a patient lead research initiative aiming to develop and collect PROs to improve hemophilia care. The initial phase of the PROBE study was questionnaire development and feasibility testing of the PROBE questionnaire adoption into a multinational network of participating non-government organizations [17]. Psychometric properties of the PROBE questionnaire were evaluated and shown to be valid for assessing PROs in both patients with hemophilia and participants without bleeding disorders [18, 19].

The PROBE project aims to collect PRO globally. The PROBE questionnaire was originally developed in English, but subsequently translated into 20 local versions using the forward - backward translation method. Translation and cultural adaptation was achieved according to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidance statement [20]. The translation process was conducted by the professional translation agency CETRA Language Solutions (Elkins Park, PA, U.S.), and checked by mother tongue patient representatives.

Besides language and cultural variability, hemophilia management varies around the world with regards to availability of factor concentrates, type of products, dose regimen, or availability of multidisciplinary comprehensive care [21, 22]. The wide variation of hemophilia care across countries may result in different patient outcomes and health-related quality of life. More importantly, the translated instruments must capture the complex ideas of the participants from various cultures and languages [23].

This study aims to investigate the variation of the PROBE questionnaire driven measurements across four broad geographical regions, representing a variety of cultural and economic settings. Our lead hypothesis is that the variability of the PROBE instrument's measurement contributed by geographical location or educational achievements of participants would be trivial.

## METHODS

### Population

This study recruited participants with and without hemophilia. Participants were invited to participate in the study by local patient organizations from 6 regions (Western pacific, North America, South America, Europe and Africa), involving 21 countries. Subjects were recruited between January 2016 and February 2017. We ended excluding cases from Africa due to a disproportionately low number of participants. Participants who were younger than 10 years, who were hemophilia carriers and who had other bleeding disorders were excluded from the analysis.

### Study procedure

Subjects were asked to complete the PROBE questionnaire. The questionnaire was available as both paper- and web-based versions. We did not collect subjects' identifiers (e.g. name, date of birth or health card number). Completed questionnaires were transferred from local hemophilia organizations to McMaster University for data extraction and analysis. The PROBE questionnaire comprises of 4 parts and 29 questions. Part I is the participants' demographic data, including age, sex, hemophilia diagnosis, year of education and country of residence. Part II (the PROBE PRO core) comprises of a patient-reported-outcome items, including problems related to health, frequency of using mobility devices, frequency of using pain medication, presence of acute and chronic pain, difficulties with activities of daily living, absence from work or school, past joint-related surgical procedures and co-existing medical conditions. Part III comprises of hemophilia-

related questions, including severity of hemophilia, inhibitor status, frequency of joint bleeding, presence of target joint(s), presence of limitation of range of motion of any joint and other bleeding. Only subjects with hemophilia were asked to complete part III. Part IV comprises of questions regarding to health-related quality of life.

**Health measures and PROBE score**

Health measures were evaluated from Part II of the questionnaire, the PROBE PRO core. The answer from each item was converted to a return-to-scale score, ranging from 0 to 1 (0 indicated normal health status and 1 indicated worst possible health status). All item scores were combined into a single value using the additive value function with each item score weighted equally. Finally, we subtracted combined item scores from 1 in order to obtain the PROBE score for each subject (0 to 1, with 0 worst and 1 best possible score).

**Statistical analyses**

Demographic data of participants were summarized using descriptive statistics. Continuous variables were presented as mean with standard deviation (SD). Categorical variables were described as frequencies and percentages. All data were classified by the region where the questionnaire was completed.

We quantified the variability of each health measure and the overall PROBE score using analysis of co-variance (ANCOVA). We investigated the magnitude of variation explained by region (West Pacific, North America, South America and Europe), hemophilia diagnosis (hemophilia or no bleeding disorders), age group (<25 years, 25-45

years or >45 years), years of education (≤12 years or >12 years) and individuals. The variability between individuals represented the residual variability not attributed to hemophilia diagnosis, age, education or region but other factors (e.g. level of residual factor VIII activity, hemophilia treatment, number of bleeds). The magnitude of variation was presented as percentage of total variation.

We carried out ordinary least square (OLS) regression analysis. We calculated the coefficients using multivariable regression model. We examined the effects of hemophilia diagnosis, age group, regions and years of education. We repeated the analysis adding the interactions in the multivariable model. We examined the goodness-of-fit of the final regression model. Normality of residuals was evaluated using graphical approach. We examine the Homoscedasticity of residuals was examined using the Whites' test and the Breusch-Pagan test [24]. P-value less than 0.05 were considered to indicate statistical significance.

## RESULTS

Demographics. We analyzed data on a total of 862 participants; 195 (22.6%) from the Western Pacific region, 324 (37.6%) from South America, 136 (15.8%) from North America and 207 (24.0%) from Europe). Table 1 demonstrates characteristics of participants by the regions. Mean age (SD) of participants was 46.77 (15.25) years for North America, 44.29 (11.61) years for Europe, 39.77 (15.54) years for Western Pacific and 34.41 (10.99) years for South America. Male were predominant in all regions, ranging from 58.82% to 85.99%. The proportion of patients with hemophilia ranged from 40.44% to 83.57%. The majority of participants had more than 12 years of education in all regions (ranging from 68.21% to 86.76%).

### PROBE's items and score raw measures across the four regions

Table 2 shows the central tendency and variability of each of the PROBE outcome measures in the four regions. There is variability among the regions both for individual items and for the PROBE score. The mean (SD) PROBE score was highest in South America, 0.80 (0.15), followed by Western Pacific 0.77 (0.16), North America 0.77 (0.15) Europe 0.69 (0.17).

### Sources of variation of the PROBE items and PROBE score.

Table 3 demonstrates variance partitioning, according to diagnosis, age, region, education and residual variability (individual). Hemophilia diagnosis contributed the highest variance component among the PROBE items (ranging from 3.78 to 12.75%) and the PROBE score (22.42%). Age of participants contributed 0.70% to 4.97% of the

variance component in PROBE items and 3.42% in the PROBE score. Region contributed 0.44% to 7.98% of the variance component in item score and 0.26% in the PROBE score. Years of education of participants contributed 0.02% to 2.08% of the variance component in item score and 0.34% in the PROBE score.

Multivariable regression analysis revealed that hemophilia diagnosis and age of participants significantly affected the PROBE score (Table 4), but not so instead regions and years of education. Diagnosis and region had a significant interaction (p 0.04); the association of hemophilia and age of participants minimally changed after adding the interaction terms in the regression model (Table 4), Figure 1. Figure 2 demonstrates the PROBE score, by region, stratified for 3 age groups. There was no significant interaction between region and age groups.

When including hemophilia diagnosis and age of participants in the ordinary least square regression model, the standardized normal probability plot showed trivial deviation from normality, indicating that the residuals were close to a normal distribution. With regards to homoscedasticity testing of the residual, the Whites' test and the Breusch-Pagan test had p-value less than 0.001, indicating that the variance of residuals was not homogenous.

## DISCUSSION

The PROBE project aims at collecting PRO in persons with and without hemophilia across different geographical and socio-economic settings to generate an evidentiary knowledge base allowing to explore the impact of treatment availability, models of care and societal support and ultimately improve hemophilia care globally. To this scope the PROBE study group has developed a multilingual instrument. The study here reported demonstrates the cross-cultural validity of the PROBE questionnaire. In essence, the PROBE score variability does reflects the individual group (hemophilia versus control) and all the disease-related characteristics assessed by the questionnaire, but is not affected by geographical location, age and education level. This indicated that the PROBE questionnaire has the potential to be a valid instrument to be adopted in multicentric international efforts to characterize the impact of hemophilia care.

The majority of tools assessing PROs and health-related quality of life were developed in the English language and were intended for use in English speaking countries [25, 26]. Both improved health care in developing nations, and increasing population diversity have led to a need for multinational, cross-cultural research tools that are validated in diverse populations [27]. With this respect, the diversity of cultures of the target population must be taken into account beyond the translation process and before implementing questionnaires in a multicultural setting, and at a multinational level.

A few examples of cross-language and cross-cultural validation has been published. Dib et al developed a Turkish language version of assessment tools for patients

with multiple sclerosis [28]. The investigators compared the results when using the Turkish version with those obtained using the United Kingdom version. This study found that linguistic equivalence did not guarantee measurement equivalence. According to a systematic review by Maneesriwongul et al, validation techniques for translation varied among studies [29]. It has been suggested that the psychometric properties of the translated version should be assessed in comparison with the original one [30].

A recent Systematic review by Limperg et al appraised the measurement properties of the questionnaire assessing patient reported outcomes in patients with hemophilia [31]. This review included 22 articles involving 8 questionnaires. All of the questionnaires were developed to assess health related quality of life. Seven of eight questionnaires were translated into 3-161 languages. However, only 1 questionnaire was validated for cross-cultural validity in four countries (Germany, Spain, Canada and United States of America) [32]. Authors concluded that additional research is needed in order to improve the measurement properties of the questionnaires.

In this study, we evaluated the PRO measures in four regions using English and translated versions of the PROBE questionnaire, whatever the patient felt more appropriate. All versions were considered linguistically equivalent. There are variations of the mean PROBE score among the regions. The sources of variation are mostly explained by the diagnosis of hemophilia and residual variability (e.g. individual characteristics, including treatment regimen, product or residual factor activity). We observed some inconsistencies of the variance component among the sub-items. More specifically, items asking about mobility, the use of pain medications, absences from

work or school, having joint surgery and co-morbid disease had a relatively low variance component attributed from hemophilia diagnosis, as compared to items asking about acute or chronic pain and activities of daily living.

There is trivial variation attributed to region and years of education across all subitems, except for the mobility score. The findings remain the same when we carried out multivariable regression analysis with or without interaction terms. These findings indicate that the PROBE questionnaire has low variability when implemented across cultural and language barriers.

