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ISBN: 978-94-6458-552-0

Provided by thesis specialist Ridderprint, ridderprint.nl
Printing: Ridderprint
Design cover and chapter pages: Okki Poortvliet, www.okkipoortvliet.com
Layout and design: Erwin Timmerman, persoonlijkproefschrift.nl

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op woensdag 30 november 2022
klokke 13:45 uur

door

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geboren te Groningen
in 1980

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The work described in this thesis was performed at the department of Clinical Epidemiology of Leiden University Medical Center
Financial support for printing of this thesis was kindly provided by Chipsoft and CSL Behring

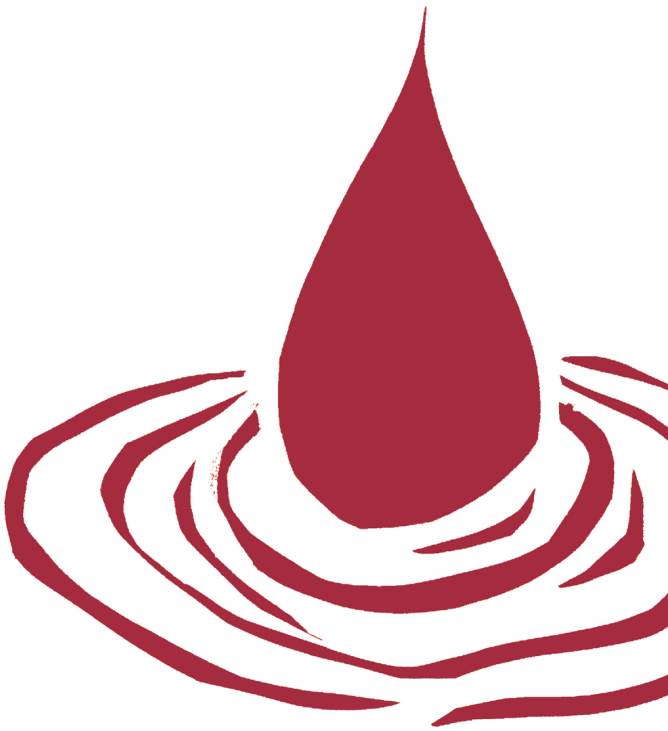
Waar een wil is, is een weg.
En waar een Erna is, is een wil.

Voor iedereen met hemofilie

Contents

CHAPTER 1

General introduction, aims and outline, and study populations



Once known as the 'royal disease', hemophilia is a condition that affects approximately 1,125,000 individuals worldwide.[1] Advancements in medical science in the second half of the 20th century have led to efficacious treatment and improvements in life expectancy and health outcomes for persons with hemophilia.[2, 3] However, outcomes assessment for hemophilia is complex, due to the heterogeneity in disease characteristics and co-morbidities, types of outcomes and methods to measure such outcomes. This thesis aims to define, measure and quantify relevant health outcomes for persons with hemophilia, with the overall goal to improve care for this group of people.

Hemophilia

Persons with congenital hemophilia have a lack of either functional protein coagulation factor VIII (hemophilia A, 80-85 percent of cases) or IX (hemophilia B, 15-20 percent of cases), preventing the formation of stable fibrin blood clot.[1, 4] As a result, persons with hemophilia have an increased bleeding tendency. In severe hemophilia, coagulation factor VIII or IX concentrations are below 0.01 IU/mL (<1 percent of normal), this often manifests itself as spontaneous bleeding into joints (hemarthrosis), muscles, and internal organs. Intracranial hemorrhage, gastrointestinal bleeding and bleeding in the neck and throat area can be life-threatening.[5] Approximately 70 to 80 percent of bleeding occurs in the synovial joints: ankles, knees, elbows, shoulders, hips and wrists. The number of bleeds is often expressed as the annualized bleeding rate (ABR) and annualized joint bleeding rate (AJBR).[3, 6, 7]

In moderate hemophilia, coagulation factor concentrations are between 0.01 and 0.05 IU/mL (or 1-5 percent of normal). This leads to occasional spontaneous bleeding and prolonged bleeding after minor trauma or surgery. Persons with mild hemophilia have coagulation factor concentrations of 0.05-0.40 IU/mL (5-40 percent of normal), and generally only experience bleeding after major trauma or surgery. They may not experience prolonged bleeding until triggered by such events [5] and may remain undiagnosed until later in life.[8] Coagulation factor concentrations generally correlate well with bleeding phenotype, although individuals with the same concentrations may still have different bleeding phenotypes due to differences in genetics, joint health status and behavior (e.g. with activities that increase the chance of a bleed), but also due to yet unknown causes.[5, 9]

Joint bleeds are mainly triggered by mechanical stress such as weightbearing or trauma.[10] Clinically, a joint bleed results in swelling, pain and a loss in range of motion.[5] When a bleed occurs, blood accumulates in the synovium and synovial cavity (Figure 1).[10] Iron present in erythrocytes causes inflammation of the synovium, which then becomes more susceptible to mechanical damage and subsequent bleeding. Recurrent joint bleeding results in cartilage degeneration and structural changes through synovitis

and oxidative stress. In later stages the underlying bone is also affected. The result is hemophilic arthropathy,[10] with disability and pain.

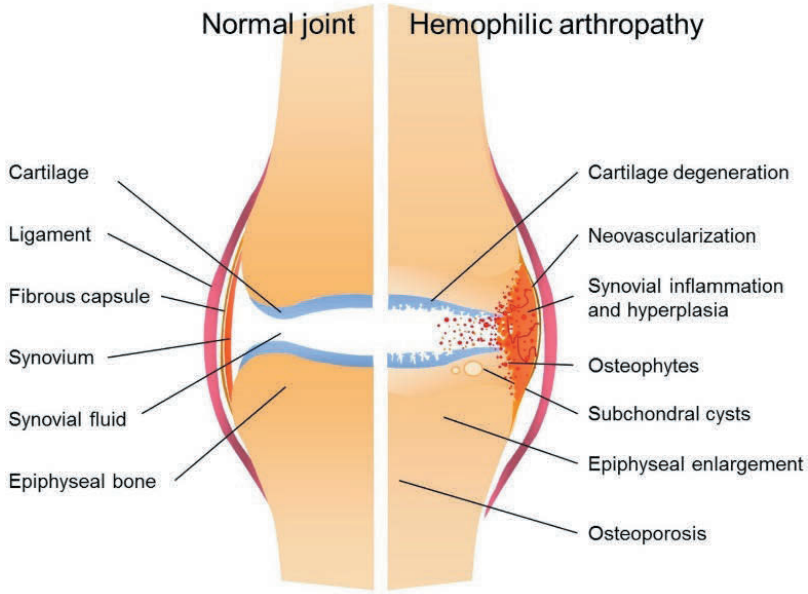


Figure 1: Schematic representation of a healthy joint (left) and hemophilic arthroparthy (right). Reprinted from Pulles et al (2017)[10], with permission from Elsevier.

Diagnosis of hemophilia is based on clinical features (bleeding without an apparent trigger, easy bruising, excessive bleeding after trauma or surgery), family history, coagulation screening tests (prothrombin time (PT) and activated partial thromboplastin time (APTT), and coagulation factor activity assays. Comprehensive laboratory testing is important to rule out other bleeding disorders and to start appropriate treatment as soon as possible.[5]

The deficiency in coagulation factor VIII or IX in congenital hemophilia originates from mutations in the F8 and F9 coagulation genes.[5] For severe hemophilia A the most common causative mutation is an intron 22 inversion, which is present in 30-45 percent of cases. Both the F8 and F9 genes are located on the long arm of the X-chromosome.[5] The inheritance is X-linked, meaning that hemophilia occurs mostly in men.[5] However, women may also have hemophilia, with a diagnosis based on a combination of personal bleeding history and baseline plasma FVIII or IX concentrations.[11] The most prominent hemophilia symptom in women is excessive bleeding during menstruations.[5]

Hemophilia is a rare disease, which is defined as a disease with a prevalence of less than 5 in 10,000 in the population.[12] In the Netherlands, the prevalence of hemophilia

was estimated at 1.6 per 10,000 males,[13] and the prevalence at birth was estimated at 2.06 per 10,000 male live births in 1986.[14] Based on these estimates, the Dutch hemophilia population was expected to consist of 1364-1756 individuals in 2018. More recent international estimates based on national patient registries in 6 high-income countries, however, indicate that the prevalence of hemophilia is 2.46 and 0.5 per 10,000 male live births for hemophilia A and B, respectively, and 1.71 and 0.38 per 10,000 live males.[1] These higher estimates likely result from better diagnostic techniques, completeness of population testing, and the precision in case reporting.[1] The updated estimates of prevalence means that the number of persons with hemophilia in the Netherlands may amount to 2500 to 2600 individuals.

Treatment of hemophilia

Prior to the 1960s, the only treatment available for hemophilia consisted of whole blood or plasma transfusions.[15] The discovery of high amounts of FVIII in fresh-frozen plasma precipitate (cryoprecipitate) in the mid-1960s was the first step towards modern hemophilia treatment products.[16] Next, FVIII products were extracted from human plasma. Nowadays, FVIII and FIX products may either be derived from human plasma obtained from blood donors, or, more commonly, produced using recombinant techniques.[5]

Coagulation factor replacement is by intravenous infusion, either as episodic (on-demand) treatment to treat a bleed, or as prophylaxis to prevent bleeds. Prophylaxis may be initiated as primary, secondary or tertiary prophylaxis, depending on starting age and on whether joint disease is present or not.[5] Prophylaxis does not prevent all bleeds, but it is recommended for persons with a severe bleeding phenotype, as is often the case for persons with severe hemophilia and for some persons with moderate hemophilia.[5, 17] Non-severe hemophilia A may also be managed with desmopressin.[8, 18]

Both recombinant and plasma-derived treatment products are currently on the market for hemophilia A and B in the Netherlands.[19] Dosing is based on bodyweight and depends on the goal of treatment, cost, bleeding phenotype, daily activities, venous access and vial volume of the treatment product.[20] Dosing regimens applied in high-income countries such as the Netherlands are intermediate-dose or high-dose prophylaxis: 15-25 IU/kg or 25-40 IU/kg 3 times a week for hemophilia A and 20-40 IU/kg or 40-60 IU/kg twice a week for hemophilia B.[5, 20] In the past few years, innovations have led to alternative forms of treatment: coagulation factor products with a prolonged half-life reduce the burden of treatment because they allow for fewer injections.[5, 15] In addition, a non-coagulation factor based product (emicizumab) has been developed for treatment of hemophilia A that mimics the function of FVIII and that can be administered subcutaneously as prophylaxis. It initially became available for persons who develop inhibitors against infused coagulation factor VIII,[21] but as of 2020 it may also be used in persons without inhibitors.[22]

Coagulation factor replacement therapy has some disadvantages. First, blood-borne transmission of pathogens made persons with hemophilia vulnerable for infections with the human immune deficiency virus (hiv) between 1982 and 1985 and with hepatitis C virus until 1992. Approximately 17 percent of Dutch persons with hemophilia were hiv-positive in 1988 [23] and 68 percent were infected with the hepatitis C virus (hcv; at the time known as non-A non-B hepatitis).[24] Acquired immune deficiency syndrome (aids) was the cause of death for 26 percent of deaths among Dutch persons with hemophilia between 1992-2001,[2] and for two percent between 2001-2018.[25] Of those with hcv, approximately 20 percent of infected persons cleared the virus spontaneously,[24, 26, 27] the others developed chronic hcv infection. Of them, 13 percent developed end-stage-liver disease and 3 percent developed hepatocellular carcinoma.[27] Complications of hcv were the cause of death for 22 percent of deaths among Dutch persons with hemophilia between 1992-2001 [2] and for 40 percent between 2001-2018.[25] Improved selection of healthy blood and plasma donors, screening of donations and pathogen inactivation and removal techniques have virtually eliminated transmission of hiv and hcv and other pathogens of concern.[28]

A second complication of treatment with coagulation factor replacement therapy is the development of neutralizing antibodies (inhibitors) against infused coagulation factor VIII or IX. In these cases, coagulation factor replacement therapy is no longer effective in preventing or treating bleeds. It is estimated that one third of persons with severe hemophilia A develop inhibitors during their lifetime, and that this risk is higher in those using recombinant products than in those using plasma-derived products.[29] Inhibitor development occurs only rarely in hemophilia B.[5]

Finally, hemophilia treatment is costly. Several studies have assessed the cost of annual coagulation factor replacement product for persons with severe hemophilia in the Netherlands [7] and Europe.[30] The cost of the Dutch intermediate-dosing prophylaxis regimen was estimated at a mean of US$179,600 (€135,210) per patient per year,[7] and on average €199,541 in five European countries in 2014.[30]

Innovations in treatment continue to be developed, including hemostasis-rebalancing agents that target natural anticoagulants in hemostasis, such as reduction of antithrombin production and anti-tissue factor pathway inhibitor (anti-TFPI) monoclonal antibodies. Phase 2/3 studies are currently ongoing for these products.[31] Also, gene therapy for hemophilia is still under study. Using adeno-associated viral vectors, a healthy copy of the F8 or F9 gene can be delivered to hepatocytes, which then start to produce coagulation factor VIII or IX. Trials for both hemophilia A and B have shown FVIII and FIX expression since 2009 for FIX [32] and since 2015 for FVIII. Recent reports show a decline in FVIII expression over time.[33]

In summary, hemophilia may largely be viewed as a medical success story. The missing coagulation function can be replaced with either coagulation factors or by-passing therapies, even for those with inhibitors.[21] Recombinant techniques have limited

transmission of pathogens considerably, and health outcomes have improved tremendously since the 1960s.[2, 13, 25, 34-40] In the near future, gene therapy will become available to correct the coagulation factor deficiency. Yet, hemophilia continues to affect many patient-relevant outcomes, especially for those who grew up without appropriate prophylactic treatment. Long-term follow-up will show the intended and unintended effects of treatment innovations and to further improve health outcomes.

Assessing health outcomes for hemophilia

Improving health outcomes is the goal of clinical care.[41, 42] Appropriate assessment of health outcomes for hemophilia is therefore crucial in efforts to improve quality of care for persons with this condition.

Health outcomes assessment for hemophilia is complex. First, there is a large heterogeneity between patients; those with mild hemophilia are thought to have few health problems, few bleeds and a life expectancy that is near that of the general population.[2, 3] On the other hand, persons with severe hemophilia may still experience bleeding, despite the availability of prophylaxis. Both the ABR and the AJBR have improved over time, but older generations who grew up without appropriate prophylactic treatment developed arthropathy and disability.[3] Persons who contracted hiv or hcv still suffer from the consequences of these infections.[3, 26] Personalized treatment is therefore warranted. Individual patient decision-making about treatment (type of product, dose) will help optimize patient-relevant outcomes.

Second, there is heterogeneity in what is considered a health outcome. For example, health outcomes may be classified as biological and physiological factors (genotype, coagulation factor VIII or IX concentrations), symptoms (e.g. pain, swelling), functional status (e.g. limitations in self-care, occupational disability), health perceptions (e.g. about the severity of hemophilia, ability to manage treatment) and health-related quality of life [42] (HRQoL, e.g. constructs such as physical functioning, social functioning, psychological functioning and pain).[43, 44] How such health outcomes are defined and which ones are the most relevant from hemophilia patients' perspectives is largely unknown. For example, HRQoL is often poorly defined and conceptualized in research studies [45-47] and the majority of studies fail to describe which domains of HRQoL are measured.[48]

What is considered a relevant health outcome may also depend on the source of information, such as patients, clinicians, or caregivers.[49] For example, 'health outcomes' such as coagulation factor VIII or IX peak and trough concentrations are usually not directly meaningful for persons with hemophilia, but they are useful indicators of disease control for clinicians. Similarly, frequently used process outcomes to evaluate quality of care, such as adherence to guidelines or the number of patients treated,

are not relevant for individual patients.[41] Such biological and process variables are not considered true health outcomes.[41, 42] Examples of health outcomes that are often relevant to patients are physical functioning, pain, mental health and social and economic participation.[36, 50-52] Such health outcomes are called patient-reported outcomes (PROs) because they cannot be measured directly, but can only be reported by patients.[49] There may be different views on the relevance of measured health outcomes among patients and clinicians.

Finally, measuring patient-reported outcomes may be challenging. Patient-reported outcomes are measured with questionnaires (patient-reported outcome measures, or PROMs),[53, 54] that need to be valid, reliable and responsive for use in hemophilia populations.[54] Several PROMs have been developed for hemophilia, each measuring slightly different constructs, and each with different measurement properties and scoring systems.[55-57] This makes it difficult to compare health outcomes over time and between settings.

Heterogeneity among patients and types and measurement of health outcomes makes it difficult to assess the effects of health care and to identify areas for improvement. This may result in suboptimal care that is not aimed at improving the most relevant health outcomes. Calls have therefore been made to standardize health outcomes assessment for hemophilia.[58] Standardized measurement of relevant health outcomes will help optimize individualized treatment, facilitate individual decision-making and allow for comparison of outcomes across settings and over time,[5, 41, 59-61] which will contribute to improved quality of care for persons with hemophilia.

Aim and outline of this thesis

With an overall aim of improving care for persons with hemophilia, this thesis explores hemophilia outcomes and their contexts from several perspectives, using both qualitative and quantitative methods.

Part I of this thesis is about how treatment decisions affect outcomes and part II is about defining, measuring and quantifying relevant outcomes for hemophilia. In part I, **Chapter 2** describes a qualitative study in Vancouver (Canada) that aims to understand patients' experiences with a clinic program designed to encourage independent patient decision-making about dosing and frequency of prophylactic treatment. The clinic team provided personalized treatment information in visual formats to facilitate such decisions. Because these decisions have the potential to affect health outcomes, it is important to gain a better understanding of how hematologists and patients make treatment decisions. In addition to treatment decisions, persons with hemophilia also have the option to choose different types of product (e.g. coagulation factor with an extended half-life). **Chapter 3** therefore reports on a qualitative study in which Dutch persons with hemophilia were interviewed about how they view their current treatment

and, in the light of novel emerging therapies, how they would make decisions about whether or not to switch to a new treatment product.

In part II, **Chapter 4** introduces the concept of value-based health care and how it applies to hemophilia care. One of the first steps in implementing value-based health care is to define a standard set of relevant health outcomes that should be targeted in hemophilia care. The development of such a health outcomes set is described in **Chapter 5.** In this project named 'HaemoValue' an iterative nominal consensus process was performed to define the most relevant health outcomes and to make recommendations for disease-specific as well as generic instruments to measure these health outcomes. **Chapter 6** investigates structural validity, internal consistency, and construct (convergent and discriminative) validity of one of these instruments for use in hemophilia populations: the Dutch-Flemish version of the PROMIS Profile-29. The data for this study were collected as part of the sixth Hemophilia in the Netherlands study. Finally, **Chapter 7** evaluates socio-economic participation of persons with hemophilia. Using internationally recognized standards, the study described in this chapter compares educational outcomes, labor market outcomes and social participation with those in the Dutch general male population.

Study populations

The studies described in this thesis use several sources of data to explore health outcomes for hemophilia: 1) interviews conducted with persons with hemophilia, who were recruited through the Netherlands Hemophilia Society (**Chapter 3**) and through the British Columbia Adult Haemophilia Team (Canada, **Chapter 2**); 2) an international consensus project in which patient representatives, interdisciplinary hemophilia experts and researchers were involved in defining important health outcomes in the HaemoValue project (**Chapter 5**); and 3) the sixth nationwide Hemophilia in the Netherlands (HiN-6) study (**Chapters 6** and **7)**, described in more detail below.

The Hemophilia in the Netherlands studies

The Hemophilia in the Netherlands (HiN) studies are a series of cohort studies that were initiated in 1972 (Figure 2). HiN is the oldest still running hemophilia study in the world. The goal of the HiN studies is to evaluate the medical, psychosocial and economic situation of persons with hemophilia in the Netherlands.[2, 13, 34-39] Each edition of HiN consisted of a survey that evaluated important medical aspects of hemophilia, including treatment, bleeds, joint impairment and family history. In addition, each HiN study focused on topics that were relevant at the time the studies were conducted, such as home treatment (1978), hiv (since 1985), psychosocial problems (since 1992), and comprehensive care at specialized hemophilia treatment centers (2001).

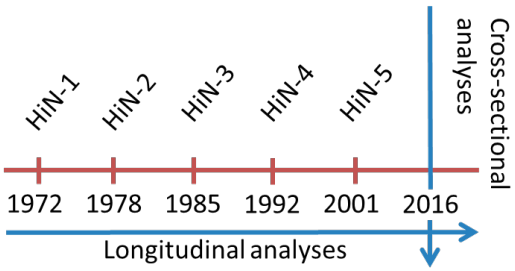


Figure 2: Overview of HiN studies

The sixth Hemophilia in the Netherlands study was initiated in 2015. A steering group was formed that consisted of representatives from all hemophilia treatment centers as well as patient representatives. The steering group was involved in the design and execution of HiN-6. The overall aims of HiN-6 are 1) to describe the health status of the Dutch hemophilia population, with special focus on viral infections, inhibitor development and age-related co-morbidities; 2) to gain insight into HRQoL; 3) to evaluate quality of care; 4) to explain the variability in clinical phenotype and 5) to gain insight into the mechanisms underlying the humoral and cellular immune response to FVIII. This thesis focuses on health outcomes and thereby addresses the second goal of HiN-6: to gain insight into HRQoL.

All male adults and children with mild, moderate or severe congenital hemophilia A or B registered at one of the six Dutch hemophilia treatment centers were invited by letter to participate. They were included during their regular scheduled outpatient clinic appointment. Data collection consisted of a comprehensive questionnaire (online or in hard copy), information collected from electronic medical records, and blood and urine sampling. Part of the blood samples and all urine samples collected were stored in a decentral national biobank to be used for future research.

The questionnaire was based on that of previous HiN surveys, supplemented with additional questionnaires that have become available since previous surveys. Separate versions of questionnaires were available for parents of children aged 0-11, teenagers aged 12-17, and adults of 18 and older. Questionnaires contained questions on demographic characteristics, socio-economic characteristics, clinical characteristics (bleeds, treatment, inhibitors, other medication, joint limitations), hiv and hepatitis C status, medical history (other chronic conditions, hospital admissions, colon cancer screening), sexuality, acute and chronic pain, needle fear, experience with care and novel treatment options. Data on age, type and severity of hemophilia, hcv and hiv status and treatment schedule were verified with data from electronic medical records. In order to ensure comprehensibility of the questionnaire, most questions about the above topics were

tested with cognitive interviews with five adults with hemophilia and with a group of children with hemophilia.

When possible, existing generic and hemophilia-specific questionnaires frequently used in hemophilia research and clinical practice were used to assess PROs. The RAND-36 (generic; health status),[62, 63] PROMIS-29 (generic; several domains of HRQoL),[64] and the Hemophilia Activities List (HAL; hemophilia-specific activities of daily living) [65, 66] were used for this thesis (Chapters 6 and 7).

The data collected as part of the HiN-6 study will provide hemophilia researchers in the Netherlands with insights from a nationally representative sample for years to come.

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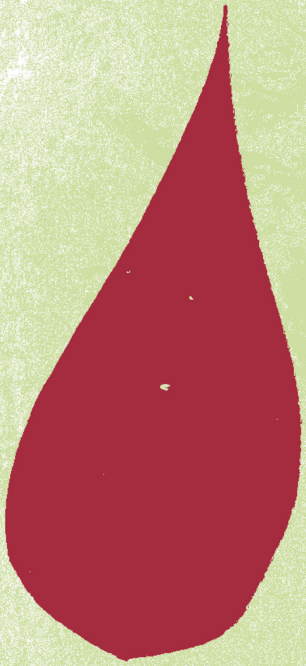
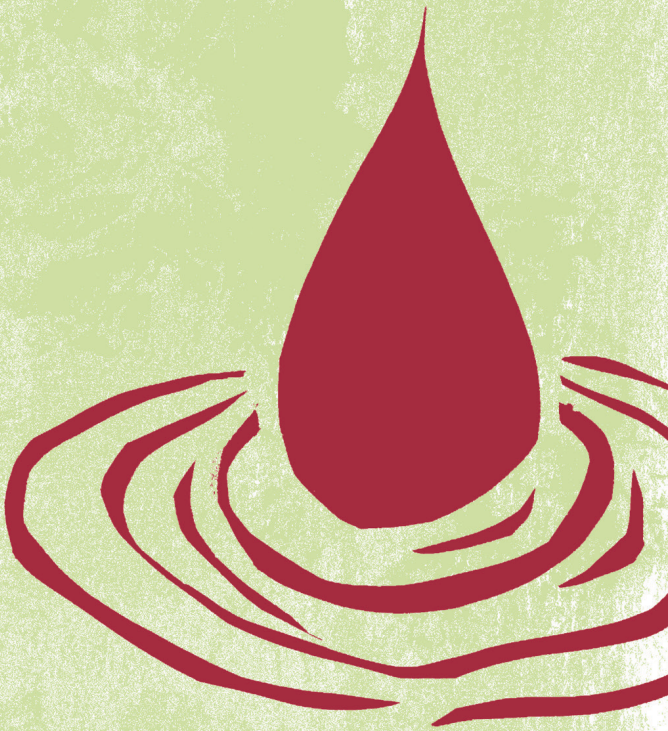


PART 1

TREATMENT DECISIONS



CHAPTER 2

Patient-centered care in hemophilia: patient perspectives on visualization and participation in decision-making

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Haemophilia. 2019;25:938–45

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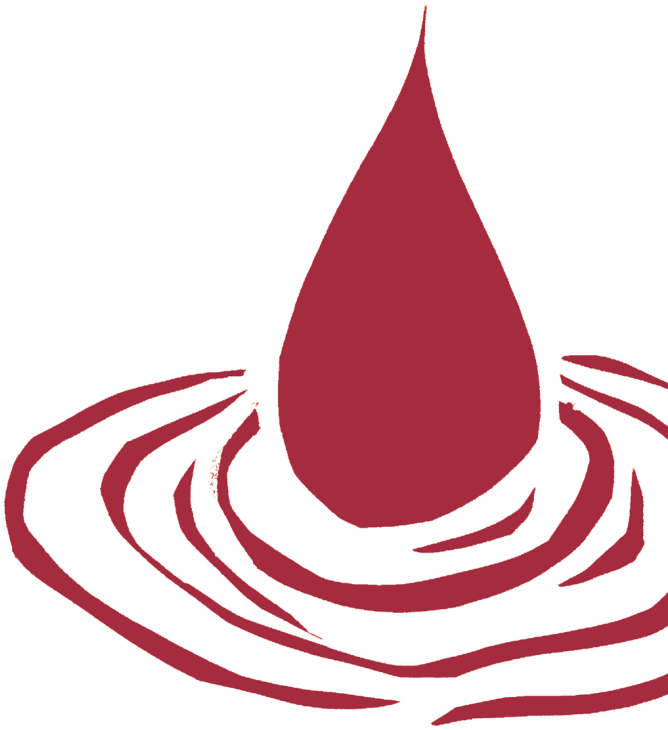

Abstract

Introduction and aim

The British Columbia Adult Hemophilia Team recently adopted a patient-centered care approach. The team presented visual information on an individual's pharmacokinetic profile and bleed history and encouraged patients to participate in treatment decisions. This qualitative study explored how this approach changed patients' understanding of hemophilia and how it facilitated them to make treatment decisions.

Methods

We interviewed 18 males with mild, moderate or severe hemophilia, using a convenience sample from the adult hemophilia clinic at St. Paul's hospital in Vancouver, Canada. Interviews were recorded and transcribed verbatim and analyzed using descriptive content analysis.

Results

Most participants reported that reviewing visual information with the clinic team helped them in their communication with their care providers during their annual review clinic appointment. Despite this improved communication, for some the most important feature of their treatment was that they had switched from on-demand treatment to prophylactic treatment in recent years and were able to prevent bleeds. Almost half of the participants reported that the visual information presented increased their understanding of hemophilia and the pharmacokinetics of coagulation factor. Three patients improved their treatment adherence or had changed their prophylaxis schedules based on this. Most participants felt they were involved in decision-making about their treatment schedule, which they appreciated. On the other hand, two participants thought the clinic team should make these decisions.

Conclusion

Participants perceived the patient-centered prophylaxis approach helpful because it enhanced communication with the clinic team, increased their understanding of hemophilia and pharmacokinetics of coagulation factor and facilitated treatment decisions.

Introduction

Over the last decades, the availability of treatment has improved life expectancy of people with hemophilia (PWH)[1] and decreased bleeding rates and joint impairment.[2]

While guidelines exist for preventing and managing bleeds, the optimal dosing strategy is variable,[3] due to differences in pharmacokinetics[4] and bleeding phenotypes between patients.[5] This variability provides an opportunity for patients to be involved in the decision-making process in their disease management,[6] for example in determining the timing and frequency of coagulation factor administration.

Patient-centered care is increasingly being promoted in order to deliver high-quality care,[7] including in hemophilia.[8] Dimensions of patient-centered care include respect for patients' preferences; coordination and integration of care; information and education; physical comfort; emotional support; involvement of family or friends; continuity and transition; and access to care.[7, 9] Research suggests that patient-centered care may positively affect patients' disease management skills, which has been shown to improve adherence and health outcomes in a range of conditions.[10, 11]

In British Columbia, Canada, some PWH had not attended a regular hemophilia review clinic recently. Also, some with severe hemophilia started long-term prophylaxis within the past 5-10 years.[12] Therefore, the Clinic Team piloted a new patient-centered "prophylaxis clinic" approach in order to improve patient engagement, individualize prophylaxis regimes, and improve health outcomes. The approach consisted of 1) a shift in focus from adherence to prophylaxis toward a more comprehensive approach that included PWH's preferences and needs to manage their lives with hemophilia, 2) sharing and discussing visuals of a patient's bleeds and treatment history, and individualized pharmacokinetic (PK) profiles where appropriate. The approach was aimed at facilitating shared decisions about treatment.

A better understanding of how PWH perceive these patient-centered strategies is needed. With this knowledge, hemophilia care can be improved further, eventually resulting in better outcomes for PWH. Therefore, we conducted a qualitative study that aimed to describe PWH's perspectives on the new patient-centered prophylaxis clinic approach.

Methods

Study design

We conducted a qualitative study in 2016 and 2017 to gain insight into perspectives of PWH on the patient-centered prophylaxis clinic. We invited people who were scheduled for their regular clinic review appointment to participate in an interview study (convenience sampling) with the intent to obtain a diverse sample of people regarding their age, self-reported type and severity of disease, country of birth and education level. Topic

lists used during the interviews included questions on participants' perspectives on how their needs were addressed, data visualization and participation in decision-making. In 2017, the interview questions were revised to reflect the change in practice of the prophylaxis clinic approach. The topic list is included in the Supplement. Interviews were recorded and transcribed verbatim.