The ultimate goal of the PROBE study is to compare population-level PROBE scores in different countries or regions. More specifically, we would like to determine differences in health scores measured by PROBE in countries that have various policies with regards to coagulation factor reimbursement programs, product availability, access to specialized hemophilia treatment centers or access to home treatment programs for prophylaxis. We also expect to observe changes in the PROBE score over time at a country level, if a country adopts a new treatment program or changes health policy. The implication of this study is that in order to compare the crude PROBE score from different countries or regions, the proportion of patients with certain underlying characteristics needs to be comparable, for example, age group and severity of hemophilia.

## CONCLUSIONS

This cross-cultural, multi-language study, conducted in four regions and 21 countries as part of the PROBE study and found that geographic regions and levels of education of participants provide only a minor contribution to the variability of the outcome measures when using the PROBE questionnaire. Despite being used in disparate groups of patients, in 21 countries, four regions, and in 20 languages, the tool produced comparable results, suggesting it can be reliably used across these groups. The results demonstrate that the PROBE questionnaire is valid to implement for assessing health status among patients with hemophilia and participants without bleeding disorders across regions.

## REFERENCES


1. Franchini M, Mannucci PM: **Hemophilia A in the third millennium**. *Blood Rev* 2013, **27**(4):179-184.
2. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC *et al*: **Guidelines for the management of hemophilia**. *Haemophilia* 2013, **19**(1):e1-47.
3. Berntorp E, Shapiro AD: **Modern haemophilia care**. *Lancet* 2012, **379**(9824):1447-1456.
4. Roosendaal G, Lafeber FP: **Pathogenesis of haemophilic arthropathy**. *Haemophilia* 2006, **12 Suppl 3**:117-121.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, Ingram JD, Manco-Johnson ML, Funk S, Jacobson L *et al*: **Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia**. *N Engl J Med* 2007, **357**(6):535-544.
6. Gringeri A, Lundin B, von Mackensen S, Mantovani L, Mannucci PM, Group ES: **A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT Study)**. *J Thromb Haemost* 2011, **9**(4):700-710.
7. Iorio A, Marchesini E, Marcucci M, Stobart K, Chan AK: **Clotting factor concentrates given to prevent bleeding and bleeding-related complications in people with hemophilia A or B**. *Cochrane Database Syst Rev* 2011(9):CD003429.

8. Tagliaferri A, Rivolta GF, Iorio A, Oliovecchio E, Mancuso ME, Morfini M, Rocino A, Mazzucconi MG, Franchini M, Italian Association of Hemophilia C *et al*: **Mortality and causes of death in Italian persons with haemophilia, 1990-2007**. *Haemophilia* 2010, **16**(3):437-446.

9. Plug I, Van Der Bom JG, Peters M, Mauser-Bunschoten EP, De Goede-Bolder A, Heijnen L, Smit C, Willemse J, Rosendaal FR: **Mortality and causes of death in patients with hemophilia, 1992-2001: a prospective cohort study**. *J Thromb Haemost* 2006, **4**(3):510-516.

10. Chai-Adisaksopha C, Hillis C, Thabane L, Iorio A: **A systematic review of definitions and reporting of bleeding outcome measures in haemophilia**. *Haemophilia* 2015, **21**(6):731-735.

11. Fischer K, de Kleijn P: **Using the Haemophilia Joint Health Score for assessment of teenagers and young adults: exploring reliability and validity**. *Haemophilia* 2013, **19**(6):944-950.

12. Feldman BM, Funk SM, Bergstrom BM, Zourikian N, Hilliard P, van der Net J, Engelbert R, Petrini P, van den Berg HM, Manco-Johnson MJ *et al*: **Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score**. *Arthritis Care Res (Hoboken)* 2011, **63**(2):223-230.

13. Pettersson H, Ahlberg A, Nilsson IM: **A radiologic classification of hemophilic arthropathy**. *Clin Orthop Relat Res* 1980(149):153-159.

14. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S: **Patient reported outcome measures in practice**. *BMJ* 2015, **350**:g7818.

15. Rotenstein LS, Huckman RS, Wagle NW: **Making Patients and Doctors Happier - The Potential of Patient-Reported Outcomes**. *N Engl J Med* 2017, **377**(14):1309-1312.

16. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM *et al*: **Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial**. *J Clin Oncol* 2016, **34**(6):557-565.

17. Skinner MW, Driessens M, Curtis R, Frick N, Iorio A, Nichol M, Noone D, O'Mahony B, Page D, Stonebraker J: **The Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Phase 1 Methodology and Feasibility**. *Haemophilia* 2016, **22 (Suppl. 4)**:118.

18. Chai-Adisaksopha C, Iorio A, Curtis R, Frick N, Nichol M, Noone D, O'Mahony B, Page D, Stonebrake J, Skinner MW: **Test-Retest Reliability Analysis of The Patient Reported Outcomes Burdens and Experiences (PROBE) Study**. *Haemophilia* 2017, **23 (Suppl.2)**:29-140. [abstract P037].

19. Chai-Adisaksopha C, Iorio A, Curtis R, Frick N, Nichol M, Noone D, O'Mahony B, Page D, Stonebrake J, Skinner MW: **Psychometric properties of the Patient Reported Outcomes Burdens and Experiences (PROBE) Questionnaire**. *Blood* 2017, **[abstract]**.

20. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P, Translation ITFf, Cultural A: **Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation**. *Value Health* 2005, **8**(2):94-104.

21. Srivastava A, You SK, Ayob Y, Chuansumrit A, de Bosch N, Perez Bianco R, Ala F: **Hemophilia treatment in developing countries: products and protocols**. *Semin Thromb Hemost* 2005, **31**(5):495-500.

22. De Kleijn P, Odent T, Berntorp E, Hilliard P, Pasta G, Srivastava A, Iliescu A, Mohanty S: **Differences between developed and developing countries in paediatric care in haemophilia**. *Haemophilia* 2012, **18 Suppl 4**:94-100.

23. von Mackensen S, Campos IG, Acquadro C, Strandberg-Larsen M: **Cross-cultural adaptation and linguistic validation of age-group-specific haemophilia patient-reported outcome (PRO) instruments for patients and parents**. *Haemophilia* 2013, **19**(2):e73-83.

24. Hayes AF, Cai L: **Using heteroskedasticity-consistent standard error estimators in OLS regression: an introduction and software implementation**. *Behav Res Methods* 2007, **39**(4):709-722.

25. Guillemin F, Bombardier C, Beaton D: **Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines**. *J Clin Epidemiol* 1993, **46**(12):1417-1432.

26. Weldring T, Smith SM: **Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs)**. *Health Serv Insights* 2013, **6**:61-68.

27. Beaton DE, Bombardier C, Guillemin F, Ferraz MB: **Guidelines for the process of cross-cultural adaptation of self-report measures**. *Spine (Phila Pa 1976)* 2000, **25**(24):3186-3191.

28. Dib H, Tamam Y, Terzi M, Hobart J: **Testing patient-reported outcome measurement equivalence in multinational clinical trials: An exemplar using the 12-item Multiple Sclerosis Walking Scale**. *Mult Scler J Exp Transl Clin* 2017, **3**(3):2055217317728740.

29. Maneesriwongul W, Dixon JK: **Instrument translation process: a methods review**. *J Adv Nurs* 2004, **48**(2):175-186.

30. Sperber AD: **Translation and validation of study instruments for cross-cultural research**. *Gastroenterology* 2004, **126**(1 Suppl 1):S124-128.

31. Limperg PF, Terwee CB, Young NL, Price VE, Gouw SC, Peters M, Grootenhuis MA, Blanchette V, Haverman L: **Health-related quality of life questionnaires in individuals with haemophilia: a systematic review of their measurement properties**. *Haemophilia* 2017, **23**(4):497-510.

32. Rentz A, Flood E, Altisent C, Bullinger M, Klamroth R, Garrido RP, Scharrer I, Schramm W, Gorina E, Members of the H-Q-ASC: **Cross-cultural development and psychometric evaluation of a patient-reported health-related quality of life questionnaire for adults with haemophilia**. *Haemophilia* 2008, **14**(5):1023-1034.

## FIGURE LEGENDS AND TABLES

Figure 1 PROBE score in participants with or without hemophilia, classified by regions

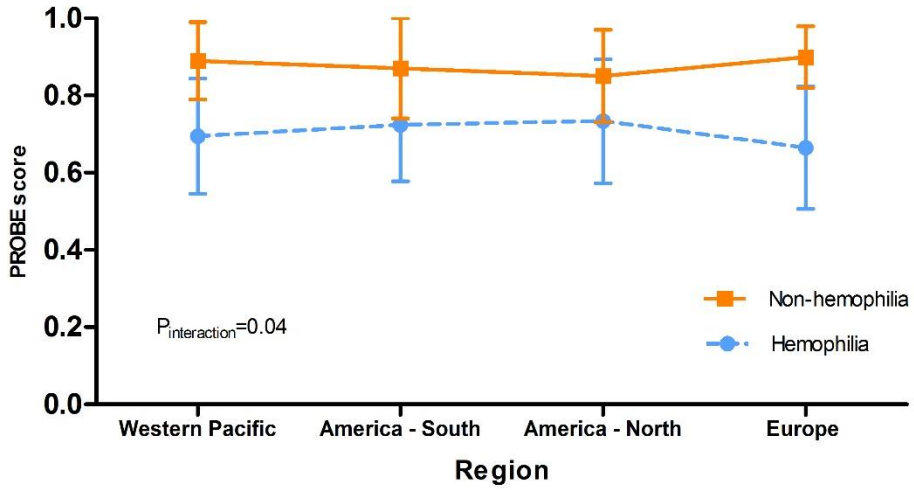

Figure 2 PROBE score in participants with different age groups, classified by regions

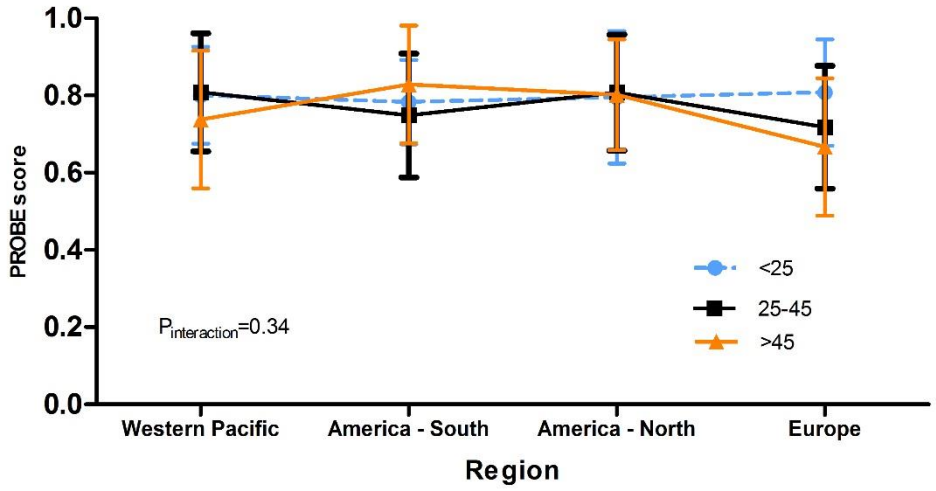

Table 1. Characteristics of participants, classified by the region

| **Characteristics** | **Western Pacific (n=195)** | **South America (n=324)** | **North America (n=136)** | **Europe (n=207)** |
|---|---|---|---|---|
| Age, years mean (SD) | 39.77 (15.54) | 34.41 (10.99) | 46.77 (15.25) | 44.29 (11.61) |
| Age group | | | | |
| - <25 years | 44 (22.56) | 47 (14.51) | 9 (6.62) | 6 (2.90) |
| - 25-45 years | 69 (35.38) | 192 (59.26) | 48 (35.29) | 96 (46.38) |
| - >45 years | 82 (42.05) | 85 (26.23) | 79 (58.09) | 105 (50.72) |
| Male, n (%) | 166 (85.13) | 211 (65.12) | 80 (58.82) | 178 (85.99) |
| Hemophilia diagnosis, n (%) | | | | |
| - No bleeding disorders | 64 (32.82) | 121 (37.35) | 81 (59.56) | 34 (16.43) |
| - Hemophilia | 131 (67.18) | 203 (62.65) | 55 (40.44) | 173 (83.57) |
| Years of education, n (%) | | | | |
| ≤12 years | 62 (31.79) | 82 (25.31) | 18 (13.24) | 50 (24.15) |
| >12 years | 133 (68.21) | 242 (74.69) | 118 (86.76) | 157 (74.69) |

**Abbreviation**: SD; standard deviation

Table 2. Item scores and PROBE score in participants from four regions

| Item | **Western Pacific (n=195)** | **South America (n=324)** | **North America (n=136)** | **Europe (n=207)** |
|---|---|---|---|---|
| Mobility score | 0.15 (0.09) | 0.09 (0.09) | 0.06 (0.07) | 0.13 (0.11) |
| Pain Medication score | 0.29 (0.25) | 0.38 (0.26) | 0.30 (0.29) | 0.38 (0.29) |
| Acute pain occurrence score | 0.23 (0.24) | 0.21 (0.24) | 0.19 (0.23) | 0.24 (0.27) |
| Acute pain interference score | 0.31 (0.29) | 0.26 (0.29) | 0.22 (0.26) | 0.31 (0.32) |
| Chronic pain occurrence score | 0.24 (0.26) | 0.26 (0.29) | 0.26 (0.30) | 0.38 (0.30) |
| Chronic pain interference score | 0.25 (0.28) | 0.27 (0.31) | 0.22 (0.27) | 0.41 (0.30) |
| ADSL score | 0.18 (0.24) | 0.13 (0.19) | 0.10 (0.19) | 0.25 (0.26) |
| Absence from work/school score | 0.10 (0.24) | 0.08 (0.18) | 0.03 (0.13) | 0.13 (0.26) |
| Joint surgery score | 0.11 (0.21) | 0.12 (0.19) | 0.15 (0.24) | 0.26 (0.28) |
| Co-morbid disease score | 0.05 (0.06) | 0.04 (0.08) | 0.05 (0.07) | 0.07 (0.09) |
| **PROBE score** | 0.77 (0.16) | 0.77 (0.15) | 0.80 (0.16) | 0.70 (0.17) |

Table 3. Variance component of health measures and PROBE score

| **Item** | **Variance component (%)** | | | | |
|---|---|---|---|---|---|
| | **Region** | **Diagnosis** | **Age** | **Education** | **Individual** |
| Mobility score | 7.98 | 4.07 | 0.70 | 0.02 | 84.45 |
| Pain Medication score | 1.42 | 5.81 | 2.44 | 1.64 | 88.97 |
| Acute pain occurrence score | 0.44 | 12.06 | 0.98 | 0.14 | 86.96 |
| Acute pain interference score | 0.55 | 11.74 | 0.76 | 0.07 | 86.62 |
| Chronic pain occurrence score | 0.89 | 10.62 | 2.30 | 0.04 | 85.41 |
| Chronic pain interference score | 0.99 | 12.03 | 1.65 | 0.09 | 82.78 |
| ADSL score | 0.87 | 12.75 | 4.97 | 1.02 | 77.88 |
| Absence from work/school score | 0.64 | 4.12 | 0.76 | 2.71 | 89.72 |
| Joint surgery score | 2.08 | 5.60 | 4.88 | 2.08 | 84.99 |
| Co-morbid disease score | 0.85 | 3.78 | 2.42 | 0.83 | 91.24 |
| **PROBE score** | 0.26 | 22.42 | 3.42 | 0.34 | 70.74 |

Table 4. Multivariable regression analysis

| Variable | Multivariable regression model | | Multivariable regression model with interactions | |
|---|---|---|---|---|
| | Coefficient (95% CI) | P-value | Coefficient (95% CI) | P-value |
| **Diagnosis** | | | | |
| No bleeding | 1 | | 1 | |
| Hemophilia | -0.18 (-0.20 to -0.15) | <0.001 | -0.26 (-0.34 to -0.18) | <0.001 |
| **Age** | | | | |
| <25 | 1 | | 1 | |
| 25-45 | -0.07(-0.11 to -0.04) | <0.001 | -0.1 (-0.16 to -0.04) | 0.001 |
| >45 | -0.10 (-0.14 to -0.07) | <0.001 | -0.16 (-0.27 to -0.05) | 0.005 |
| **Region** | | | | |
| Western Pacific | 1 | | 1 | |
| South America | 0.01 (-0.02 to 0.03) | 0.686 | -0.03 (-0.08 to 0.03) | 0.332 |
| North America | 0.0 (-0.03 to 0.04) | 0.842 | 0.09 (-0.22 to 0.05) | 0.202 |
| Europe | -0.02 (-0.05 to 0.01) | 0.321 | -0.09 (-0.18 to 0.01) | 0.080 |
| **Education** | | | | |
| ≤12 years | 1 | | 1 | |
| >12 years | 0.02 (-0.00 to 0.05) | 0.078 | 0.02 (-0.00 to 0.05) | 0.083 |
| Region*Diagnosis | N/A | N/A | 0.02 (0.00 to 0.04) | 0.040 |
| Region*Age | N/A | N/A | 0.01 (-0.01 to 0.02) | 0.335 |

Abbreviations: Diagnosis: hemophilia diagnosis (hemophilia or no bleeding disorders), age: age group; <25 years, 25-45 years or >45 years), region: Western Pacific, North America, South America or Europe, Education: years of education (≤12 years or >12 years)

# CHAPTER 5

# EVALUATION OF THE SEXUAL HEALTH

# IN PATIENTS LIVING WITH HEMOPHILIA

Evaluation of the sexual health in patients living with hemophilia

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**Running title:** Sexual difficulty in patients living with hemophilia

**Keywords:** hemophilia, patient reported outcome, sexual health

**Word count:** Abstract 252, Text 3524

**Table and Figure:** 5 tables, 1 figure

## ABSTRACT

**Background:** The impact of hemophilia on psychological and social aspects of life has been investigated and demonstrated. Knowledge about sexual difficulty in patients with hemophilia is little understood.

**Objectives:** The primary objective was to determine the prevalence of sexual difficulty in patients living with hemophilia. The secondary objectives include comparing the prevalence of sexual difficulty among patients living with hemophilia with that of patients without hemophilia; and to determine factors associated with having sexual difficulty among patients with hemophilia.

**Methods:** This was a cross-sectional analysis of the PROBE study. We recruited patients who had hemophilia A or B (PWH) and participants without a bleeding disorder who were 18 years old or older. Participants were recruited through the non-government organization from 21 countries. All participants were asked to complete the PROBE questionnaire which consisted of items asking about general health problems, co-morbid diseases and sexual difficulty. Only PWH were asked to complete items related to hemophilia health problems. Proportion of participants who have sexual difficulties was calculated. Odds ratios (OR) with 95% confidence interval (CI) was calculated.

**Results:** A total of 1485 participants (964 PWH and 521 participants without bleeding disorders) were included in the analysis. Mean age (SD) was 39.5 (15.2) in PWH and 45.0 (13.6) in healthy controls. The majority of PWH were male (93.2%), whereas majority of participants without bleeding disorders were female (male 13.6%). Difficulty

with sexual intimacy was reported in 131 participants (13.6%, 95%CI 11.5%-15.9%) with hemophilia and 19 healthy control participants (3.6%, 95%CI 2.2%-5.6%). Age adjusted odds ratio for sexual difficulty was significantly higher in PWH as compared to controls (4.7, 95% confidence interval 2.8-7.7). Among PWH, older age, experiencing acute or chronic pain in the past 12 months, experiencing bleeds within the past two weeks, having limitation of range of motion of any joints and having any life- or limb-threatening bleeds in the past 12 months were associated with sexual difficulty.

**Conclusions:** Sexual difficulty is more prevalent in patients with hemophilia and associated with markers of disease severity. Sexual health issues should be incorporated in comprehensive hemophilia care, future research and hemophilia related health policy.