Setting

The new patient-centered prophylaxis clinic had been piloted as part of a larger approach to engage patients, individualize prophylaxis schedules and stimulate shared decision-making for those with severe hemophilia. The prophylaxis clinic was an addition to regular hemophilia clinic appointments and consisted of a meeting between the PWH and all members of the treatment team (hematologist, nursing specialist, physiotherapist). Two types of graphs were shown on a large screen: 1) an individual PK profile and 2) treatment and bleeds frequency data. Individual PK data were obtained from the Web Accessible Population Pharmacokinetic Service; WAPPS. WAPPS can be used to simulate the effects of different dosing regimens on peak and trough levels. Treatment and bleeds frequency data were obtained from the on-line Inherited Coagulopathy and Hemoglobinopathy Information Portal; iCHIP. Examples of graphs shown during prophylaxis clinic are shown in Figures 1 and 2. More information about iCHIP and WAPPS is included in the Supplement.

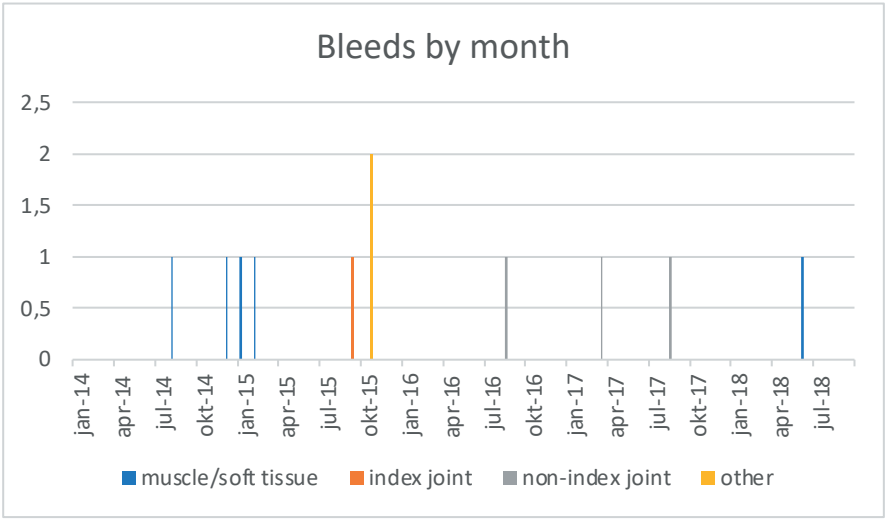

Figure 1: Example of bleeds history data from iCHIP. The presented data are based on real patient data. These patients did not participate in the interviews and provided informed consent to use their data in this paper for illustration purposes.

Dose (IU)	Infusion Interval	Peak (IU/mL)	Trough (IU/mL)	Weekly Dosage (IU)
2000	72 hr (3 Days)	0.7854	0.0571	4667

The line with hollow points shows the measured concentrations used to estimate (dashed line) the PK profile for the patient. The solid line shows the predicted PK profile for the simulated regimen.

The further the predicted (solid) line is from the measured (hollow point) line and from the estimated (dashed) predicted individual PK profile, the lower our confidence in the precision of the calculation; please consider drawing one or more samples on the new regimen to confirm the new individual PK profile.

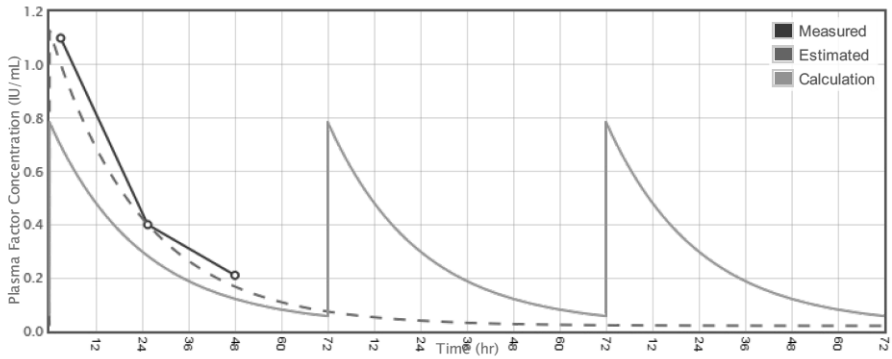

Figure 2: Example of a personal pharmacokinetic profile based on a dose of 2000 IU and a dosing interval of 72 hours. Graphs are generated based on blood samples taken at two to three time points after infusion with factor VIII or IX. The WAPPS program can then be used by clinicians to simulate the effects on peak and trough levels if different dosing regimens are chosen. The presented data are based on real patient data. These patients did not participate in the interviews and provided informed consent to use their data in this paper for illustration purposes.

The prophylaxis clinic format was piloted in 2015 and 2016. By 2017, the prophylaxis clinic approach as described above (i.e. focus on patients' needs and stimulating participants in decisions) was integrated in all clinic visits. The approach was also used for those with mild hemophilia and those treated on-demand.

Interviews and participants

The study was conducted in two phases (13 interviews in March and April 2016 and 5 in May 2017). Participants were eligible for the study if they had participated in the prophylaxis clinic (people with severe hemophilia) or if they had attended their annual review clinic in 2016 or 2017. People with mild hemophilia had not been shown individualized PK and bleed graphs during their scheduled review appointment but had an opportunity to look at anonymized PK data during the interviews. They were also asked about how the clinic addressed their needs and about their participation in decision-making.

The first author, a PhD student in clinical epidemiology and some knowledge of qualitative research methodology, and the second author, a medical anthropologist with experience in ethnographic research, conducted semi-structured interviews.

The study team approached potential participants two weeks before their scheduled outpatient clinic appointment by a letter that explained the study procedures. All invited participants provided informed consent.

Analyses

The software program MAXQDA (version 12) was used for coding and organization. Qualitative data from the interviews were analyzed using descriptive content analysis as described by Green and Thorogood.[13] The first author read and summarized all the transcripts. Several rounds of coding were applied to understand the data in their context. Then, the same researcher identified themes in the data set based on the research question. Codes and larger themes were discussed and refined through a series of analysis meetings with the research team.

Ethical considerations

Approval for this study was obtained from St. Paul's Hospital's Research Ethics Board as part of a larger study about integrating a Quality of Life Assessment and Practice Support System in Routine Clinical Practice (QPSS).[14]

Results

Participants in our study reflected the variety of people with hemophilia receiving treatment from the British Columbia Adult Hemophilia Interdisciplinary Team. Their ages ranged from 20 to 76 years old; twelve had hemophilia A and 6 had hemophilia B. Eight had severe, four had moderate and six had mild hemophilia (self-report). Of the participants with severe hemophilia, seven were on a regular prophylaxis regimen, but only one of them had been on prophylaxis since he was a child. PK data were available for six participants (one with mild hemophilia, two with moderate hemophilia and three with severe hemophilia). Three others were scheduled for PK in the near future. iCHIP data were available for eleven participants. Participants' characteristics are summarized in table 1.

Participants' perspectives were grouped into three main topics: 1) communication with the Clinic Team, 2) understanding the effects of treatment and 3) active participation in treatment decisions.

Table 1: Participant characteristics at the time of their interview

Characteristic	*N* = 18
Mean age (range), years	37.7 (20-76)
Type of hemophilia, *n*	
Hemophilia A	12
Hemophilia B	6
Severity, *n*	
Mild	6
Moderate	4
Severe	8
Treatment type, *n*	
On-demand	6
Prophylaxis	12
On home therapy	15
Education level[a], *n*	
Upper secondary education	2
Post-secondary non-tertiary	6
Bachelor	6
Master	4
Visualizations	
PK available	6
Use iCHIP	11

[A] Education levels (finished or in progress) according to the International Standard Classification of Education (ISCED)[15]

Communication with Clinic Team

All eleven iCHIP users (two with mild, four with moderate, five with severe hemophilia) reported that reviewing their treatment and bleeds history data in a visual format was useful to them. Four of them (three severe, one mild with a severe bleeding phenotype) said that it made their annual review appointment more focused, because the bleeds and infusion history data from iCHIP helped them remember the bleeds they had in the past year and the amount of coagulation factor they used. A few patients commented that they were well aware of their own bleed and infusion history because they had tracked it in the app themselves. However, they still found it useful to review this information together with the Team. As participant 6 puts it:

> *"So I think they* [the Clinic Team] *should make it available to each person to look at their own data [of their bleeds history]. I mean, I can look, of course. I can go back to the history and I can print if I want. But the way [as a graph] they had it there was good because it showed a little bit what had happened, in my case, during the last year."*

Because the interactive WAPPS program visualized the effects of infusions on trough levels for people with severe hemophilia, it also facilitated the conversation about further individualizing the patient's prophylaxis schedule.

Four participants (three severe, one mild) reported that they felt connected to the team because of iCHIP, because it automatically sends a message to the clinic when a bleed is registered (which may or may not be real-time). Although the alerts are not systematically monitored, participant 1 felt safe knowing that the clinic staff has access to his bleeds data in case he wants to discuss his bleeds:

> *"Yeah, it's useful just to keep the record of the history. You can call them* [the treatment team] *back if any injury happens, like on the same joint back-to-back. So it's nice to have."*

Nine participants (one mild, two moderate and six severe) said they felt comfortable discussing any issues with their treatment team and felt attended to in their treatment needs. Participant 7 commented that the patient-centered prophylaxis clinic approach was also useful because it improved communication about needs that were not directly treatment-related. As he explained:

> *"I think there are absolutely two sides of medicine. You know, there's a treatment side you have to understand (...) but then there's also the more personal side of medicine where you need to check in on the patients, get a sense of the patient's quality of life, how things are going for them. I thought it was useful that I was asked about how do I actually feel about having to treat myself every day"*

Though useful for most participants, three of them (two severe and one mild) pointed out that the visual information presented was of less importance compared to actual bleed prevention and treatment. Two of them had struggled with bleeds in the past and had only recently switched to prophylaxis. In the words of participant 11:

> *"And these* [visualizations] *have been really helpful with the little adjustments, but to be honest, from my perspective, the big change was just doing any kind of prophylaxis. (...) Like if I was someone who really loved molecular biology or statistics or graph making, these things might be more important. I just don't want to bleed."*

Finally, two participants (both with severe hemophilia) said it was more important for the team to track their bleeds and treatment data than it was for themselves. However, they thought they would benefit from the information in the long-term because they thought it helped the clinic team gain insight into their bleeds history.

In summary, participants felt visualizing their treatment-related data helped them better communicate with the Clinic Team.

Understanding the effects of treatment

Seven participants (two mild, one moderate, four severe) said visual information about their bleed history or PK data increased their understanding of both their condition and the effects of coagulation factor infusions. They reported a better understanding of their trough levels and how their factor levels were affected by infusion with coagulation factor. For participant 3 the visual information made him feel more comfortable because he now understood that if he had a bleed, it was because his factor IX level was low. It also made him realize that he should take prophylaxis seriously:

> *"So the more information you get, the more comfortable I think that you are. (...) So I want to know everything. (...) I just think [this is cool] information because then you can literally gauge it* [factor level] *to exactly the way that you feel and with the numbers. (...) Like, this says that you should have this much or whatever if you aren't as responsible with that* [taking prophylaxis]."

Participant 7 changed his approach based on this new knowledge of his personal PK data.

> *"It was good to see exactly how far my factors fall at the trough and then how far they spike up at their peak. And based off that, I've actually changed the way I do my infusions, day to day, a little bit."*

Participant 15 commented that tracking his bleeds and infusions helped him adhere to his prophylaxis regimen better, because he seemed to realize that bleeds occurred when he did not take his prophylaxis.

> *"When I stick in my prophylaxis treatment it's through the iCHIP program. When I was taking my prophylaxis treatment we don't see any bleeds. But then when I kind of don't enter anything* [prophylaxis] *for three or four days, we'll see that I enter a bleed in there."*

Two participants with mild hemophilia who had not had personal PK profiling themselves, had been shown sample population PK profiles during review clinic. They said they would be interested in knowing their personal coagulation factor levels before and after treatment. One participant felt the benefit might be that he would be able to continue his active lifestyle without bleeding.

In summary, patients felt visualizations helped them understand their condition and the effects of treatment with coagulation factor.

Participating in treatment decisions

A majority of ten participants (four mild, six severe) said they were actively encouraged by the Clinic Team to participate in decisions about dosing and frequency of on-demand or prophylactic treatment. They perceived they had the freedom to adjust their schedules to their needs and base it on their experience. Participant 12 explained that he has the freedom to infuse extra before physical activities.

> *"Yes, we have freedom. We can basically make that decision, which is pretty good because... They like to have us independent, which is very good, and we have at-home treatment."*

Participant 7 commented that for larger changes in his schedule, he would contact the Clinic Team. He makes smaller changes on his own.

> *"A smaller change, I might probably make the decision on my own and then comment to them* [the Clinic Team] *that, "I'm doing this now. Is that okay?" But I'd say it's quite self-directed in a way, [but] with outside influence."*

All eight participants with severe hemophilia, one with moderate and two with mild hemophilia appreciated that they were encouraged to make decisions about dosing and frequency of prophylactic or on-demand treatment. Two participants, one with moderate and one with mild hemophilia, said the doctor should make the decisions about treatment, because they were the experts. Both of these participants had experienced few bleeding problems.

Twelve participants had switched to a prophylactic treatment schedule from on-demand treatment only in the past five to ten years. They felt the decision to start prophylaxis was a joint decision with the Clinic Team. For some of them, determining dosing and frequency of prophylaxis involved some negotiation with the Clinic Team. Participant 3 felt more comfortable infusing a higher dose.

> *"I negotiate with them* [treatment team]*, and I would feel more comfortable if I did just a little bit more* [prophylaxis] *to push myself a little bit so that I'm covered completely, 100%. But they like me to just be at the level where they know that I'm okay."*

Discussion

The goal of this exploratory study was to gain insight into participants' perspectives on the new patient-centered prophylaxis clinic approach used by the British Columbia Adult Hemophilia Interdisciplinary Team. This approach included the use of visual representations of condition-related information and stimulating patients to participate in their treatment decisions. We found that this approach enhanced communication with the Clinic Team. It also increased understanding of hemophilia and treatment effects, particularly through visualizing individualized PK profiles and bleed and infusion history data. Participants also found the prophylaxis clinic approach useful because they perceived the freedom to participate in treatment decisions.

Patient-centered care is a widely-recommended practice in hemophilia.[8] Our results, based on the perspectives of patients, suggest that visualization techniques could be a helpful patient-centered care strategy. First, tools such as iCHIP and WAPPS may help increase patients' understanding, even for those with mild hemophilia. A previous qualitative study demonstrated that a better understanding determines the ability to practice prophylaxis. This, in turn, determines self-reported adherence.[16] Reviews have also shown that a better understanding improves self-management skills and adherence in hemophilia.[17, 18] In another study,[19] the use of an app similar to iCHIP was associated with an improvement in patient adherence to prophylactic treatment in one year. This resulted in increased patient quality of life (QoL) and enhanced illness perception and stabilization of joint health after one year.[19] In concordance with previous studies, PWH in our sample also reported that iCHIP served as a good reminder for their infusions, possibly improving adherence. It should be noted that aids such as iCHIP only work if PWH are engaged in their care and feel comfortable to accurately record their data.

A second benefit of the prophylaxis clinic approach is that it may improve patient-clinician communication, strengthening the relationship. This patient engagement was an important objective of the British Columbia Adult Hemophilia Interdisciplinary Team. Both people with severe and with non-severe hemophilia in our sample found it useful to use visuals in their interaction with the Team. Indeed, a good relationship between care providers and PWH has been found to be associated with treatment adherence in hemophilia.[17, 18]

A third potential advantage of the prophylaxis clinic approach is improved patient participation in decisions about their treatment schedules. The Team has encouraged people with severe hemophilia to switch to prophylaxis from on-demand treatment. Participation in decision-making may improve adherence and reduce bleeds,[12] as some participants in our sample reported. Whether this leads to an actual improvement in outcomes needs to be investigated further. As life-long experts, PWH may feel they have the knowledge to make their own treatment decisions. Indeed, in our study, many PWH

perceived they had the freedom to make their own decisions. Making decisions about dosing and frequency of prophylaxis or on-demand treatment is important in hemophilia due to the lack of a standard treatment regimen and inter-individual differences in response to treatment.[3-5] Decision aids such as pamphlets, videos or web-based tools can be used to support treatment decisions. Information about different options and their harms and benefits may be presented in graphical formats.[20, 21] Several decision aids have been developed for hemophilia.[22] Yet, to the best of our knowledge, we are not aware of any tools available for decisions such as setting a treatment schedule. Naturally, these tools are particularly relevant for those on prophylaxis. Also, people with mild hemophilia may benefit from a better understanding of how their factor levels change after an infusion. This may make them feel more comfortable in managing a bleed, including altering their physical activity during recovery.