## BACKGROUND

Sexuality is a crucial component of human beings. Healthy sex fulfils personal identity, self-worth and relationships. Sexual activity is a complex process involving physical, psychological, emotional and hormonal status [1, 2]. Functionality and satisfaction of sexuality can be altered by aging [3-5], relationship with partner [6], sexual difficulties (e.g. vaginal dryness, erectile dysfunction, physical pain during sexual intercourse) [7] or physical illness [8].

Patients with a chronic disease often have difficulties with sexual functioning [5, 9]. In a cross-sectional study of elderly people, chronic diseases were associated with reduced odds of sexual activity [10]. Individuals who had a poor health status had reported more sexual problems and they were less likely to be sexually active [4, 11]. In addition, people with poorer health were associated with less interest in sex as compared to those who were healthy [11]. Chronic pain has a negative impact on physical and emotional functioning. The study in patients living with chronic pain demonstrated that a majority of patients (73%) had pain-related difficulty with sexual activity [12]. Sexual functioning is also affected by the consequences of pain management [8].

Improvement in the treatment for patients with hemophilia (PWH) has resulted in significantly increased life expectancy [13]. There are growing numbers of PWH who have chronic conditions due to bleeding related long-term complications (e.g. hemophilia arthropathy) and aging-associated diseases or cancer [14-16]. Substantial numbers of PWH who received blood products before the development of viral inactivation

procedures are affected by transfusion transmitted diseases, more specifically, human immunodeficiency virus (HIV) and hepatitis C virus infections [17, 18]. Sexuality in PWH may be affected by physical problems (e.g. hemophilic arthropathy, hemarthrosis, iliopsoas bleeding, HIV or HCV infection), treatments or medications [8, 19]. Lastly, PWH may have psychosocial problems, for instance, less interest in sexual activity, depression, impaired relationship with healthy partner or disparity of sexual functioning with partner [1, 20, 21].

Understanding of the burden of sexual difficulty in PWH is extremely limited. Tobase et al [22] conducted a pilot survey study in 20 respondents (65% having hemophilia), examining sexual health by using a 54-item patient reported questionnaire [22]. Forty percent (8 out of 20) of respondents believed that their bleeding disorder had a negative impact on their sexual life.

Having knowledge about sexuality in PWH is important in order to inform clinicians, other healthcare providers and stakeholders involved with policy development and comprehensive hemophilia care. The ultimate goal is to improve sexual health and well-being in PWH. The objective of the present study was to determine the prevalence of sexual difficulty in patients living with hemophilia. The secondary objectives include comparing the prevalence of sexual difficulty among patients living with hemophilia with that of patients without hemophilia; and to determine factors associated with having sexual difficulty among patients with hemophilia.

## METHODS

The PROBE initiative comprises a data collection network and a questionnaire aiming to explore the impact of hemophilia on patient reported outcomes [23]. The PROBE is a questionnaire requiring 7-15 minutes for compilation and is intended for anonymous filling by patients recruited by National Member Organizations of the World Federation of Hemophilia (NMOs) and matched control groups in 21 countries. The PROBE questionnaire is available in paper-based and web-based versions. Both versions were validated in a test-retest reliability study [24]. The PROBE survey includes specific questions on sexual intimacy.

The current study reports a retrospective analysis of PROBE data collected for the main PROBE initiative purposes. The main objective is to compare the frequency of sexual difficulty in PWH and control groups. The secondary objective is to compare, within PWH, the characteristics of those with and without sexual difficulty. Additional details on the project are provided in the subsequent sections.

### Participant recruitment

We enrolled participants through NGOs working in hemophilia and bleeding disorders from 21 countries between January 2016 to February 2017. We recruited PWH (hemophilia A or hemophilia B) and participants without bleeding disorders of any age who did not require special assistance to complete the questionnaire. However, for the analysis, we decided to exclude participants who were younger than 18 years old during

the study period, who were carriers of hemophilia, who had other bleeding disorders or who had missing data on the hemophilia diagnosis.

**Measures**

The questionnaire included the following items:

**Demographic data**

Participants were asked to complete the items related to demographic data, including current country of residence, language, sex, hemophilia diagnosis, year of birth, marital status or long-term relationship and parenthood status.

**General health problems**

General health problems were defined as problems that were unrelated to hemophilia. Both PWH and participants without bleeding disorders were asked to complete general health problem questions. The items comprised of questions as follows; health problems in the past 12 months, using mobility aids or assistive devices, using pain medication in the past 12 months, when acute pain occurred, what acute pain interfered with, when chronic pain occurred, what chronic pain interfered with, and having joint surgery or invasive procedures. Acute pain was defined as pain that arose in response to an event, for instance, an injury or bleeding disorder. Chronic pain was defined as pain from a persistent cause, for instance, back pain or pain from hemophilic arthropathy.

### Co-morbid diseases

All participants were asked to complete items related to co-morbid diseases. The questions asked about the following conditions: hepatitis B, hepatitis C, HIV/acquired immune deficiency syndrome (AIDS), stroke, high blood pressure, diabetes, arthritis, gingivitis and others.

### Hemophilia-related health problems

Only PWH were asked to complete items regarding hemophilia-related health problems. The questions asked about the following items: severity of hemophilia, presence of any clinically significant inhibitor over patient's life, current clinically significant inhibitor, number of joint bleeds in the past 12 months, bleeding in the past two weeks, having any target joint, having 3 or more spontaneous bleeds into any joint in the past 6 months, having limitation of range of motion of any joint, and having any life- or limb-threatening bleeding in the past 12 months.

### Data collection and statistical analysis

Paper-based questionnaires were shipped to the data coordinators and were stored centrally at McMaster University. Both paper-based and web-based questionnaires were extracted and stored in the PROBE electronic database.

Baseline demographic data (sex, age, marital status, parenthood status, hemophilia diagnosis, severity of hemophilia and history of clinically significant inhibitor) were described using descriptive statistics. The primary outcome of this analysis is the

frequency of sexual difficulty among PWH and participants without bleeding disorders. We calculated multivariable odds ratio (OR) with 95% confidence interval (CI) comparing the association between sexual difficulties among PWH and the control group.

We explored the relationship between general health problems, co-morbid diseases and sexual health in PWH and participants without bleeding disorders. The prevalence and proportion of sexual difficulty were reported for each item. We used a univariate, stratified logistic regression model to estimate the association between health problems and sexual difficulty. In order to examine how health problems have an impact on PWH and control group, the P-value for interaction was calculated.

As a secondary objective, we examined, only in PWH, the relationship between hemophilia-related problems and sexual health. We carried out univariate and multivariable logistic regression models to estimate the effect of each variable on sexual difficulty. The effect estimates were reported as ORs with 95% CI. The Wald's test for each variable was carried out. Variable selection was based on biological plausibility. We excluded variables that were likely to be collinear with other items (e.g. use of pain medication and acute or chronic pain). Multicollinearity among selected variables was assessed using variance inflation factor and tolerance. The Hosmer-Lemeshow test was used to evaluate goodness-of-fit of the multivariable logistic regression model. P-values less than 0.05 were considered statistically significant for all analyses. Analyses were performed using STATA software version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.).

# RESULTS

## Participant characteristics

There were 2041 participants from 21 countries that completed survey questionnaires in the main PROBE initiative. We excluded a total of 556 participants. The reasons for exclusion are demonstrated in Figure 1. Overall, there were 1485 participants included in the analysis. Table 1 shows the demographic data of participants. Of 1485 participants, 964 were PWH (83.9% hemophilia A and 16.1% hemophilia B). In addition, 521 were participants who did not have hemophilia nor any other bleeding disorder and were not hemophilia carriers. Participants with hemophilia were younger (mean 39.5 (SD 15.2) years) as compared to participants without bleeding disorders (mean 45.0 (SD 13.6) years). The majority of PWH were male (93.2%), whereas the majority of participants without bleeding disorders were female (male 13.6%). Sixty-one percent of PWH and 80.8% of participants without bleeding disorders were married or in a long-term relationship. Having children was reported in 45.4% of PWH and 71.4% of participants without bleeding disorders. A majority of PWH identified themselves as having severe disease (57.8%), following by moderate (15.3%) and mild (12.6%) disease. Twelve per cent of PWH reported that they had ever been diagnosed with a clinically significant inhibitor. Only 4.0% of participants reported that they currently had a clinically significant inhibitor.

**Prevalence of difficulty with sexuality**

Difficulty with sexual intimacy was reported in 131 PWH (13.59%) and 19 participants without bleeding disorders (3.65%). Using multivariable logistic regression model, sexual difficulty was significantly more common among PWH as compared to controls with an OR of 4.66 (95% CI 2.82-7.70). There was no significant difference in sexual difficulty across various regions (data not shown).

**Impact of general health problem on sexual health**

Table 2 displays the association between general health problems and sexual health, comparing between PWH and participants without bleeding disorders. In PWH, sexual difficulty was significantly more frequent among participants who reported any health problems in the past 12 months (OR, 4.94, 95% CI 2.53- 10.77), who used mobility aids or assistive devices (OR 2.69, 95% CI 1.69- 4.41), who used pain medication in the past 12 months (OR 3.55, 95% CI 1.62- 9.22), who had had acute pain in the past 12 months (OR 4.08, 95% CI 2.23-8.04) or who had had chronic pain in the past 12 months (OR 5.28, 95% CI 2.71-11.49). The odds of sexual difficulty increased in correlation with higher percent of time participants used pain medication (data not shown). PWH who reported acute or chronic pain interfering with their relationship had worse sexual health as compared to those who did not report pain (OR 3.82, 95% CI 2.13-7.38 for acute pain and OR 5.44, 95% CI 2.86-11.39 for chronic pain). We did not observe a statistical difference in sexual health among patients who reported a history of

joint surgery or invasive procedures compared with those who did not report any surgery (OR 1.21, 95% CI 0.82-1.81).

In the control populations, the percent of participants who had sexual difficulty was lower than PWH in all items. We observed similar associations between general health problems and sexual health in most items. However, participants who had acute pain in the past 12 months or who had acute pain that interfered with relationships were not associated with more frequent sexual difficulty (OR 2.64, 95% CI 0.94-7.72 and (OR 2.64, 95% CI 0.94-7.72, respectively). The interaction between PWH and the control group was not statistically significant in all items.