A limitation of our qualitative study is that we cannot quantify the effect of the patient-centered prophylaxis approach on health outcomes. Another limitation is that clinical factors such as joint status, duration of prophylaxis use and background bleeding phenotype likely affect how patients perceive patient-centered engagement efforts. Though we aimed to include a variety of patients, we may not have captured all possible patient perspectives. Still, this qualitative study helps understand how investing in the approach may positively affect self-reports of patient outcomes such as satisfaction with care, a good relationship with the team, a better understanding and improved self-management skills. Further research is needed that quantitatively measures hemophilia outcomes longitudinally.

Another potential limitation of this study is that the convenience sampling approach makes it more likely to include PWH who are already willing to accept their condition and its treatment and engage with the Clinic Team. However, we included a variety of PWH, including a few that had not been to clinic in recent years, thus representing perspectives of those who had not yet established a long-term relationship with the Clinic Team.

Conclusion

Participants reported that the use of tools to visualize bleeds history and pharmacokinetic data enhanced patient-clinician communication. Also, it enabled PWH to better understand hemophilia and its treatment. Participants felt they were involved in decision-making about their treatment. Some of them found that the tools helped them to make better informed decisions about their treatment. This patient-centered approach may help improve care in hemophilia.

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Supplement

Topic list with interview questions (2017)

Introductory / ice-breaking questions
Can you tell me what it is like to live with hemophilia?
What does your hemophilia care look like? (go through clinic appointment, what happens, what is discussed)
Quality of life
What topics related to living with hemophilia should be addressed during your clinic appointment?
Information sharing
What type of information do you receive from the clinic team, and in what format?
What type of information has been or would be the most helpful or educational for you and why? (does it address needs and concerns, why or why not, how to deliver this information)
Decision-making
Can you describe how you make decisions about your care?

Topic list with interview questions (2016)

1. The hemophilia team has started a prophylaxis clinic that uses visual aids to chart your bleed history, factor utilization, and quality of life.
a. Do you like the information being presented in this way?
b. If yes, what do you like about the information being presented this way?
c. If not, what don't you like about the information being presented this way?

2. What is the most important information about your hemophilia that you want to know about?

3. What is the most important information about your hemophilia that you want the team to know about?

4. What is the most important information about your hemophilia treatment and support that would help you to determine if it is the best it can be?
a. Is there additional or alternate information that is not currently collected that the clinic should be collecting and reporting back to you about?

5. How do you think this information can be used by yourself and the clinical team to make shared decisions about your treatment?
a. How would you like to see this information used in your care planning?

6. Were you a participant in the recent project using the handheld tablets?
a. If so, do you feel that they could be used in regular clinics to make your visit more efficient or educational for you?
b. Can you describe any other ways of visualizing your data that would be helpful to you?

7. Would you like the ability to create your own reports using data from other sources (e.g. iCHIP)?
a. If yes, would you want to be able to send them to the clinic team and have them be part of the clinic appointment?
b. If no, why not?

8. What do you think of having the prophylaxis clinic through a video link where you could see both visualized data and clinic staff from your home computer?

9. What do you feel have been the most important changes in your hemophilia care in recent years?

10. How has your quality of your day to day life changed since you've started prophylaxis?

11. Do you feel that attending the prophylaxis clinic, in addition to the regular review clinic, has improved your hemophilia care?
a. Why or why not?
b. Do you feel any different in your relationship with the team as a result of attending the prophylaxis clinic in addition to the regular review clinic?

12. Is there anything else you can think of that the team can do to improve your quality of life?

Examples of graphs shown in clinic

Most people with moderate or severe hemophilia in British Columbia use iCHIP for recording bleeds and factor use available as a smartphone app. The Team can review summary data during clinic appointments with PWH. The system can send an alert to the Clinic Team when a bleed is entered, however the arrival of the alert is dependent upon when the patient chooses to enter the data, and therefore often not "real-time". Personalized PK profiles had been created by WAPPS for five people in our sample (four people with severe hemophilia and one with mild hemophilia but a severe bleeding phenotype). The program was used to show peak and trough coagulation factor levels if frequency or dosing are changed.

The presented data in the iCHIP and WAPPS examples are based on real patient data. These patients did not participate in the interviews and provided informed consent to use their data in this paper for illustration purposes.

CHAPTER 3

Patient perspectives on novel treatments in hemophilia: a qualitative study

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The Patient. 2020;13:201-10

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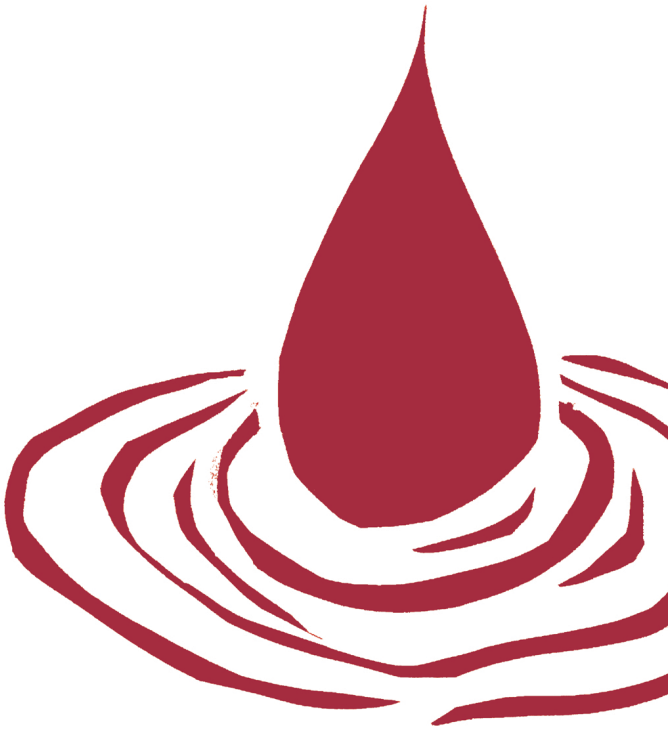

Abstract

Introduction and aim

New treatments for hemophilia are under development or entering the market, including extended half-life products, designer drugs and gene therapy, thereby increasing treatment options for hemophilia. It is currently unknown how people with hemophilia decide whether or not to switch to such a new treatment. Therefore, we aimed to explore what factors may play a role when Dutch patients and parents of boys with moderate or severe hemophilia make decisions about whether or not to switch to a different treatment, and how disease and treatment characteristics may affect these decisions. This may aid clinical teams in tailored information provision and shared decision-making.

Methods

We conducted interviews among adults with moderately-severe or severe hemophilia and parents of young bots with severe hemophilia. We aimed to include participants from a variety of backgrounds in terms of involvement in the hemophilia community, age, treatment center and treatments. Participants were recruited through the Patients Society and a hemophilia treatment center. Semi-structured interviews were recorded and transcribed verbatim. Thematic content analysis was used to analyze the data.

Results

Twelve people with hemophilia and two mothers of boys with hemophilia were included. In general, participants reported to be satisfied with their current treatment. However, they considered ease of use of the medication (fewer injections, easier handling, alternative administration) an added value of new treatments. Participants were aware of the high cost of coagulation factor products and some expressed their concern about society's long-term willingness-to-pay for current and novel treatments, especially for increased usage due to high-risk activities. Participants also expressed their concerns about short-term and long-term safety of new treatments and believed the effects of gene therapy were not yet fully understood. Participants expected their treatment team to inform them when a particular new treatment would be suitable for them.

Conclusion

With the number of treatment options set to increase, it is important for health care providers to be aware of how patient experiences shape patients' decisions about new therapies.

Introduction

Hemophilia is a rare congenital coagulation disorder caused by a deficiency in either factor VIII (hemophilia A) or factor IX (hemophilia B), affecting 1 in 10,000 live births.[1] Hemophilia is classified into severe hemophilia (< 1 percent of normal), moderate hemophilia (1 to 5 percent of normal) and mild hemophilia (5 to and 40 percent of normal).[1, 2] The lack of coagulation factor VIII or IX causes spontaneous bleeds in patients with severe hemophilia, mainly into joints and muscles, causing debilitating and painful joint damage.[3] Treatment has evolved from whole blood transfusions prior to the 1960s to modern concentrated recombinant factor VIII and IX products. The deficient coagulation factor is administered two to three times a week by intravenous injection to prevent bleeds (prophylaxis). Unfortunately, many people with hemophilia were infected with hiv and / or hepatitis C (hcv) through whole blood products in the 1980s and early 1990s.[4] In the last few years, products with an extended half-life (requiring less frequent administration) have become available. The availability of treatment has improved life expectancy of people with hemophilia (PWH) [1, 5] and decreased bleeding rates and joint impairment.[6]

Despite these advancements,[6] a cure for hemophilia is not widely available yet and current treatment is still far from optimal. According to patients, products could be improved for frequency of administration,[7] efficacy of coagulation products (preventing bleeds),[8] mode of administration,[7] easier storage,[7, 8] fewer side effects (potential transmission of pathogens, antibodies against infused factor VIII or IX) and package (size, components of medication, logistics).[7, 8] Intravenous infusion of coagulation factor may pose a problem, especially for young children with delicate veins or for older people, for example due to increased difficulty in self-administration with increasing age.[9]

New treatments are under development or have recently been marketed that aim to address the disadvantages mentioned above, such as products with an extended half-life, gene therapy and products that affect the coagulation cascade through different mechanisms than replacing the absent coagulation factor. Some of these products may be administered subcutaneously and no longer require intravenous injections. However, new treatments may have drawbacks of their own, including known and unknown risks, as summarized in table 1.[10-14]

The Netherlands is a small country with high-quality health care and social security systems. The cost of coagulation factor is covered under public health insurance, with a deductible for specialist care. Several Factor VIII and Factor IX products are available to patients and providers. People with hemophilia receive care from one of six Dutch Hemophilia Treatment Centers and most people with severe hemophilia attend their clinic appointment annually.

Table 1: Overview of hemophilia A and B treatment products currently under development or marketed recently, with their benefits, potential disadvantages and mechanism of action.[10-14]

Type of product	Mechanism of action	Potential benefits	Potential disadvantages	On the market in the Netherlands
Extended half-life	Suppletion (Fc-protein or albumin fusion, PEGylation, albumin fusion decrease clearance)	Fewer infusions Higher trough levels	Fewer peaks for high-risk activities (e.g. sports) Unknown side effects of the accumulation of PEGs	Yes, since 2016
Non-factor coagulation replacement therapy	Bispecific antibody that links activated FIX and FX, mimicking the function of FVIII (emicizumab)	Option for persons with Hemophilia A (with or without inhibitors) No inhibitor development against FVIII Subcutaneous administrations Long half-life Excellent bleed control	Long-term risks still unknown Non-neutralizing antibodies against emicizumab Thrombotic complications (if combined with FEIBA) Cost	Yes (for patients with inhibitors only), since 2018
Products that rebalance the coagulation scale	Inhibition of TFPI (concuzimab), antithrombin (fitusiran) or activated protein C	No inhibitor development against FVIII or FIX Mode of administration Frequency of administration Long half-life	Thrombotic complications (fitusiran)	No, phase III trial
Gene therapy	(AAV) viral vector transfers FVIII or FIX DNA to liver, where it is expressed	Potential 'cure' for hemophilia, transforming severe into mild hemophilia or normality. No need for prophylaxis with factor concentrates.	Vector insertion into host genome Cancer (never observed in AAV-based gene therapy) Liver inflammation (transaminitis)	No, phase III trial (Hemophilia B) or phase I (Hemophilia A)

TFPI: tissue factor pathway inhibitor; AAV: adeno-associated virus

It is currently not sufficiently known which factors play a role in patients' decisions about whether or not to switch to a new therapy. Previous internet surveys conducted in Australia, Canada, the U.S. and Sweden reported that the frequency of clotting factor treatment administration,[15, 16] efficacy to prevent bleeds,[15, 16] manufacturer of the product,[15] and shared decision-making.[16] Finally, a study in Germany, Austria and Switzerland found that parents were more hesitant to switch to an extended half-life product than patients.[8] However, these questionnaires mostly presented a finite number of factors that may play a role in decision-making. Questionnaires also provide little information on how individuals' personal backgrounds (e.g. age) and their disease and treatment characteristics and experiences (e.g. bleeds history, experience with self-administration of coagulation factor, history of blood-borne infections) may affect decision-making. A better understanding of all factors that may play a role in decisions about treatment (both treatment and personal characteristics) will help hemophilia care providers provide tailored information when making shared decisions on the optimal management strategy of hemophilia,[17, 18] all of which are elements of patient-centered care.[19-21] Therefore, we aimed to explore what factors may play a role when Dutch patients and parents of boys with moderate or severe hemophilia make decisions about whether or not to switch to a different treatment, and how disease and treatment characteristics may affect these decisions.

Methods

Study design

We conducted a qualitative study among people with hemophilia A or B or parents of young boys with hemophilia A or B, using interview methods. We aimed to include participants with varying involvement in the hemophilia community, age, treatment center, and dosing, type and frequency of treatment (purposive sampling).[22] Prior to the interviews topic lists were prepared based on literature and clinical experience. These included questions about current and novel treatments, burden of hemophilia and its treatment and involvement in decision-making. Interview questions were revised iteratively after each interview so that new interesting issues that were raised could be explored in future interviews.[23] The topic list is included in the Electronic Supplemental Material.

Recruitment and data collection

Participants were approached through the Dutch Hemophilia Patient Society by an advertisement in a private Facebook group moderated by the Patient Society and the quarterly e-mail newsletter to members. Participants were also approached with an invitation letter of the hemophilia outpatient clinic of the Amsterdam University Medical

Centers, the Netherlands, or through word-of-mouth. After a positive response, interviewers introduced themselves over the phone and an appointment was established.

Authors BB and MLW, undergraduate students in health sciences with some experience in interviewing, conducted semi-structured interviews between March and December 2017 at the participants' homes. The number of interviews was pre-determined to be 12 to 14. A sample size of 12 to 15 is considered sufficient to understand participants' experiences in thematic content analysis.[23] Interviews lasted between 37 and 82 minutes and were audio-recorded and transcribed verbatim.

Analysis

Thematic content analysis [23] was used to analyze the data. All interview transcripts were initially coded using open coding with the software program MAXQDA version 12 (http://www.maxqda.com). Three researchers (EvB, BB, MLW) discussed codes and agreed on a coding scheme, which was then applied to all transcripts. Codes were organized into main topics and reorganized into themes that were relevant to the research question, creating a thematic map. This map consisted of themes related to experiences with current and past treatment, reasons for whether or not to switch to new treatment options, and sources of information for these decisions. Within themes, we looked for differences and similarities between participants. Authors EvB, JvdB, SG and MJW discussed final codes and themes. Quotes were extracted to illustrate aspects of themes using participants' own words.

Ethics

Exemption from full dossier ethical approval was obtained from the research ethics board at the Amsterdam University Medical Centers. All participants provided written informed consent.