**Impact of co-morbid diseases on sexual health**

Table 3 displays the association between co-morbid diseases and sexual health in PWH and the control populations. The odds of having sexual difficulty were significantly higher among PWH who had hepatitis B (OR 2.74, 95% CI 1.22-5.79), hepatitis C (OR 2.06, 95% 1.35-3.12), hypertension (OR 2.62, 95% CI 1.50-4.53), arthritis (OR 2.69, 95% CI 1.56-4.69) and gingivitis (OR 2.44, 95% CI 1.42-4.18).

In the control populations, there was no significantly increased odds of sexual difficulty in participants who reported stroke (OR 4.54, 95% CI 0.08-59.70), hypertension (OR 1.51, 95% CI 0.34-5.23), diabetes (OR 2.53 0, 95% CI 0.25-13.26) and gingivitis (OR 1.04, 95% CI 0.11-4.93). Only participants who reported arthritis had significantly higher odds of sexual difficulty (OR 5.31, 95% CI 1.42-17.87).

**Impact of hemophilia-related problem on sexual health**

Table 4 displays the impact of hemophilia-related problems on sexual health. The odds of sexual difficulty were significantly higher among PWH who had severe disease (OR, 2.64 95% CI 1.31-5.31) as compared to those with mild disease. PWH who had ever been diagnosed with a clinically significant inhibitor had greater odds of sexual difficulty (OR, 1.69 95% CI1.00-2.84). PWH with a greater numbers of bleeds in the past 12 months had worse sexual health as opposed to those who reported a lower number of bleeds. The odds of sexual difficulty was also greater among PWH who had bleeding in the past two weeks (OR 3.46, 95% CI 2.27-5.29), who currently had any target joints (OR 1.86, 95% CI 1.09-3.17), who had ≥3 spontaneous bleeds in the past 6 months (OR 3.32, 95% CI 1.39-7.91), who had reduced range of motion of any joints (OR 11.90, 95% CI 2.89-48.94), who had life- or limb-threatening bleeds in the past 12 months (OR 2.83, 95% CI 1.80-4.45) or who had iliopsoas bleeding in the past 12 months (OR 4.16, 95% CI 1.87-9.25).

**Multivariable logistic regression analysis**

Table 5 demonstrates the multivariable logistic regression analysis between participants' demographics, general health, co-morbid diseases and sexual health. The variables that were associated with more frequent sexual difficulty among PWH included older age (OR 1.03, 95% CI 1.02-1.04), experiencing acute pain in the past 12 months (OR 2.67, 95% CI 1.39-5.10), experiencing chronic pain in the past 12 months (OR 4.23, 95% CI 1.78-10.02), bleeding within the past two weeks (OR 2.29, 95% CI 1.45-3.61),

limitation of range of motion of any joints (OR 5.23, 95% CI 1.22-22.32) and having any life- or limb-threatening bleeds in the past 12 months (OR 1.81, 95% CI 1.11-2.96). Variance inflation factor and tolerance were unremarkable, indicating no potential multicollinearity. Hosmer-Lemeshow analysis was applied in the multivariable logistic regression model and showed a p-value of 0.31, indicating the goodness-of-fit of the model.

## DISCUSSION

Our findings indicate that sexual difficulty is much more prevalent among PWH than people without bleeding disorders. To the best of our knowledge, no other studies have been conducted to examine sexual health in a large sample of PWH across various countries. General health problems and co-morbid diseases affected sexual health in PWH and the control group. Hemophilia-related health problems substantially contributed to poor sexual health in PWH.

We found 13.6% of PWH experienced sexual difficulty compared to only 3.7% of the control group. The prevalence of sexual difficulty observed in the present study is lower than previous studies conducted in patients with other chronic diseases, which reported the prevalence of sexual difficulty in 36-54% of patients with head injury, up to 60% of patients with multiple sclerosis and 58.6% of patients with prior stroke [25-28]. The differences in the prevalence of sexual difficulty among people who suffer from chronic disease may be explained by the onset of disease (patients with congenital disease may be more susceptible to sexual difficulty than those with acquired disease), severity of disease, treatment related complications and methods assessing sexual health.

General health problems had a negative impact on sexual health in both PWH and the control group. Participants who reported current health problems had higher odds of sexual difficulty as opposed to those who did not report health problems. These findings replicated those reported in previous studies of the general populations and patients living

with hemophilia [5, 8-10, 20]. We observed participants who reported the use of mobility aids or assistive devices had higher odds of sexual difficulty both in PWH and the control populations. People who reported the use of mobility aids were likely to have physical impairment for various reasons. The study conducted in people with physical disability demonstrated that these people struggled with sexual barriers associated with physical impairments [29]. In addition, people with more severe physical impairments had more higher levels of sexual depression and lower levels of sexual satisfaction than those with milder impairments [30].

Our study demonstrated that having both acute pain or chronic pain in the past 12 months, and the use of pain medications were associated with higher odds of sexual difficulty in both PWH and participants without bleeding disorders. Pain has direct and indirect effects on sexual functioning. Ambler et al conducted a survey in 237 patients with chronic pain [12]. This study reported 73% of patients had pain-related difficulty with sexual activity (e.g. arousal, position or exacerbating pain). Moreover, patients who reported sexual difficulty were more likely to indicate they had difficulty with relationships. Moreover, the psychological problems, for instance, depression, anxiety or decreased interest of sex, may contribute to sexual difficulty in people who concurrently have pain [12, 31].

Pain medications can cause sexual dysfunction and difficulties. Opioids, which are common pain medications prescribed for patients who have arthritic pain, reduce levels of sex hormones and may consequently cause erectile dysfunction [32]. A study by Ajo et al reported high prevalence of sexual dysfunction in patients who had opioid-induced

androgen deficiency [33]. Participants who had pain and who took pain medication were therefore associated with more frequent sexual difficulty from pain per se and pain related therapy.

The association between self-reported co-morbid diseases and sexual health was higher in PWH as compared with the control group. Hepatitis B, hepatitis C, hypertension, arthritis and gingivitis had a negative impact on sexual health in patients with hemophilia. Arthritis was associated with more frequent sexual difficulty among both PWH and participants without bleeding disorders. We observed a trend of increased sexual difficulty among patients who had HIV infection. This finding concurred the previous studies which reported high frequency of sexual dysfunction among HIV infected patients [34, 35]. The sexual health in participants without bleeding disorders who had hepatitis B, C and HIV/AIDS could not be assessed due to too few controls reporting these diseases.

This study has highlighted the associations between hemophilia related problems and sexual health. We observed that PWH who reported recent psoas bleeding had more frequent sexual difficulty than those who did not. Iliopsoas muscle bleeding can limit sexual intercourse because this muscle functions in the thrusting movement during sexual intercourse [19]. The multivariable logistic regression model revealed that older age, experiencing acute pain or chronic pain in the past 12 months, having bleeds within the past two weeks, reduced ranged of motion of any joints and having life- or limb-threatening bleeds in the past 12 months were independent factors for sexual difficulty.

Lack of mobility and joint pain can restrict sexual intercourse and sexual position [20, 36], resulting in sexual difficulty.

One of the strengths of the present study is that we assessed the outcomes in both PWH and people who did not have a bleeding disorder. We were able to display the contrast in the frequency of sexual difficulty in these two groups. In addition, we recruited participants from multiple countries and cultures. Sample populations in this study were appropriate representatives for both PWH and people without a bleeding disorder.

However, the study has some limitations. First, this study was conducted as a cross-sectional study without random sampling of cases and exact match of the control group. However, the large sample and the multicentric nature are expected to partially mitigate selection bias. We assessed only the prevalence of sexual difficulty among participants during study period. Our findings are likely to underestimate the incidence of sexual problems. Second, we did not investigate the specific problems related to sexual difficulty: whether the participants had reduced sexual interest, increased sexual anxiety, decreased frequency of sexual intercourse, restricted sexual position, difficulties during sexual intercourse or having bleeds caused by sexual activities. Longitudinal studies with more comprehensive assessment are needed to determine the underlying problems related to sexual difficulties in PWH. However, from the perspective of assessing prevalence and association of sexual difficulties as a basic concept, our data collection modality is less likely to have introduced bias in the assessment. Third, there was a large baseline imbalance between PWH and the control population in terms of proportion of male and

female participants. Since hemophilia is an X-link recessive inherited disease, males are predominately affected. Sexual activity and quality of sexual life were reportedly differently among males and females in previous studies [4, 11]. We could not perform a sensitivity analysis due to insufficient sample size, and therefore further studies with better gender balance between PWH and the control group would provide a more precise comparison.

**Implications for health care providers and policy makers**

Currently, the data on sexual health in PWH is limited. Sexual difficulties in PWH are not discussed adequately in routine hemophilia care due to lack of awareness, understanding and resources [19]. A Canadian study reported that there were lower levels of knowledge in the areas of sexual activity among adults males with hemophilia [37]. Sexual health may be difficult to assess because healthcare providers may be reluctant to ask questions regarding sexual problems and patients may feel embarrassed to discuss [38]. It will be imperative for initiative programs or policies to assess and improve the sexual health of PWH in comprehensive hemophilia care. Policies may focus on multidisciplinary approaches to overcome these barriers.

## CONCLUSIONS

Sexual difficulty is more prevalent in patients living with hemophilia. General health problems, co-morbid diseases and hemophilia-related problems resulted in more frequent sexual health difficulties in patients with hemophilia and people without bleeding disorders. Healthcare providers, researchers and policy makers should incorporate sexual health discussion in comprehensive hemophilia care, future research and health policy.