Results

Participants

Of 14 individuals who participated, 12 had moderate or severe hemophilia. Two were mothers of children with severe hemophilia (aged 7 and 10 years). The 14 participants reflected a variety of the Dutch population with moderate and severe hemophilia in terms of age, treatment center, needle fear, hiv and hcv infection status, perceived involvement in decision-making and membership of the Dutch Hemophilia Patients Society (table 2). Thirteen participants were on home-treatment (12 prophylaxis, one on-demand). One participant did not self-infuse but visited the hospital when he had a bleed. All used standard half-life recombinant coagulation factor products.

Table 2: Participant characteristics

Participant number	Age group[a]	Severity and type of hemophilia	Type of product (standard half-life recombinant coagulation factor concentrate)	Reported needle fear	Hiv or hcv infection	Perceived involvement in decision-making[b]	Member of Patients Society
P1	65-70	Severe HA	Prophylaxis, 500 IU daily	No	hcv (cleared)	Yes	Yes
P2	70-75	Severe HA	Prophylaxis, 1000 IU, 2 times per week	Yes	hcv	No	Yes
P3	25-30	Severe HB	Prophylaxis, 1000 IU, once every 4-5 days	No	hcv (cleared)	Yes	Yes
P4	Child <12	Severe HA	Prophylaxis, 750 IU, 3 times per week	Sometimes	None	No	Yes
P5	65-70	Moderate-severe HA	On-demand (mild phenotype)	No	None	Yes	Yes
P6	Child <12	Severe HA	Prophylaxis, 500 IU, 3 times per week	No	None	Yes	Yes
P7	40-45	Severe HA	Prophylaxis, 2000 IU, every other day	No	hcv (cleared)	Sometimes	Yes
P8	60-65	Severe HA	Prophylaxis, 1000 IU, 3 times per week	No	hcv (cleared)	No	Yes
P9	20-25	Severe HA	Prophylaxis, 1000 IU, 2-3 times per week (but irregular)	No	None	Yes	No
P10	60-65	Moderate-severe HA	On-demand (mild phenotype)	Unknown	hcv (cleared)	No	Yes
P11	55-60	Severe HA	On-demand (mild phenotype)	No	hcv (cleared), hiv	No	No
P12	35-40	Severe HB	On-demand (mild phenotype)	No	hcv	No	No
P13	25-30	Severe HA	Prophylaxis, 1500 IU, every other day (but irregular)	No	None	No	Yes
P14	55-60	Severe HA	Prophylaxis, 1000 IU daily	No	hcv (cleared)	No	No

HA: hemophilia A; HB: hemophilia B; IU: international units

[a]Participants' ages are presented in age groups to protect their privacy.

[b]Participants were asked whether they felt they were involved the decision-making about product and dose.

The results are described in three themes: 1) Current treatment, experiences and perspectives, 2) Factors related to deciding to switch to a new therapy, and 3) Sources of information regarding novel treatments.

Current treatment, experiences and perspectives

Experiences with current treatment were mostly positive, but self-administering treatment was sometimes described as a challenge.

In general, participants reported that current coagulation factor treatment was easy to administer, safe and effective in preventing bleeds. Younger participants reported it had always been part of their daily lives. On the other hand, older participants remembered that in the past treating themselves was more burdensome than nowadays because of the larger volume of past products, the need to carefully mix components of the medication and the longer time it required to infuse intravenously. They appreciated how much easier administration had become. Those on prophylaxis all reported that they adjusted their infusion schedules depending on their daily activities, but considered themselves adherent.

Three individuals in their 60s and 70s (P1, P2 and P8) said injecting at home had become more difficult in recent years due to scarring of the injection site or reduced eyesight. Participants 8 and 13 commented that self-infusing could be 'a hassle', and participant 8 found ordering, picking up and storing the treatment product quite an effort. Two participants sometimes experienced slipping of the needle from the injection site. One of the mothers said she sometimes felt pressure to perform the venipuncture when her son had an acute bleed.

All participants were aware that new treatments had recently become available or were under development. Despite the challenges they described with their current treatment, they said they did not need new products for themselves, but welcomed this development.

Many participants were aware of the high costs and tried to use their products responsibly. Eight participants (six on prophylaxis, two on-demand) spontaneously mentioned the current high costs of their coagulation factor products. The six participants who were asked about costs were aware that their treatment was expensive. Interestingly, six participants (three on on-demand treatment) reported that they avoided injections when possible in order to save costs for the health care system, against their physician's advice to take their coagulation factor when they needed it.

Participants reported to be grateful that the cost of their coagulation factor was covered by the health care system. Some were concerned about a perceived societal trend in which patients are increasingly responsible for their own health care costs. Participant 2, for example, remembered that sufficient amounts of coagulation factor were not always available in the past:

> *"It is a concern to me, because I can imagine [...] that treatment will become scarce again.* [The availability of] *treatment is not a given if costs get out of control. We are dependent on the solidarity of society"*

Furthermore, three of the older participants (P1, P2 and P8) expressed their concerns about younger patients engaging in physical activities such as skiing, soccer and mountain biking, because the costs of the increased prophylactic coagulation factor usage are for society. They thought the availability of hemophilia treatment may ultimately depend on society's willingness-to-pay for this increased usage. On the other hand, one of the mothers and four other younger participants said practicing sports should be possible for persons with hemophilia as long as they were careful and used prophylaxis. One young participant wondered about the costs of new extended half-life products:

> *"You would save a lot of injections* [with EHL products]*, and I don't know whether that would outweigh the higher costs of [this] new product. I don't mind the injections, I don't mind to infuse a bit more often, [...] I wouldn't necessarily want to do that* [higher cost] *to society".* (participant 3)

Factors related to deciding to switch to a new therapy

When asked, eight participants were open to trying new treatments (although some felt they did not urgently need them). Three younger participants (P9, P12, P13) with few bleeding problems (two on prophylaxis with irregular schedules, one on-demand) did not feel the need to switch because they were satisfied with their current treatment. The two mothers expressed a wait-and-see attitude for novel treatments because at the time of their interviews they thought new treatments would not be available soon, and they did not want to be the first to try a new therapy because of potential unknown risks. Decisions on whether or not to switch to a new therapy were multifactorial and not self-evident. Factors that may play a role in these decisions are summarized in table 3. Facilitating factors were improved ease of use of medication and better efficacy. Barriers were fear of unknown (short and long-term) safety and efficacy, and not wanting to be a research subject if there were risks involved. Below, we highlight some factors that shape participants' treatment decisions and describe them in more detail: ease of use of the medication and fear of the unknown.

Table 3: Factors that may play a role in making decisions about switching to new therapies

Reason	Barrier/facilitator	Key points
Ease of use of the medication	Facilitator	The ease of use of the medication could be improved by: easier to carry, store and mix. less frequent injections, or a (perceived) lack of need for injections altogether with a cure. alternatives for intravenous injections: other locations for injecting (subcutaneous) or alternative administration routes (tablet or nasal spray).
Equally good or better bleed prevention	Facilitator	A new therapy should: provide protection against bleeds that is at least as good or even better than their current therapy. have sufficiently high peak and trough levels.
Fear of the unknown	Barrier	Participants were concerned about still undiscovered transmittable pathogens and antibody development. For gene therapy, they were concerned about long-term safety of the therapy and thought these effects were not yet fully understood.
Do not want to be a guinea pig / research subject	Barrier	Participants felt uncomfortable to participate in a trial because of unknown risks or to be the first to try a new therapy.

Facilitator: Ease of use of the medication

A majority of eight participants (of whom seven had been co-infected) mentioned that they preferred to inject less frequently. Three young adults (participants P3, P9 and P13) who reported no problems with their current injection schedules viewed fewer injections as an added value to new therapies that they were looking forward to, but they did not consider fewer injections to be absolutely necessary for them. They each mentioned an example of others for whom extended half-life products with lower injection frequency would be especially valuable: for children, for a brother who was not as adherent, or for others who had more bleeds. Participant 1 reported to look forward to being able to inject every three days instead of daily, which he expected to be a reality in five years. For another older participant (P2) with a hepatitis C infection in the past, each injection meant a presumed infection risk and for this reason he was looking forward to any reduction in injection frequency.

Participants 3 and 12 would prefer a cure for hemophilia instead of fewer injections, although they said they had few bleeding problems. Furthermore, participant 8, who was reluctant to switch because of his experiences with hepatitis C treatment in the past, commented that he would only switch if the frequency of injections of extended half-life products was considerably lower:

> *"If I had to switch to a different medication, I would switch to one with a longer half-life. That would be a bit better for me so I have to inject less often. But the savings* [in half-life] *are not that big [...], from 14 to 17 hours. I didn't think that was very impressive. For that reason I have not switched this time."*

Other reasons participants wanted to inject less frequently were the effort it required to plan injections and carry and store their coagulation factor products. For example, participant 12 travelled frequently for work and thought the packaging should be easier to carry with him. Participant 13 proposed alternative locations for his intravenous injections, such as a finger or a thigh. When asked about their recommendations for drug development companies, several participants also suggested different administration routes such as a tablet, a nasal spray, an ingestible nanotube with coagulation factor or a subcutaneous device as alternatives.

Barrier: Fear of the unknown

A few participants were concerned about potential risks of new coagulation factor products, such as inhibitor development and potential undiscovered transmittable pathogens. For extended half-life products, participants 8 and 3 expressed their concerns about having a low trough level for a longer time than with standard half-life products, making them more vulnerable to bleeds. A young participant (P3) was not convinced safety was properly studied. On the other hand, he and one of the mothers were willing

to try an extended half-life product because they thought they could always return to the standard half-life product.

Many participants thought gene therapy was promising, but they were also concerned about its long-term safety and the risks of adverse effects.

> *"It's a virus that you inject in your body, which may cause a liver infection, which would have to be inhibited with corticosteroids.[...] On the other hand, it's such a temporary side effect, and if you benefit from that the rest of your life..."* (participant 3)

An older participant (P2) said he was hesitant to switch to a new treatment, because he currently used a product that was effective in controlling bleeds, and he did not want to risk replacing his current treatment for one with uncertain effects. He considered the experience of two others with hemophilia who had undergone gene therapy as part of a trial in his decision:

> *"I know two guys that participated in a gene therapy trial. One was out of luck, he didn't achieve higher factor levels. The other one did. Yes, fantastic if it works. [But] they don't know it yet. [...] So you have to ask yourself... [...] it would be a pure gain if it works. On the other hand, if you have good treatment, why would you change it?"* (Participant 2)

When asked, participants often mentioned they wanted to be well informed about possible risks and side effects when making decisions about new treatments.

Sources of information regarding novel treatments

Participants reported that their most important source of information was their physician or nurse. Six of them (all age groups, members and non-members, different perceptions of involvement in decision-making) said they discussed the development of new therapies with their treatment team during their clinic appointment and trusted that their physician would inform them at the time a particular new treatment was suitable for them.

> *"The doctors are specialists [...] and at some point they'll say: 'hey, we have this new treatment for you', so I'll say: 'sure, bring it on!'" (participant 11)*

Those who were members of the Dutch Hemophilia Patients Society also expected the society to provide information about the types of treatment that are under development. Participants regularly received information from this source, for example from annual general meetings, the society's website, Facebook page, annual camping weekend and their biannual magazine. Some participants were active in the Facebook group and used it to exchange experiences with peers. Participant 11, on the other hand, was not particularly interested in the information provided by the patients' society.

A few people also searched for information on the internet. However, participant 14 said it was difficult to know what terms to search for and participant 8 said information from other countries, with their different care settings, was difficult to apply to his own situation.

Discussion

In our interview study we found that people with moderate or severe hemophilia and parents of young boys with hemophilia were generally satisfied with their current treatments. They considered different aspects of novel treatments important in their treatment decisions, including ease of use of the medication, better bleed control and safety. However, some participants shared concerns about unknown risks of new therapies. As an additional finding, the financial burden of current treatment on the health care system appeared to be a concern for a few participants, because they felt societal willingness to pay might not be a given in the future. Participants wished to receive information about new treatments, including their risks and benefits from the Patients Society as well as their hemophilia treatment team.

Previous studies have identified similar considerations of persons with hemophilia as important features of extended half-life products.[8, 16] For example, in assessing a series of hypothetical treatment scenarios with three treatment attributes each (injection interval, participation in physical activity, annual risk of bleed), patients and parents of boys with hemophilia ranked bleed control as the most important.[16] Another questionnaire study about expectations and concerns of extended half-life products reported injection frequency to be the most important feature of these products.[8] Our study enriched this knowledge by describing the reasons for the desire for a lower injection frequency: a presumed infection risk, planning injections and not having to carry and store treatment products. Interestingly, many participants considered themselves adherent even though they skipped infusions, and found treatment products with lower injection frequency especially suitable for 'others'.

An interesting finding is that the societal financial burden of current hemophilia treatment is a concern for some participants. Costs of current treatment have been identified as an important feature of hemophilia treatment in previous discrete choice experiments that aimed to elicit patient preferences.[24, 25] Several participants in our study tried to save costs for the health care system. Older participants appeared to be more conservative in allowing people with hemophilia to engage in high-risk activities than younger participants. Unlike older generations, younger participants grew up with treatment available and may therefore consider it a given. One participant spontaneously mentioned his concern for the cost of new therapies specifically. Given that the costs of current treatment were important to most participants, it is probable that costs also play a role in decisions about novel therapies. In the Netherlands, the cost

of coagulation factor is covered by the health care system, but all participants in our sample were aware of the high costs and some even tried to save costs by avoiding self-infusion, even when they had a bleed. Possibly, recent media attention surrounding health technology assessments, pricing and reimbursement decisions for expensive drugs in rare diseases may have shaped participants' opinions.[26] Costs of future novel treatment options, for example of gene therapy, are still unknown, making this difficult to address in patient-clinician interactions. However, it may be of value to patients if care providers are able to share what they do and do not know about costs of current and future treatments.

Knowledge about which features of novel treatments are important, including real and perceived risks such as pathogen transmission, may help the hemophilia treatment team tailor information provision and patient education efforts. In order to structure this information in these interactions a shared decision-making tool may be used. An interactive digital platform may further personalize information provision. Our findings may serve as a starting point for the contents of a shared decision-making tool. We suggest to explore this further in focus groups of patients and caregivers of patients.

Strengths and limitations

A strength of our study is that it included a variety of perspectives on new treatments, illustrated by quotes. We purposively included people of different ages, including parents of young boys, and with varying involvement in the hemophilia community (active or no membership of the Dutch Hemophilia Patients Society). This was done because we presumed differences in knowledge of new treatments. We also considered it important to include parents of young boys with hemophilia to explore how they viewed treatment decisions for their sons. Although the disease context of mothers is different from that of patients, we included them because they are responsible for making treatment decisions on behalf of their sons. In line with previous research,[8] the mothers in our sample were somewhat more hesitant than patients to switch to a new treatment. Our study adds that this was because they preferred to wait for more information to become available on effectiveness of these treatments.

A potential limitation may be that the first six participants responded to an advertisement through the Patients Society and therefore may have been better informed and more interested than average to discuss their views on treatment. Therefore, in order to obtain perspectives of representatives of the complete hemophilia community, the next eight participants were approached through the outpatient clinic at the Amsterdam University Medical Center. In both groups, participants knew about gene therapy and extended half-life products, but other options, such as by-passing agents or other non-factor replacement treatments, were not mentioned.

A second limitation may be that participants could have expressed a more positive satisfaction with their current treatment than their true experience. Participants were

interviewed at their homes by two investigators relatively new to the field of hemophilia, and the experiences participants shared about their current treatment may have been more positive than what they would have shared with their own care provider. However, our aim was not to elicit all possible problems participants may experience with their current treatment, but to explore the factors that may play a role in patients' and parents' decisions about current and new treatment options.