**Countries of residence of participants**

Argentina, Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Ireland, Italy, Japan, Mexico, New Zealand, Nigeria, Poland, Spain, Netherlands, United States of America, United Kingdom, Venezuela and Vietnam

## REFERENCES


1. Parish KL: **Sexuality and haemophilia: connections across the life-span**. *Haemophilia* 2002, **8**(3):353-359.
2. Fugh-Berman A, Scialli AR: **Testosterone and sexual function**. *Curr Opin Urol* 2017.
3. Morton L: **Sexuality in the Older Adult**. *Prim Care* 2017, **44**(3):429-438.
4. Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ: **A study of sexuality and health among older adults in the United States**. *N Engl J Med* 2007, **357**(8):762-774.
5. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, Wang T, Group GI: **Sexual problems among women and men aged 40-80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors**. *Int J Impot Res* 2005, **17**(1):39-57.
6. DeLamater J, Karraker A: **Sexual functioning in older adults**. *Curr Psychiatry Rep* 2009, **11**(1):6-11.
7. Heywood W, Lyons A, Fileborn B, Hinchliff S, Minichiello V, Malta S, Barrett C, Dow B: **Sexual satisfaction among older Australian heterosexual men and women: Findings from the Sex, Age & Me study**. *J Sex Marital Ther* 2017:0.
8. Nusbaum MR, Hamilton C, Lenahan P: **Chronic illness and sexual functioning**. *Am Fam Physician* 2003, **67**(2):347-354.

9. Wandell PE, Brorsson B: **Assessing sexual functioning in patients with chronic disorders by using a generic health-related quality of life questionnaire**. *Qual Life Res* 2000, **9**(10):1081-1092.

10. Hyde Z, Flicker L, Hankey GJ, Almeida OP, McCaul KA, Chubb SA, Yeap BB: **Prevalence of sexual activity and associated factors in men aged 75 to 95 years: a cohort study**. *Ann Intern Med* 2010, **153**(11):693-702.

11. Lindau ST, Gavrilova N: **Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing**. *BMJ* 2010, **340**:c810.

12. Ambler N, Williams AC, Hill P, Gunary R, Cratchley G: **Sexual difficulties of chronic pain patients**. *Clin J Pain* 2001, **17**(2):138-145.

13. Darby SC, Kan SW, Spooner RJ, Giangrande PL, Hill FG, Hay CR, Lee CA, Ludlam CA, Williams M: **Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV**. *Blood* 2007, **110**(3):815-825.

14. Rodriguez-Merchan EC: **Musculoskeletal complications of hemophilia**. *HSS J* 2010, **6**(1):37-42.

15. Franchini M, Mannucci PM: **Co-morbidities and quality of life in elderly persons with haemophilia**. *Br J Haematol* 2010, **148**(4):522-533.

16. Philipp C: **The aging patient with hemophilia: complications, comorbidities, and management issues**. *Hematology Am Soc Hematol Educ Program* 2010, **2010**:191-196.

17. Patel H, Heathcote EJ: **When to treat and the benefits of treating hepatitis C in patients with haemophilia**. *Haemophilia* 2009, **15**(1):20-32.

18. Aledort LM, Evatt BL, Lusher JM, Brownstein AP: **HIV and hemophilia**. *J Thromb Haemost* 2007, **5**(3):607-610.

19. Gianotten WL, Heijnen L: **Haemophilia, aging and sexuality**. *Haemophilia* 2009, **15**(1):55-62.

20. Bar-Chama N, Snyder S, Aledort L: **Sexual evaluation and treatment of ageing males with haemophilia**. *Haemophilia* 2011, **17**(6):875-883.

21. Dune T: **Sexual expression, fulfilment and haemophilia: reflections from the 16th Australian and New Zealand Haemophilia Conference**. *Haemophilia* 2012, **18**(3):e138-139.

22. Tobase P, Mahajan A, Francis D, Leavitt AD, Giermasz A: **A gap in comprehensive care: Sexual health in men with haemophilia**. *Haemophilia* 2017, **23**(4):e389-e391.

23. Skinner MW, Driessens M, Curtis R, Frick N, Iorio A, Nichol M, Noone D, O'Mahony B, Page D, Stonebraker J: **The Patient Reported Outcomes, Burdens and Experiences (PROBE) Study Phase 1 Methodology and Feasibility**. *Haemophilia* 2016, **22 (Suppl. 4)**:118.

24. Chai-Adisaksopha C, Iorio A, Curtis R, Frick N, Nichol M, Noone D, O'Mahony B, Page D, Stonebrake J, Skinner MW: **Test-Retest Reliability Analysis of The Patient Reported Outcomes Burdens and Experiences (PROBE) Study**. *Haemophilia* 2017, **23 (Suppl.2)**:29-140. [abstract P037].

25. Basson R, Rees P, Wang R, Montejo AL, Incrocci L: **Sexual function in chronic illness**. *J Sex Med* 2010, **7**(1 Pt 2):374-388.

26. Ponsford J: **Sexual changes associated with traumatic brain injury**. *Neuropsychol Rehabil* 2003, **13**(1-2):275-289.

27. Lundberg PO: **Sexual dysfunction in female patients with multiple sclerosis**. *Int Rehabil Med* 1981, **3**(1):32-34.

28. Kimura M, Murata Y, Shimoda K, Robinson RG: **Sexual dysfunction following stroke**. *Compr Psychiatry* 2001, **42**(3):217-222.

29. Taleporos G, McCabe MP: **Physical Disability and Sexual Esteem**. *Sex Disabil* 2001, **19**(2):131-148.

30. McCabe MP, Taleporos G: **Sexual esteem, sexual satisfaction, and sexual behavior among people with physical disability**. *Arch Sex Behav* 2003, **32**(4):359-369.

31. ter Kuile MM, Weijenborg PT, Spinhoven P: **Sexual functioning in women with chronic pelvic pain: the role of anxiety and depression**. *J Sex Med* 2010, **7**(5):1901-1910.

32. Daniell HW: **Hypogonadism in men consuming sustained-action oral opioids**. *J Pain* 2002, **3**(5):377-384.

33. Ajo R, Segura A, Inda MM, Planelles B, Martinez L, Ferrandez G, Sanchez A, Cesar M, Peiro AM: **Opioids Increase Sexual Dysfunction in Patients With Non-Cancer Pain**. *J Sex Med* 2016, **13**(9):1377-1386.

34. Florence E, Schrooten W, Dreezen C, Gordillo V, Nilsson Schonnesson L, Asboe D, Koitz G, Colebunders R, Eurosupport Study G: **Prevalence and factors associated with sexual dysfunction among HIV-positive women in Europe**. *AIDS Care* 2004, **16**(5):550-557.

35. Luzi K, Guaraldi G, Murri R, De Paola M, Orlando G, Squillace N, Esposito R, Rochira V, Zirilli L, Martinez E: **Body image is a major determinant of sexual dysfunction in stable HIV-infected women**. *Antivir Ther* 2009, **14**(1):85-92.

36. Rosenbaum TY: **Musculoskeletal pain and sexual function in women**. *J Sex Med* 2010, **7**(2 Pt 1):645-653.

37. Arnold E, Lane S, Webert KE, Chan A, Walker I, Tufts J, Rubin S, Poon MC, Heddle NM: **What should men living with haemophilia need to know? The perspectives of Canadian men with haemophilia**. *Haemophilia* 2014, **20**(2):219-225.

38. Wylie K, Kenney G: **Sexual dysfunction and the ageing male**. *Maturitas* 2010, **65**(1):23-27.

## FIGURES AND TABLES

Figure 1 Flow diagram of patient selection

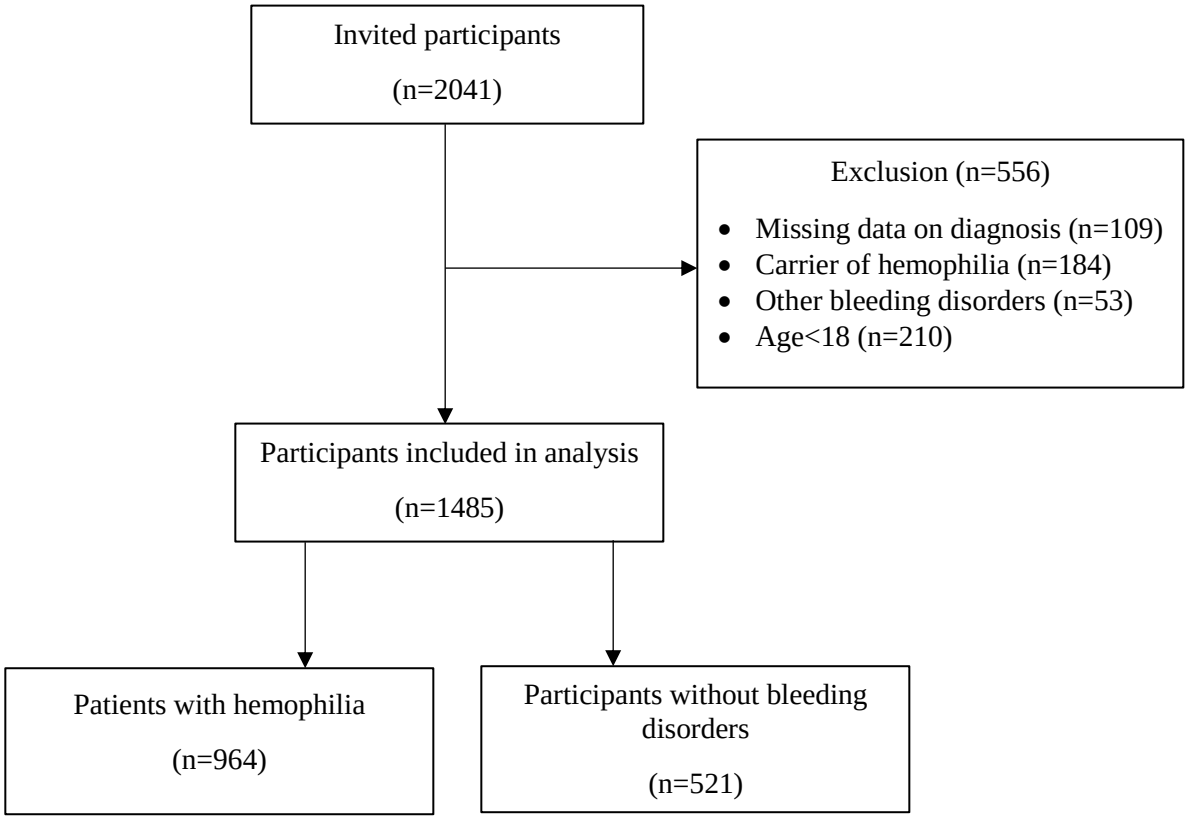

Table 1 Characteristics of the participants

| | Patients with hemophilia (n=964) | Participants without bleeding disorders (n=521) | P-value |
|---|---|---|---|
| Gender (n, %)<br>Male | <br>897 (93.15) | <br>169 (32.44) | <br><0.001 |
| Age, Mean (SD) | 39.54 (15.17) | 45.04 (13.56) | <0.001 |
| Diagnosis (n, %)<br>Hemophilia A<br>Hemophilia B | <br>809 (83.92)<br>155 (16.08) | N/A | N/A |
| Severity of hemophilia*<br>Normal factor level<br>Mild<br>Moderate<br>Severe | <br>2 (0.21)<br>121 (12.55)<br>148 (15.35)<br>557 (57.78) | N/A | N/A |
| Have been diagnosed with clinically significant inhibitor (n, %) | 118 (12.24) | N/A | N/A |
| Currently having a clinically significant inhibitor (n, %) | 39 (4.05) | N/A | N/A |