Lastly, extended half-life products and non-factor replacement products have become available in the past two years. It is possible that participants are now better informed about these novel therapies than they were at the time of their interviews. Participants' perceptions may have changed as a result of this: acceptability of newer products may have increased. However, we believe that many of the concerns expressed may be applicable to decisions on any type of treatment product switch, regardless of whether the switch is made to a novel therapy or an existing one.

Conclusion

New treatments for hemophilia are becoming available in the next few years, increasing the number of options patients and providers can choose from. Patients have a voice in these decisions. We confirmed previously identified barriers and facilitators that play a role in making these decisions, and added that costs of treatment may play a role. It is important for hemophilia treatment teams to be aware of these factors in providing information to facilitate shared decision-making.

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Supplement

Topic list for interviews[1]

Questions that were added after the initial interviews are underlined

Opening questions:

1) Please tell me a bit about yourself
2) Type of haemophilia

Questions below were phrased as 'In the past.... How is that going now?' and 'Some people say they need a change, others are satisfied with the way things are. How is that for you?'

Past

- History of disease
  - Co-infections, inhibitors
  - Can you feel the start of a bleed?
- History of treatment
  - Treatment schedule
- What went well / bad?
- Do you still notice the consequences?
  - Impact on daily life
  - View on treatment

Today

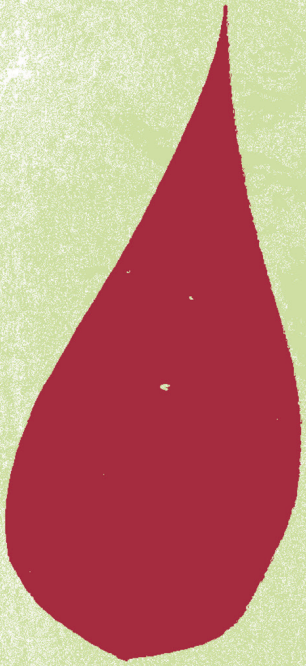
- How do you experience your current treatment?
  - Impact on daily life
  - Treatment of the consequences of haemophilia (e.g. physiotherapy)
  - Costs
- What goes well / bad?
  - Needle fear
  - Adherence
  - Specific situations
  - Advice on lifestyle (agreement?)
  - Logbook
  - Social life
- Freedom of choice in treatment
  - Who decides?
  - Relationship treating physician (has it changed?)
  - Does care provider share knowledge / provide information?
- Which aspect of treatment would you change?
  - With whom to share this?
  - In contact with other patients?

Future

- Opinion new therapies
  - What do you need? (mechanism, mental health, clinic review)
  - Reasons whether or not to switch
  - Other needs?
- Knowledge of new treatments
  - Source of information
  - Information needs
  - Influence of treating physician
- Willingness to participate in research
- Ageing independently
  - What do you need for that?

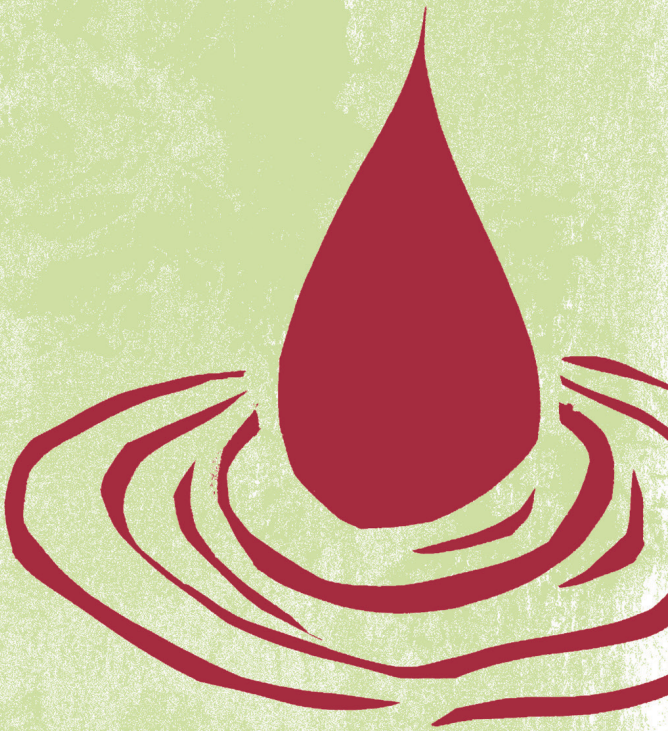
Ending questions:
Looking at the past, the present and future, what advice would you give to drug development companies?
Information about respondent (age, education, which treatment centre, member of Patients Society)

[1]Because of the exploratory nature of this study, the topic list contains more questions than can be addressed in the paper. In the results section, we focus on the topics most relevant to the research question.



PART 2

DEFINING, MEASURING AND QUANTIFYING OUTCOMES



CHAPTER 4

Defining patient value in hemophilia care

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Haemophilia. 2018;24(4):516-8

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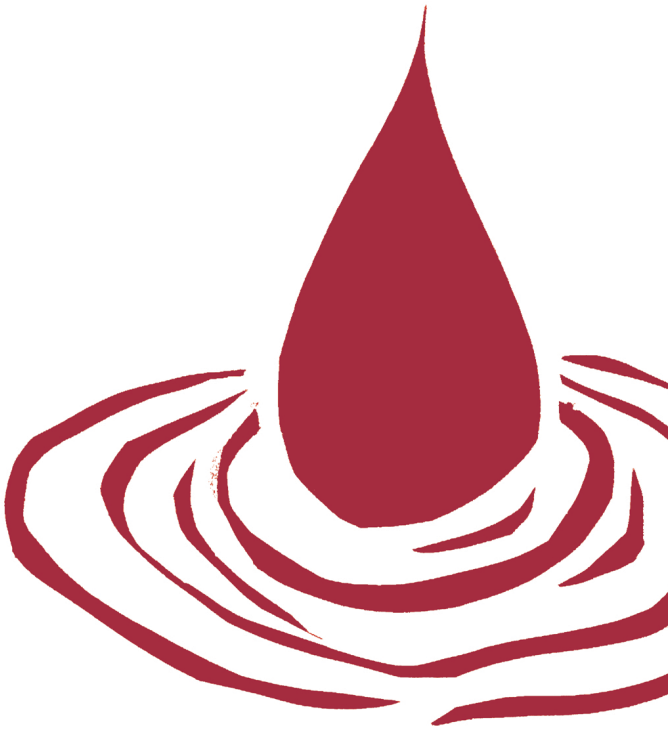

Once upon a time, before the age of modern medicine, death ór miraculous survival was the most common outcome for many diseases, including hemophilia. Nowadays, hemophilia outcomes also include bleeding episodes, arthropathy and inhibitors, and more patient-centered outcomes such as quality of life (QoL) and participation in society. There is no doubt that these outcomes have improved dramatically in most countries in the past decades, due to increased availability of safe clotting factor concentrates and prophylactic treatment. But has 'value' for individuals with hemophilia increased? If so, can the hemophilia community worldwide improve 'value' further? And will 'value' increase with novel and promising, but costly treatment options?

That depends on the definition of value. Value comes down to: is it worth it? Value is about achieving patient-relevant outcomes relative to costs. What value is depends on the role played within the health care field: providers traditionally focus on clinical outcomes (e.g., clotting factor levels, annual bleed rates), while costs are usually the domain of policymakers and insurers. For people with hemophilia, outcomes are also about QoL (e.g. pain relief, functional ability) and costs can be both monetary and non-monetary (e.g. travel time to the treatment center, loss in productivity).[1, 2] For someone with mild hemophilia, the most relevant question may be: is it worth taking a morning off from work for a routine visit to the treating physician? Is administering prophylaxis to prevent spontaneous bleeding always worth the time investment for an individual with severe hemophilia? Contrastingly, for someone in a developing country with limited access to treatment, the value may be in surviving severe bleeds.

Delivering value to patients should be the overarching goal of health care provision, argues Michael Porter, professor at Harvard Business School. He is the founding father of value-based health care, a concept introduced in 2006. This strategy consists of six essential elements that should be implemented simultaneously: 1) organize care into integrated practice units (around the consumer or need), 2) measure outcomes and costs for every patient (so progress over time can be tracked), 3) move to bundled payments for care cycles (paying for outcomes rather than services), 4) integrate care delivery across separate facilities (eliminating duplication of care and optimizing care in each location), 5) expand excellent services across geography (increase catchment area for an excellent hospital) and 6) build an enabling information technology platform (that helps the parts of an integrated practice unit work together). Together, these elements can improve value of care in many settings. The need is urgent: many hospitals and even health ministries have started to work towards improving value rather than profit.[3]

How about hemophilia? The first two elements, organizing care into integrated practice units and measuring outcomes and costs for every patient, are the starting points.[3] Integrated practice units provide services to people with the same medical condition and needs in terms of outcomes. They do not only treat the medical condition but also related conditions and complications (e.g., arthropathy, hepatitis C, hiv infections, inhibitors),[1, 3] all highly relevant for hemophilia. Can and should hemophilia

be defined as a single medical condition? Medically, it is clearly defined as factor VIII or factor IX levels below 0.40 IU/mL, but outcomes and subsequent clinical management are much more heterogeneous:[4] functional outcomes and QoL are perhaps similar for individuals with severe arthropathy and people with other orthopedic conditions, but different for mild hemophilia. Many hemophilia treatment centers worldwide provide multi-disciplinary care for hemophilia,[5] but true value-based health care goes further: all team members, regardless of specialty, share the responsibility to improve outcomes, and are accountable for the results.[3]

The second step is to establish so-called minimum outcomes sets or core sets of outcomes (both clinical and patient-reported). These combined sets have already been developed for several conditions, including lower back pain,[6] advanced prostate cancer[7] and hip and knee osteoarthritis.[8] With the help of Delphi-like processes and involvement of both patients and different clinical specialists, organizations such as the International Consortium for Health Outcomes Measurement (ICHOM) and the Core Outcome Measures in Effectiveness Trials (COMET) focus on defining outcomes that matter most to patients and that are to be used as effectiveness endpoints in clinical trials,[9] with the patient's voice becoming increasingly important.[10]

As with value, outcomes are not all similar and equal, but they form a hierarchy.[1] Porter divides patient-relevant outcomes into three tiers: 1) *health status achieved or retained*, for example mortality rates or functional status; 2) *outcomes related to the nature of the care cycle and recovery*, for example preventing hospital readmissions, because they are a burden on patients and clinicians as well as on the system; and 3) *outcomes related to the sustainability of health*, for example recurrence of health problems.[3] A core set of combined clinical and patient-reported outcomes does not yet exist for hemophilia. Brian O'Mahony, Gerard Dolan and colleagues[11] set off to map value in hemophilia onto the three-tiered framework of outcomes. They defined hemophilia outcomes in each tier and subsequently applied the framework to three clinical scenarios (e.g. the impact of receiving care at a hemophilia treatment center versus not receiving care at a specialized center; the superiority of prophylaxis over on-demand therapy; and the utilization of extended half-life products versus standard therapy). They conclude that the framework can be used to evaluate added value of hemophilia health care interventions and to reduce low-value services.

The framework is an important step towards a core set of outcomes. However, additional work is needed in order to make hemophilia care truly value-based. A first and indispensable step in solving any problem is to define the overall goal.[3] We see the overall goal as continuing to improve hemophilia care by improving value for patients. Once all agree on the goal, measuring outcomes that are relevant to and reported by individual patients is next. By tracking these outcomes over time, progress will become visible and care providers can be held accountable to achieve this goal, while allowing them to compare outcomes between centers, countries and health care settings.[3]

Then the central question is: which outcomes should we track? O'Mahony and colleagues suggest outcomes relevant for individuals with hemophilia, including mortality, QoL and pain in tier 1, time to recovery from a bleed and time missed from school or work in tier 2 and joint preservation and lifelong productivity in tier 3. There is no doubt that these are important, but as O'Mahony and colleagues point out, implementation of the framework will require further review and validation of these outcomes by patient groups, including those from low and middle-income countries.[12] Then, these outcomes should be measured appropriately. Already, an abundance of tools exists to measure a variety of outcomes, such as joint health status,[13] QoL,[14] activities and participation,[13, 15] as well as outcomes specifically for people with inhibitors.[16] However, the quality of these tools differs as well as their availability and applicability globally.[14, 15] Therefore, standardization of which tools to use is being advocated.[17]

An important motivation to implement value-based care now, besides the need to make care more patient-centered, is the rising cost of health care. Implementing value-based health care may reduce costs, as care becomes more efficient when it focuses on achieving value, eliminating services that do not contribute to that goal.[3] The issue of high costs is no different for hemophilia: with an average annual cost of almost €200.000 per severe hemophilia patient, it is among the conditions with the highest financial burden on society in Europe.[18] Value-based health care may help make choices about novel treatment options such as extended half-life concentrates, gene therapy and alternative hemostatically active products that may be even more expensive than current treatment. Are they truly more valuable for patients than current approaches? Visibly improved outcomes may be worth the cost. Already, 99 per cent of costs of hemophilia care is spent on coagulation factor replacement therapy. On the other hand, lowering costs while maintaining good outcomes, such as the use of the less costly desmopressin in non-severe hemophilia A[19] or using products of which the patent has expired, will also increase value.

Has value increased for individuals with hemophilia? Certainly. The hemophilia community is well aware of the importance of patient-relevant outcomes, as illustrated by papers by O'Mahony and others. However, although the tale is starting to be told, the story is not yet finished. First, the hemophilia community should define the goals we aim to achieve and which value should be improved. Then, a chapter should be written about a widely agreed upon minimal core set of practical and well-defined outcomes that can be used in a variety of settings, including a set of validated tools to measure outcomes in a standardized manner. And finally, the epilogue should address the need for integrated practice units for hemophilia in which team members share the responsibility for documenting and improving patient outcomes. If we can start to write this book, we believe value-based health care in hemophilia will live in prosperity ever after. And so will people with hemophilia.

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CHAPTER 5

Patient-relevant health outcomes for hemophilia care: development of an international standard outcomes set

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Res Pract Thromb Haemost. 2021;5:e12488.

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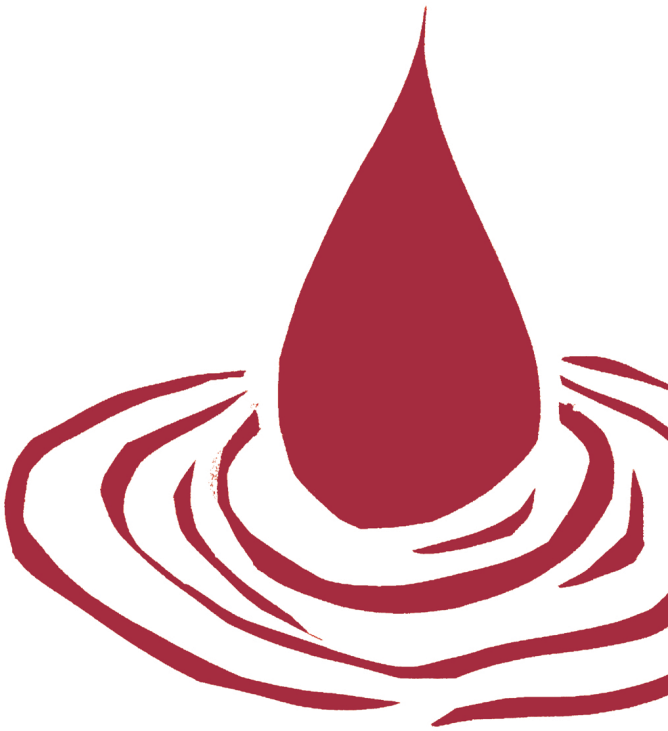

Abstract

Background

Patient-relevant health outcomes for persons with hemophilia (PWH) should be identified and prioritized in order to optimize and individualize care for PWH. Therefore, an international group of PWH and multidisciplinary health care providers set out to identify a globally applicable standard set of health outcomes relevant to all individuals with hemophilia.

Methods

A systematic literature search was performed to identify possible health outcomes and risk adjustment variables. PWH and multidisciplinary health care providers were involved in an iterative nominal consensus process to select the most important health outcomes and risk adjustment variables for PWH. Recommendations were made for outcome measurement instruments.

Results

PWH were defined as all males and females with an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII or IX with plasma activity levels below 0.40 IU/mL. We recommend collecting the following ten health outcomes at least annually, if applicable: 1) cure, 2) impact of disease on life expectancy, 3) ability to engage in normal daily activities, 4) severe bleeding episodes, 5) number of days lost from school or work, 6) chronic pain, 7) disease and treatment complications, 8) sustainability of physical functioning, 9) social functioning, and 10) mental health. Validated clinical as well as patient-reported outcome measurement instruments were endorsed. Demographic factors, baseline clinical factors and treatment factors were identified as risk-adjustment variables.

Conclusion

A consensus-based international set of health outcomes relevant to all persons with hemophilia, and corresponding measurement instruments, was identified for use in clinical care to facilitate harmonized longitudinal monitoring and comparison of outcomes.

Introduction

Hemophilia is an X-linked inherited bleeding disorder caused by a congenital deficiency of either coagulation factor VIII (hemophilia A) or coagulation factor IX (hemophilia B), which affects 24.6 and 5.0 per 100,000 male live births, respectively.[1] The lack of functional coagulation factor VIII or IX causes spontaneous bleeding in persons with severe hemophilia (PWH), especially affecting joints and muscles.[2] Recurrent bleeding into joints causes arthropathy and pain.[3] Persons with a milder form of hemophilia suffer from bleeds after (minor) trauma or surgery. Female carriers of hemophilia may have varying factor levels. Symptomatic carriers experience symptoms usually consistent with mild hemophilia, however with a predominance of reproductive tract bleeding. Overall, treatment for severe cases consists of intravenous coagulation factor replacement therapy to treat bleeds (on demand treatment) or regular infusions to prevent bleeds (prophylaxis).[4] Additional treatment options such as non-factor based replacement therapies have been marketed in recent years and gene therapy will become available in the near future.[4-6]

In recent decades, advances in hemophilia treatment have resulted in a near-normal life expectancy and lower burden of bleeding in high-income countries. However, significant disease and treatment burden still exist and availability of treatment varies across the world. Globally, 70 percent of persons with hemophilia have no access to adequate treatment.[7, 8]

Health care systems should deliver value by achieving health outcomes that matter to patients within available budgets for any given medical condition.[9] Value is measured at the medical condition level and is viewed as a ratio of patient-relevant health outcomes achieved and the cost of achieving these outcomes over the full cycle of care.[9-11] Selection of a standardized set of well-defined patient-relevant health outcomes for a medical condition such as hemophilia is an essential step towards delivering value by enabling monitoring of health outcomes of each individual over time. Concurrent collection of individual patient and treatment characteristics is required for risk-adjusted comparisons of outcomes between populations.[12]

The value-based health care framework according to Porter [11] distinguishes three hierarchically ordered tiers of outcomes, with outcomes in the lower tiers dependent on the outcomes in the higher tiers. Tier 1 outcomes are generally the most important and reflect the health status achieved or retained, including survival and the degree of health or recovery. Tier 2 outcomes typically include dimensions of time to recovery and disutility of care (discomfort or complications), and tier 3 outcomes relate to long-term consequences of the disease or treatment.[11] Health care in low-resource settings (e.g. lower-income countries, more remote areas or hospitals without a hemophilia treatment center (HTC)) may prioritize assessment and improvement of outcomes in

the higher tiers, while care providers in more resource-rich settings may aim to improve outcomes in all tiers.

Outcome sets evolve over time and build on earlier outcome sets.[13-16] The recently published patient-relevant outcomes framework for hemophilia care [13] required broader validation by PWH representatives and hemophilia care provider inputs.[17] Therefore, we assembled stakeholders including PWH and their representatives, hemophilia care providers with expertise in various disciplines and experts in value-based health care to identify a globally applicable standard set of patient-relevant health outcomes for all persons living with hemophilia.

Methods

Detailed descriptions of participants, literature search, consensus process, panel meetings and outcome measurement recommendations are documented in the Supplement.

Project overview

A nominal consensus process was applied according to Value-based Health Care methodology,[18] as endorsed by ICHOM and NHS.[19] In a parallel multistep process, including multiple web-based meetings, consensus was sought on the elements of the standard set: 1) definition of the patient group for whom the standard outcomes set is intended, i.e. the medical condition; 2) health outcomes; and 3) risk-adjustment variables.

Four panels were involved: the coordinating core team, a steering group, the Patients and Health Care Professionals Panel, and the International Academic Council (Table 1). The coordinating core team extracted lists of the definitions, health outcomes and risk-adjustment variables from the literature search, earlier outcomes initiatives,[13, 14, 16, 20] ICHOM standard sets [19] and clinical practice. The steering group and Patients and Health Care Professionals Panel members individually voted for the most relevant health outcomes and risk adjustment variables prior to each web-based meeting. Voting results were discussed during the web-based meetings until consensus was reached. Consensus was considered reached when no new topics or questions were raised. The independent International Academic Council reviewed the process and selection of results (Table 1). Finally, the core and steering group assessed and selected available outcome measurement instruments.

Table 1: Overview of the process of standard set development

Meeting dates	Working group	Meeting objectives
July 19, 2018	Core and steering group*	Introduce HaemoValue project
		Value-Based Health Care education
		Define medical condition
1) Oct 15, 2018	Core and steering group	Define medical condition and patient group
		Discuss longlist of health outcomes
2) Dec 20, 2018	Core and steering group	Discuss shortlist of health outcomes
		Discuss longlist of risk-adjustment variables
3) Jan 21, 2019	Patients and Health Care Professionals Panel†	Review and discuss shortlist of health outcomes
4) Feb 12, 2019	Core and steering group	Review shortlist health outcomes and definitions
		Discuss Shortlist risk-adjustment variables
5) Mar 11, 2019	Patients and Health Care Professionals Panel	Review and discuss shortlist of risk-adjustment variables
6) May 6, 2019	Patients and Health Care Professionals Panel	Finalize international set of health outcomes
		Select most relevant risk-adjustment variables
7) May 20, 2019	Core and steering group	Discuss final international set of health outcomes and definitions
		Discuss final list of risk-adjustment variables
8) May 27, 2019	International Academic Council‡	Review of HaemoValue process and methodology
		Review of prefinal international set of health outcomes
		Comment on value of international standard set of health outcomes
9) Jun 17, 2019	Patients and Health Care Professionals Panel	Review final international set of health outcomes and risk-adjustment variables

* The core group consisted of four epidemiologists and hematologists and two patient representatives, the steering group consisted the core group and an additional eight hematologists, a nursing specialist, a representative from the World Federation of Hemophilia and two patient representatives.
† The Patients and Health Care Professionals Panel consisted of 17 hemophilia care professionals of eight different disciplines and 15 patient representatives, including persons with hemophilia, parents of children with hemophilia and female carriers of hemophilia.
‡ The International Academic Council consisted of two hematologists, a gynaecologist, a nursing specialist, a physiotherapist, a public health expert and a value-based health care expert.

Identification of health outcomes set

Definition of the medical condition

People included in the medical condition definition have similar medical needs, and the same set of health outcomes is relevant to them. Consensus was sought on the definition of the medical condition, including patient inclusion and exclusion criteria,

identification of potential relevant subgroups for whom distinct additional outcomes are needed, establishment of first and last time points of treatment by hemophilia care teams, and available treatment types.[2, 9, 21]

Selection of health outcomes

The core team defined health outcomes as outcomes that: i) represent patient value as a result of receiving care; ii) can be acted upon and improved by the health care team; and iii) can be reported by PWH or documented by health care professionals. [10] Outcome selection was based on the degree to which health care activities affect individual health outcomes, the magnitude of impact on PWH and patient numbers for whom health outcomes were relevant.

Selection of risk-adjustment variables

Risk-adjustment variables are patient and treatment characteristics that affect the absolute value of health outcomes. When outcomes are compared between patient populations with different backgrounds, adjustment for such characteristics is required.

Recommendations for outcome measurement

For outcomes that can be measured directly from clinical or laboratory data, measurement instructions were described. For other outcomes, hemophilia-specific instruments and item banks from the Patient-Reported Outcomes Measurement Information System (PROMIS®) [22, 23] were identified. Selection was primarily based on the instrument's content's fit with the health outcome in order to properly measure the outcome. Then, selection was based on the 1) instrument's psychometric quality (extracted from systematic reviews and recent literature) [15, 20, 24-31]; 2) number of available validated translations; and 4) instruments' availability and accessibility.

Results

Literature search

The literature search, based on an earlier search strategy and longlist with health outcomes by CoreHEM,[14] yielded 382 references; 183 were excluded (Supplementary fig 1). From the remaining 199 studies, 3023 potential health outcomes were extracted. After removing duplicates, process indicators, structural indicators and cost indicators (Supplement, p. 13), 136 health outcomes were included in the longlist used for round 1 of voting (Supplement and Supplementary table 5). In total, 57 unique potential risk-adjustment variables were identified (Supplementary table 7).

Definition of the medical condition hemophilia

Consensus was reached on the medical condition definition for PWH: 'All people (male or female) with an X-linked congenital bleeding disorder caused by a deficiency of coagulation factor VIII (hemophilia A) or IX (hemophilia B) with plasma activity levels of factor VIII/IX activity below 0.40 IU/mL'. The deficiency is the result of mutations in the respective coagulation factor genes.

No subgroups were defined, as they were not considered distinctive enough to require additional, specific health outcomes not relevant to the other subgroups. Yet, it was acknowledged that there are large differences between individuals (e.g. resulting from differences in treatment availability, disease severity and gender).

The first and last time points of treatment by the hemophilia care team were from time of diagnosis (prenatal or after birth) to death. End-of-life care was explicitly included, care delivered prior to diagnosis, care related to comorbidities and secondary disease excluded. The four potential treatment modalities were: 1) continuous prophylaxis; 2) intermittent periodic prophylaxis (if available); 3) episodic 'on-demand' treatment; 4) 'curative' treatment.[2]

Health outcomes

Steering group members voted on the longlist of 136 health outcomes (Supplementary table 5). Sixty health outcomes were selected in the first voting round. Ten additional health outcomes were added based on discussions during the steering group meeting and their importance from patients' and health care perspectives. An additional outcome specific for women (heavy menstrual bleeding) was identified from the literature. In total, 71 outcomes were reviewed in the second voting round (Supplementary table 5), after which 45 health outcomes were selected. Collapsing of similar outcomes resulted in an initial shortlist of 33 outcomes. In parallel, the Patients and Health Care Professionals Panel reviewed and ranked 15 of the 45 health outcomes as the most important. Cross-checking of these 15 highest ranked health outcomes with the shortlist of 33 health outcomes from the steering group resulted in 35 outcomes for which the core team drafted preliminary definitions (Supplementary table 6). After combining similar outcomes, 27 outcomes remained on the final shortlist.

After the final voting rounds by the steering group and the Patients and Health Care Professionals Panels subsequent discussions during web-based meetings resulted in a final set of ten health outcomes. The final set was discussed in the final meetings of all panels. The health outcome 'Life-threatening bleeding episodes' was initially included in the final set because it consistently scored higher than the broader defined 'bleeding outcomes (frequency of bleeding episodes / frequency of bleeding episodes requiring treatment)'. However, several participants felt that a broader defined bleeding outcome should be included. It was proposed to replace the outcome 'Life-threatening bleeding episodes' with the modified outcome 'Severe bleeding episodes', which also covered

bleeding outcomes for women. After discussions in writing, full consensus was reached in the steering group on including the modified outcome 'Severe bleeding episodes' and its definition.

The final international set consisted of the following ten health outcomes (Fig 1): 1) cure; 2) impact of disease on life expectancy; 3) ability to engage in normal daily activities; 4) severe bleeding episodes; 5) number of days lost from school or work; 6) chronic pain; 7) complications of hemophilia and its treatment; 8) sustainability of physical functioning; 9) social functioning; and 10) mental health. Consensus-based definitions of each of the health outcomes are listed in Table 2, including the type of reporting (clinician-reported or patient-reported) and the corresponding domain of the International Classification of Functioning (ICF) model.[32]

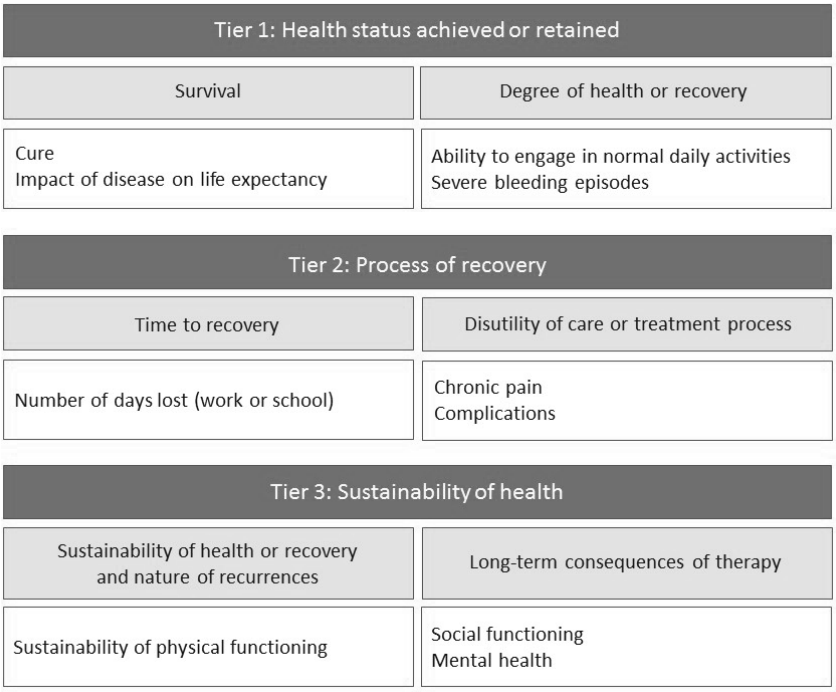

Figure 1: International set of health outcomes for hemophilia. Health outcomes are listed as a hierarchy, with the most important health outcomes in tier 1.