**Abbreviations:** N/A; not applicable, SD; standard deviation

Table 2 Impact of general health problems on sexual health in PWH and participants who did not have bleeding disorders

| Health problem | PWH (n=964) | | Control (n=521) | | P-value for interaction |
|---|---|---|---|---|---|
| | Prevalence (n, %) | Odds ratio[&] (95% CI) | Prevalence (n, %) | Odds ratio[&] (95% CI) | |
| Experiencing any health problems*<br>• Yes<br>• No | 121 (17.93)<br>10 (4.26) | 4.94 (2.53-10.77) | 14 (7.29)<br>5 (1.68) | 4.69 (1.56-16.90) | 0.93 |
| Using mobility aids<br>• Yes<br>• No | 105 (18.42)<br>26 (7.83) | 2.69 (1.69- 4.41) | 8 (9.64)<br>11 (2.75) | 3.81 (1.28-10.80) | 0.51 |
| Using pain medication*<br>• Yes<br>• No | 124 (16.19)<br>7 (5.07) | 3.55 (1.62- 9.22) | 18 (5.10)<br>1 (0.79) | 6.69 (1.03-281.14) | 0.56 |
| Having acute pain*<br>• Yes<br>• No | 119 (18.14) | 4.08 (2.23-8.04) | 11 (6.29) | 2.64 (0.94-7.72) | 0.43 |
| Acute pain interferes with relationships<br>• Yes<br>• No | 59 (36.88)<br>72 (9.76) | 3.82 (2.13- 7.38) | 5 (20.0)<br>72 (9.76) | 2.64 (0.94-7.72) | 0.50 |
| Having chronic pain*<br>• Yes<br>• No | 122 (18.46)<br>9 (3.83) | 5.28 (2.71-11.49) | 17 (10.0)<br>2 (0.67) | 17.29 (4.00-155.35) | 0.15 |
| Chronic pain interferes with relationships<br>• Yes<br>• No | 75 (39.68)<br>56 (7.92) | 5.44 (2.86-11.39) | 6 (27.27)<br>13 (2.90) | 18.76 (4.33-168.60) | 0.13 |
| Underwent joint surgery#<br>• Yes<br>• No | 72 (16.11)<br>58 (13.62) | 1.21 (0.82-1.81) | 6 (5.26)<br>13 (3.74) | 1.44 (0.43-4.18) | 0.57 |

*In the past 12 months, #Either joint aspiration, amputation, joint replacement, joint fusion, radio or chemical synovectomy, surgery to remove tumor or others, [$]Odds ratios comparing between participants who answered "yes" and those answered no,
**Abbreviations:** CI; confidence interval, PWH; patients living with hemophilia

Table 3 Impact of co-morbid diseases on sexual health

| Co-morbid disease | PWH (n=964) | | Control (n=521) | | P-value for interaction |
|---|---|---|---|---|---|
| | Prevalence (n, %) | Odds ratio[&] (95% CI) | Prevalence (n, %) | Odds ratio[&] (95% CI) | |
| Hepatitis B<br>• Yes<br>• No | 12 (30.77)<br>108 (13.95) | 2.74 (1.22-5.79) | 0<br>19 (4.31) | N/A* | N/A* |
| Hepatitis C<br>• Yes<br>• No | 51 (21.79)<br>70 (11.93) | 2.06 (1.35-3.12) | 0<br>18 (4.07) | N/A* | N/A* |
| HIV<br>• Yes<br>• No | 15 (21.74)<br>107 (14.12) | 1.69 (0.85-3.17) | 0<br>19 (4.26) | N/A* | N/A* |
| Stroke<br>• Yes<br>• No | 4 (33.33)<br>70 (16.28) | 2.57 (0.55-9.89) | 1 (25.0)<br>16 (6.81) | 4.54 (0.08-59.70) | 0.67 |
| Hypertension<br>• Yes<br>• No | 32 (29.91)<br>46 (13.98) | 2.62 (1.50-4.53) | 4 (9.76)<br>13 (6.67) | 1.51 (0.34-5.23) | 0.40 |
| Diabetes<br>• Yes<br>• No | 3 (18.75)<br>71 (16.71) | 1.15 (0.02-4.34) | 2 (15.38)<br>15 (6.67) | 2.53 (0.25-13.26) | 0.44 |
| Arthritis<br>• Yes<br>• No | 42 (25.77)<br>30 (11.41) | 2.69 (1.56-4.69) | 6 (21.43)<br>10 (4.85) | 5.31 (1.42-17.87) | 0.27 |
| Gingivitis<br>• Yes<br>• No | 36 (26.67)<br>40 (12.94) | 2.44 (1.42-4.18) | 2 (7.41)<br>15 (7.08) | 1.04 (0.11-4.93) | 0.30 |

*Too few participants to evaluate the association, [$]Odds ratios comparing between participants who answered "yes" and those answered no. **Abbreviations:** CI; confidence interval, N/A; not applicable, PWH; patients living with hemophilia

Table 4 Impact of hemophilia-related problems on sexual health

| Hemophilia-related problem | Prevalence (n, %) | Odds ratio (95% CI) | P-value |
|---|---|---|---|
| Severity | | | |
| • Mild | 10 (8.26) | Ref. | |
| • Moderate | 19 (12.84) | 1.94 (0.85-4.40) | 0.12 |
| • Severe | 93 (16.70) | 2.64 (1.31-5.31) | 0.01 |
| History of clinically significant inhibitor | | | |
| • No | 93 (14.26) | Ref. | |
| • Yes | 23 (19.49) | 1.69 (1.00-2.84) | 0.05 |
| Currently having a clinically significant inhibitor | | | |
| • No | 26 (17.33) | Ref. | |
| • Yes | 6 (15.38) | 1.00 (0.37-2.70) | 0.99 |
| Number of bleeds in the past 12 months | | | |
| • 0-1 bleed | 8 (5.19) | Ref. | |
| • 2-3 bleeds | 20 (12.35) | 3.14 (1.31-7.50) | 0.01 |
| • 4-7 bleeds | 14 (10.45) | 2.32 (0.92-5.82) | 0.07 |
| • 8-10 bleeds | 9 (12.16) | 2.54 (0.91- 7.01) | 0.07 |
| • 11-15 bleeds | 12 (15.38) | 4.40 (1.64- 11.83) | 0.003 |
| • 16-30 bleeds | 18 (20.69) | 6.69 (2.69- 16.64) | <0.01 |
| • >30 bleeds | 42 (29.17) | 10.77 (4.70- 24.70) | <0.01 |
| Bleeding within the past 2 weeks | | | |
| • No | 40 (8.64) | Ref. | |
| • Yes | 85 (21.57) | 3.46 (2.27-5.29) | <0.01 |
| Currently having any target joints | | | |
| • No | 19 (10.27) | Ref. | |
| • Yes | 89 (16.60) | 1.86 (1.09-3.17) | <0.02 |
| Having ≥3 spontaneous bleeds in the past 6 months | | | |
| • No | 7 (10.14) | Ref. | |
| • Yes | 50 (23.04) | 3.32 (1.39-7.91) | 0.01 |
| Reduced range of motion of any joints | | | |
| • No | 2 (1.53) | Ref. | |
| • Yes | 119 (17.53) | 11.90 (2.89-48.94) | <0.01 |
| Life- or limb-threatening bleeds in the past 12 months | | | |
| • No | 86 (12.59) | Ref. | |

| | | | |
|---|---|---|---|
| • Yes | 38 (28.79) | 2.83 (1.80-4.45) | <0.01 |
| Iliopsoas bleeding in the past 12 months<br>• No<br>• Yes | 112 (14.32)<br>12 (36.36) | Ref.<br>4.16 (1.87-9.25) | <0.01 |

**Abbreviations:** Ref; reference, CI; confidence interval

Table 5 Multivariable logistic regression analysis of the association between general health- and hemophilia-related problems and sexual difficulties among PWH

| Problems | Multivariable analysis | |
|---|---|---|
| | Odds ratio (95% CI) | P-value |
| Severity<br>• Mild<br>• Moderate<br>• Severe | <br>Ref.<br>0.84 (0.34-2.08)<br>1.14 (0.53-2.48) | <br>-<br>0.71<br>0.74 |
| Older age | 1.03 (1.02-1.04) | <0.01 |
| Experiencing acute pain in the past 12 months | 2.67 (1.39- 5.10) | <0.01 |
| Experiencing chronic pain in the past 12 months | 4.23 (1.78-10.02) | <0.01 |
| Bleeding within the past two weeks | 2.29 (1.45-3.61) | <0.01 |
| Reduced range of motion of any joints | 5.23 (1.22- 22.32) | <0.01 |
| Having any life- or limb-threatening bleeds in the past 12 months | 1.81 (1.11-2.96) | <0.01 |

**Abbreviations:** CI; confidence interval, PWH; patients living with hemophilia

# CHAPTER 6

# CONCLUSIONS

Patients with hemophilia have unique health problems that are different from patients with other chronic diseases. Therefore, disease specific health measurement are essential for evaluating health status in such populations. Measurement instruments are required to undergo a deep evaluation of their measurement properties in order to ensure the quality of their results [1]. The instruments must provide accurate, valid and interpretable data for assessing health status of tested populations [2]. Validity and reliability are two core elements of psychometric properties [3]. To achieve these goals for the PROBE instrument, we conducted 4 studies:

- Psychometric properties of the Patient Reported Outcomes Burdens and Experiences (PROBE) Questionnaire
- Test-retest properties of the Patient Reported Outcomes Burdens and Experiences (PROBE) questionnaire and its constituent domains and questions
- Exploring regional variations on the cross-cultural, international implementation of the Patient Reporting Outcomes Burdens and Experience study
- Evaluation of the sexual health in patients living with hemophilia

**Study I findings (Chapter 2)**

Factor analysis revealed two major components that explained 50.6% of the variance. Internal consistency was acceptable with a Cronbach's alpha of 0.84. The convergent validity showed moderate to strong correlation (r=0.39 to 0.71) when

compared with EQ-5D-5L sub-items. Known group validity analysis demonstrated validity of the PROBE questionnaire when participants were classified to a priori subgroups based on their clinical characteristics. The results suggested that the PROBE questionnaire is valid for both patients with hemophilia and participants without bleeding disorders.

**Study II findings (Chapter 3)**

Test-retest reliability test was performed in 63 participants (both patients with hemophilia and those without bleeding disorders) on 3 occasions (T1, T2 and T3). Test-retest reliability analyses revealed acceptable reliability between paper-based questionnaires (T1 vs T2), and the Kappa coefficients ranged from 0.69-0.92. Likewise, the reliability was acceptable between paper-based and web-based questionnaire (T1 vs T3), with Kappa coefficients that ranged from 0.5-1.0. The worst Kappa coefficient was observed in items evaluating acute pain. These results suggested that the PROBE questionnaire is a reliable tool for assessing health status in patients with hemophilia and participants without bleeding disorders. Moreover, we demonstrated that the web-based PROBE questionnaire can be used interchangeably with paper-based one.

**Study III findings (Chapter 4)**

Participants from 21 countries in 4 regions responded to the PROBE questionnaire. Hemophilia diagnosis contributed the second largest variance component for the subitem score and the PROBE score, after individual variability. Region contributed only 0.26% of the variance of the PROBE score. Likewise, years of education

contributed 0.34% of the PROBE score. The results suggested that the PROBE questionnaire is valid for assessing health status across countries (and languages) regardless of the education levels of participants.

Study IV findings (Chapter 5)

We performed an analysis on 965 patients living with hemophilia and 521 participants without bleeding disorders. The prevalence of sexual difficulties was significantly higher among patients with hemophilia (13.6%) as compared to control population (3.7%), odds ratio 4.7, 95% confidence interval 2.8-7.7. Among patients who had hemophilia, older age, acute or chronic pain, recent bleeding within two weeks, limitation of range of motion or life- or limb-threatening bleeding in the past year were associated with having sexual difficulties.

**STRENGTHS OF THE PROBE STUDY**

One of the strength of the PROBE study is that we evaluated core psychometric properties of the questionnaire, including convergent validity, known group validity, internal consistency and test-retest reliability. Second, we evaluated the psychometric properties in a large sample size (almost 1,000 participants), across cultures, in multiple countries. More importantly, we demonstrated that the translated versions of the PROBE questionnaire was valid across 20 languages. To the best of our knowledge, the PROBE questionnaire is the only instrument that has been tested for validity across cultural regions and languages. These results will allow the questionnaire to have an impact in regions where the hemophilia care, culture, and perception of patients toward their health

are different. Third, we included participants without bleeding disorders as control populations in the studies. We found that the PROBE questionnaire is valid and reliable in control populations. As a result, we are able to compare the health status between patients with hemophilia and general populations. Fourth, the PROBE questionnaire includes all important domains of patient reported outcome as suggested by the ICF framework [4], which comprises of hemophilia related health (body function and structure), activities, participants, hemophilia treatment (environmental factors) and personal factors. This advantage of the PROBE questionnaire allows researchers to collect more extensive and informative health status in patients with hemophilia.

**LIMITATIONS OF THE PROBE STUDY**

There are some limitations of the PROBE study. First, we did not assess the responsiveness of the PROBE questionnaire. Responsiveness of a scale is defined as the ability to detect change accurately when it occurs [5]. Moreover, we have not determined the minimal clinically important difference (MCID) [6] for the PROBE score. The data in these present studies were collected in a cross-sectional fashion. Therefore, we need to conduct a new study in populations who are expected to have a change of health status in order to test for the responsiveness and MCID. Second, we did not validate the PROBE questionnaire in other bleeding disorders or other chronic diseases that may share common clinical features with hemophilia (e.g. osteoarthritis, rheumatoid arthritis). Third, participants in the PROBE studies were asked to complete the questionnaire by themselves without help from parents or caregivers. The results from the validation studies cannot be extrapolated to populations who require help for questionnaire

administration, for example, young children or patients who have limited ability to read. Lastly, the calculation of the PROBE score is relatively complicated when compared to other scales.

## IMPLICATIONS

There has been growing interest in integrating patient reported outcomes (PRO) measures in hemophilia clinical research [7]. Recent clinical trials and observational studies have included PRO as one of the important outcomes [8-10]. The PROBE questionnaire can be incorporated in clinical studies for assessing PRO. Besides, the PROBE questionnaire collects data on clotting factor consumption, surgery or invasive procedures and work/school days lost. Therefore, the PROBE can be used in the studies evaluating health economics. This information will bridge a policy gap and engage patients' perspective are considered in assessing the value of treatment [11].

At the population level, the PROBE questionnaire allows researcher to compare the health status of populations across countries where the availability of factor concentrates, and hemophilia care are different. Researchers may incorporate the PROBE questionnaire in longitudinal data collection then compare the health status of patients when policy on treatment has changed overtime.

The PROBE questionnaire can be used in a routine practice. The benefits of the use of PRO data collection in routine hematology/oncology care include improving accuracy of symptoms assessment, improving patient-physician communication, improving patients' satisfaction, saving time, facilitating share medical decision and

liking PRO data with medical data [12]. Physicians can implement the PROBE questionnaire in the annual follow-up visit for hemophilia patients. The extensive assessment of the PROBE allows physicians to quick review health problems or initiate conversation with regards to patients' specific reported problems. One advantage of the PROBE questionnaire is that the availability of a web-based platform. Physicians can integrate the PROBE questionnaire to patients' medical data. Furthermore, patients can track their health status overtime when the PRO are collected longitudinally.

## CONCLUSIONS

This thesis is focusing on the core aspects of psychometric properties of the PROBE questionnaire. The results show that the PROBE questionnaire is a valid and reliable instrument to measure health status of patients living with hemophilia and control populations. The cross-cultural implementation of the PROBE questionnaire demonstrates that the PROBE is valid to use across the regions. Web-based and paper-based versions of the PROBE questionnaire can be used interchangeably. Therefore, the PROBE can be used as an electronic-PRO (e-PRO). Researchers can incorporate the PROBE questionnaire as a PRO measures in clinical trials, observational studies or health economic assessment. Moreover, the PROBE questionnaire has a potential to be used in routine clinical care.

## REFERENCES


1. Salmond SS: **Evaluating the reliability and validity of measurement instruments**. *Orthop Nurs* 2008, **27**(1):28-30.
2. Souza AC, Alexandre NMC, Guirardello EB: **Psychometric properties in instruments evaluation of reliability and validity**. *Epidemiol Serv Saude* 2017, **26**(3):649-659.
3. Karanicolas PJ, Bhandari M, Kreder H, Moroni A, Richardson M, Walter SD, Norman GR, Guyatt GH, Collaboration for Outcome Assessment in Surgical Trials Musculoskeletal G: **Evaluating agreement: conducting a reliability study**. *J Bone Joint Surg Am* 2009, **91 Suppl 3**:99-106.
4. WHO: **The International Classification of Functioning, Disability and Health**. *World Heal Organ* 2001, **18**:237.
5. de Bruin AF, Diederiks JP, de Witte LP, Stevens FC, Philipsen H: **Assessing the responsiveness of a functional status measure: the Sickness Impact Profile versus the SIP68**. *J Clin Epidemiol* 1997, **50**(5):529-540.
6. Wright JG: **The minimal important difference: who's to say what is important?** *J Clin Epidemiol* 1996, **49**(11):1221-1222.
7. Bullinger M, Globe D, Wasserman J, Young NL, von Mackensen S: **Challenges of patient-reported outcome assessment in hemophilia care-a state of the art review**. *Value Health* 2009, **12**(5):808-820.

8. Mondorf W, Kalnins W, Klamroth R: **Patient-reported outcomes of 182 adults with severe haemophilia in Germany comparing prophylactic vs. on-demand replacement therapy**. *Haemophilia* 2013, **19**(4):558-563.

9. Gringeri A, Leissinger C, Cortesi PA, Jo H, Fusco F, Riva S, Antmen B, Berntorp E, Biasoli C, Carpenter S *et al*: **Health-related quality of life in patients with haemophilia and inhibitors on prophylaxis with anti-inhibitor complex concentrate: results from the Pro-FEIBA study**. *Haemophilia* 2013, **19**(5):736-743.

10. Hoots WK, Ebbesen LS, Konkle BA, Auerswald GK, Roberts HR, Weatherall J, Ferran JM, Ljung RC, Novoseven I: **Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors**. *Haemophilia* 2008, **14**(3):466-475.

11. O'Mahony B, Skinner MW, Noone D, Page D, O'Hara J: **Assessments of outcome in haemophilia - a patient perspective**. *Haemophilia* 2016, **22**(3):e208-209.

12. Efficace F, Gaidano G, Lo-Coco F: **Patient-reported outcomes in hematology: is it time to focus more on them in clinical trials and hematology practice?** *Blood* 2017, **130**(7):859-866.