Table 2. Health outcomes and definitions

Health outcome	Definition	Type of data	ICF-domain
Tier 1: Health status achieved or retained			
1. Cure	Complete correction of previous bleeding tendency with normalized clotting factor levels five years after curative treatment, requiring no further treatment (with coagulation factor or other treatments), not even for surgery or bleeding. Cure is phenotypically intended, and does not include: eliminating transmission of hemophilia to children or fully reverting established damage.	Clinician-reported	Body function and structures
2. Impact of disease on life expectancy	Decrease in number of years a person is expected to live due to hemophilia compared to an age and sex-matched reference population.	Clinician-reported	Body function and structures
3. Ability to engage in normal daily activities	Actual or potential ability of individuals with hemophilia to perform activities of daily living, including self-care and looking after the household or children, and going to work or school, without support from others.	Patient-reported	Activities & participation
4. Severe bleeding episodes	Number of severe bleeding episodes or recurrent bleeding as perceived by PWH, including, but not limited to causing; acute severe pain, substantial loss of range of motion, the need for an extended treatment course. This includes any serious or life-threatening bleed requiring hospitalization, transfusion of blood products, or emergency surgery (i.e. decompression or compartment release)	Patient-reported	Body function and structures
Tier 2: Process of recovery			
5. Number of days lost (work or school)	Absence from work or school due to hemophilia (because of bleeding, hospital admission, outpatient visit, picking up medication), as a proportion of the regular number of days worked or in school.	Patient-reported	Activities & participation
6. Chronic pain	Chronic pain is patient-reported pain that is present for more than three months. Pain is multidimensional (including emotional affect and effect on PWH), may be intermittent or continuous, and may be of variable intensity over this time. Chronic pain is not due to an acute bleeding episode, and may have different causes.	Patient-reported	Body function and structures

Table 2. Health outcomes and definitions (Continued)

Health outcome	Definition	Type of data	ICF-domain
7. Complications	Any clinician-reported health complication, caused by the condition or by administration of treatment: inhibitor development and treatment-related infections, other infection-related complications, thromboembolic complications of medication, difficult venous access, infections, thrombosis or obstruction of central venous access devices (CVAD), post-partum hemorrhage and iron deficiency. Complications also include complications that result from other treatment, such as orthopedic interventions and physiotherapy.	Clinician-reported	Body function and structures
Tier 3: Sustainability of health			
8. Sustainability of physical function	Functional status over time. Functional status is defined as endurance, strength and mobility of the body and body structures.	Clinician-reported or patient-reported	Body function and structures
9. Social functioning	The degree of a person to maintain and manage interactions with other people in a contextually and socially appropriate manner, and to contribute to society.	Patient-reported	Activities & participation
10. Mental health	Degree of overall well-being, satisfaction with life, and anxiety and depression.	Patient-reported	Body function and structures

Definitions of each health outcome are listed along with the type of health outcome (clinician-reported or patient-reported) and the corresponding domain of the International Classification of Functioning (ICF).[32]

Risk-adjustment variables

Of the 57 risk-adjustment variables extracted from the literature search, the steering group removed two and added six others, resulting in a longlist of 61 risk-adjustment variables (Supplementary table 7). Steering group voting resulted in a top-15 list of risk-adjustment variables. Six non-selected risk-adjustment variables were added again during the discussions in the steering group as they were considered relevant in affecting health outcomes. Consecutive voting rounds of the steering group resulted in a shortlist of 19 risk-adjustment variables (Supplementary table 7). After final voting and steering group discussion to reach consensus, the eleven risk-adjustment variables selected were: age, gender, individual socio-economic status, availability of and access to treatment, co-morbidities, severity of hemophilia, degree of joint damage, psychological well-being, inhibitor status, health literacy and which hemophilia care professionals are involved in the management of hemophilia (Supplementary table 8).

Recommendations for outcome measurement

Measurement instructions were summarized for each outcome. The outcomes cure, impact of disease on life expectancy, severe bleeding episodes, number of days lost from work or school, and complications can be assessed directly from clinical or laboratory data. Recommended clinical instruments, hemophilia-specific instruments and generic PROMIS item banks are presented for the other outcomes (Ability to engage in daily activities, Chronic pain, Sustainability of physical functioning, Social functioning and Mental health) (Table 3).

Initially, a total of 25 potential outcome measurement instruments were identified for adults (six hemophilia-specific instruments, 11 PROMIS item banks and eight clinical instruments) and 26 instruments for children (six hemophilia-specific instruments, 12 PROMIS item banks and eight clinical instruments). Scoring of instruments led to the selection of the recommended outcome measurement instruments (Supplementary tables 3 and 9).

Hemophilia-specific instruments generally measure several domains of health-related quality of life (e.g. physical functioning, social functioning, mental health and others). The most appropriate subscales were selected if subscale scoring was available. Life satisfaction, which is part of the outcome mental health, is not measured in any hemophilia-specific instrument. It is therefore recommended to use the PROMIS item bank Life Satisfaction. We recommend choosing the instrument that is most feasible in each situation, e.g. depending on language and availability of clinical or research staff. Where possible measurement of outcomes should be embedded into routine clinical care.

Table 3: Measurement instructions and instruments for the health outcomes set. For the measurement of the standard set of outcomes we recommend to use the listed hemophilia specific outcome measurement instruments or PROMIS item banks. In resource-limited settings health care providers may start measuring outcomes (in tier 1). Based on feasibility and preference instruments may be selected for clinical practice from either category. The most recent versions of the measurement instruments are recommended for use.

Health outcome	What to measure	Recommended measurement instruments	
		Hemophilia-specific	PROMIS item bank
Tier 1: Health status achieved or retained			
Cure	Factor VIII and factor IX activity as measured by one-stage assay or chromogenic assay Absence of coagulation factor use	n.a.	n.a.
Impact of disease on life expectancy*	Age at death Cause of death	n.a.	n.a.
Ability to engage in normal daily activities	Ability to perform activities of daily living (self-care) Participation in society	**Adults, For high-income societies** HAL† Use of transportation HAL† Self-care HAL† Household tasks **For lower-income societies** FISH‡ **Children, For high-income societies** PedHAL† Use of transportation PedHAL† Self-care PedHAL† Household task **For lower-income societies** FISH‡	**Adults** Self-efficacy for managing chronic conditions - managing daily activities **Children** Upper extremity Mobility

Table 3: Measurement instructions and instruments for the health outcomes set (Continued)

Health outcome	What to measure	Recommended measurement instruments	
		Hemophilia-specific	**PROMIS item bank**
Severe bleeding episodes	Number of severe bleeds per year (ABR) Number of severe joint bleeds per year (AJBR)	n.a.	n.a.
Tier 2: Process of recovery			
Number of days lost (work or school)	Number of full or half days of absence from school/work Full time equivalent (FTE) worked or in school	n.a.	n.a.
Chronic pain	Pain duration Pain interference with daily life Pain intensity Emotional impact of pain	**Adults** PROBE§ Chronic pain **Children** PROBE§ Chronic pain	**Adults** Pain intensity¶ Pain interference¶ **Children** Pain intensity¶ Pain interference¶
Complications	Number, type, severity of complications		
Tier 3: Sustainability of health			
Sustainability of physical functioning	Fatigue Muscle strength Mobility Flexibility	**Adults** HAL†: Lying down/sitting/ kneeling/ standing HAL†: Functions of the legs HAL†: Functions of the arms HJHS** **Children** PedHAL†: Sitting/ kneeling/ standing	**Adults** Physical functioning Physical function for samples with mobility aid users **Children** Physical activity Strength impact

Table 3: Measurement instructions and instruments for the health outcomes set (Continued)

Health outcome	What to measure	Recommended measurement instruments	
		Hemophilia-specific	**PROMIS item bank**
		PedHAL†: Functions of the legs	
		PedHAL†: Functions of the arms	
		HJHS**	
Social functioning	Ability to establish and maintain social relationships	**Adults**	**Adults**
	Participation in society	Haemo-QoL-A††: role functioning	Ability to participate in social roles and activities
	Relationships with friends	**Children**	Self-efficacy for managing social interactions
		CHO-KLAT‡‡	**Children**
			Family Relationships
			Peer Relationships
Mental health	Well-being	**Adults**	**Adults**
	Satisfaction with life	Haemo-QoL-A††: emotional impact	Anxiety
	Anxiety	**Children**	Depression
	Depression	CHO-KLAT‡‡	General life satisfaction
			Positive affect
			Children
			Anxiety
			Depressive symptoms
			Life satisfaction
			Positive affect

The health outcomes Cure, Impact of disease on life expectancy, Severe bleeding episodes, Number of days lost from work or school and Complications may be measured at baseline and annually, when possible.

PROMIS: Patient-Reported Outcomes Measurement Information System; HAL: Hemophilia Activities List; PedHAL: Pediatric Hemophilia Activities List; FISH: Functional Independence Score in Hemophilia; n.a: not applicable; HJHS: Hemophilia Joint Health Score; Score; PROBE: Patient Reported Outcomes Burdens and Experiences. ABR: annualized bleeding rate; AJBR: annualized joint bleeding rate.

*Impact on life expectancy can be measured by collecting data on the number of deaths and the age at death.

† The HAL (adults) and PedHAL (children) measure self-perceived functional abilities due to hemophilia in seven domains in the previous month.

‡ The FISH is a performance-based tool to assess an individual's functional ability. Eight activities of daily living are assessed: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, and running. For children the e-FISH is currently under development (personal communication A. Srivastava)

§ PROBE measures general health issues, use of mobility aids or assistive devices, pain, daily activities, current work or student status, surgeries or procedures and comorbid diseases.

¶ PROMIS has pain-related item banks (pain intensity and pain interference). However, the fit with the HaemoValue outcome 'chronic pain' lasting >3 months is limited, as pain in the previous 7 days is assessed and the emotional impact of pain is lacking.

** The HJHS assesses functional impairment in the six main joints commonly affected by hemophilia.

†† Haemo-QoL-A is a hemophilia-specific instrument that measures health-related quality of life in six domains.

‡‡ CHO-KLAT is a hemophilia-specific instrument that measures several aspects of quality of life in children. CHO-KLAT 3.0 is currently under development. [33]

Discussion

We present a standard set of health outcomes for all PWH that can be used by hemophilia treatment centers and health systems to assess the value provided for PWH in different geographical and health care settings. The standard set was developed by PWH and their representatives and international panels of health care professionals with expertise across various disciplines. We propose appropriate measurement instruments with the best content fit and the best reported psychometric properties.

This work was performed in close collaboration with earlier working groups: the CoreHEM core outcomes set for hemophilia gene therapy trials,[14] the Patient Reported Outcomes, Burdens, and Experiences (PROBE) study,[20] the Cost of Hemophilia in Europe: a Socioeconomic Survey (CHESS),[34] the Value Framework,[13] core outcomes set for clinical research in hemophilia,[35] the SSC/ISTH definitions in hemophilia project group,[2] an expert review on tools for outcome measurement [15, 16] and systematic reviews on the psychometric properties of hemophilia-specific instruments for joint health, activities and participation and health-related quality of life.[24-26]

Improving value for PWH should be the overarching goal of health care delivery.[9] Without focus on value, limited health care resources may be wasted on activities that do not improve outcomes. In many health care systems or clinics, outcomes that matter to PWH are not measured or efforts are aimed at measuring process indicators (i.e. volume of patient visits or units coagulation factor consumption) or at outcomes that are irrelevant to PWH in their daily lives.[11] Moreover, lack of focus on value fails to provide insight into the level of patient-relevant outcomes achieved and sustained through individualized tailoring of treatment. For most conditions treated through a value-based system, a focus on achieving outcomes will eventually reduce costs, because health care activities that do not contribute to better outcomes are eliminated.[11]

In high-income countries, up to 99 percent of measured total health care costs for severe hemophilia are currently attributed to coagulation factor replacement therapy.[34] As a result, decision-makers tend to focus on a per unit or per patient cost for product. There is no tabulation of the overall cost to the health care budget or to society long-term (i.e. surgeries, hospital admissions, unemployment) of achieving the current outcomes. In spite of this, over the last 20 years most payers have agreed to increased and widespread use of coagulation factor prophylaxis in all age groups through recognition of its long-term beneficial outcomes. These benefits include reducing bleeding complications with the prevention or slowing of disability and enhancing labor market participation. Still, the relative system cost saved by avoiding poor health outcomes remains unmeasured. Measuring the relative value of therapies by comparing outcomes relevant to PWH, rather than relative costs through consumption of products, is urgently needed in the light of recently developed non-factor based therapies and gene therapy which will affect coagulation factor use and be priced similarly high, or higher.

Strengths and limitations

A strength of this study is the representation of PWH. A large representation of PWH, carriers and parents in the steering group and the Patients and Health Care Professionals Panel (26 percent and 47 percent) ensured that the standard set of outcomes is relevant for PWH. Care was taken to include a variety of PWH in the Patients and Health Care Professionals Panel including individuals with hemophilia A and B, different severities, symptomatic carriers of hemophilia, and parents of children with hemophilia from various geographic backgrounds. Furthermore, since the standard outcomes set needs to be applicable in health care settings with varying resources, participants represented high-income countries, upper-middle income countries and one lower-middle income country. Since we aimed to identify health outcomes relevant to PWH, we did not involve policy makers and payers in order to avoid bias in the selection of the outcomes.

A limitation of this work is that some (sub)groups of PWH may be underrepresented. We attempted to reach out to stakeholders from low-income countries but did not succeed, in part due to language barriers. Therefore, the applicability of the standard health outcomes set in such resource-constrained settings remains to be assessed. Furthermore, outcomes specific to women, such as menorrhagia and pregnancy issues, may have received less attention, as women and children with hemophilia were underrepresented in the panels. To overcome this, patient representatives were asked to also represent women and children with hemophilia. In addition, during the final review step, a gynecologist with extensive expertise in the area of women with bleeding disorders reviewed the standard set. Finally, persons with mild hemophilia were not included, but represented by others in the working groups. Some outcomes, notably those in tiers 1 and 2, may be less relevant for persons with mild hemophilia than outcomes in tier 3. In future revisions of the outcomes set, we will aim for a more extensive representation of women, children and individuals with mild hemophilia in order to ensure relevance of the outcomes. The majority of PWH and their representatives in the steering group and Patients and Health Care Professionals Panel were active members of regional, national and global patient organizations. Their expertise may have led to different opinions than expressed by an 'average' person with hemophilia. Even though participants were instructed to represent all PWH, we cannot rule out that this affected the selection of health outcomes. Furthermore, participants were required to be proficient in English, which is not typical for PWH around the world. However, this was necessary for participation in assignments and discussions during web-based meetings. For these reasons, relevance of the set to all PWH around the world will need to be further evaluated in practice.

It is also acknowledged that some of the recommended hemophilia-specific outcome measurement instruments still need further validation, particularly in the areas of structural validity (i.e. the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct [36]), responsiveness (i.e. the ability of an instrument to detect change over time [36]) and cross-cultural validity.[24-26, 37, 38]

It is important to note that the use of patient-reported outcomes measures (PROMs) may have some limitations. First, PROMs (including digital PROMs) may be less feasible in settings with high functional illiteracy rates. Secondly, PROMs that have been developed in high-income countries may not be culturally appropriate for lower-income countries, and vice-versa. Cross-cultural adaptation is essential to safeguard performance. Several items in the Hemophilia Activities List (HAL), for example, are not applicable in India and Jamaica, while the Functional Independence Score in Hemophilia (FISH), an instrument developed in India, performs well in these countries.[39, 40] Similarly, the FISH shows ceiling effects and fails to detect early changes in joint health in high-income countries with early prophylaxis.[41] Health care organizations may choose the tool that is most appropriate and feasible in their situation. Thirdly, PROMs are subjective by definition and may demonstrate response shift if used to assess changes over time.[42, 43] Therefore, assessment of health outcomes with clinical tools will be needed to supplement PROMs when possible. Finally, a PROM that measures all outcomes in the standard set is currently unavailable, and several instruments are needed to measure all outcomes. Having to complete multiple instruments that may be partially overlapping may pose a burden on PWH, or for parents or guardians completing an instrument for children with hemophilia. The length and unknown responsiveness of current hemophilia-specific outcome assessment instruments may hamper their usefulness in clinical practice.

We selected relevant PROMIS item banks [22] because they may in part solve these issues. PROMIS item banks have been developed for many patient-relevant outcomes and have been validated in diseased and healthy populations. PROMIS item banks are available in many languages and offer greater precision of outcome assessment than other generic instruments. Since item banks were developed based on modern Item Response Theory, they allow for selecting any number of items from the bank to produce a short form whose scores can be compared to any other selection of items from the same item bank. This increases flexibility and reduces response burden, especially if administered as computerized adaptive test (CAT).[37] However, PROMIS item banks have yet to be formally validated for use in hemophilia populations.

Implications for clinical practice

We recommend that health care providers start measuring the outcomes from the international standard set in clinical practice. This is relevant for patients because it allows individualized adjustment of treatment. Still, feasibility and applicability in different care settings and patient groups should be evaluated in annual meetings in which health care providers exchange their experiences with using the standard set.

It may not be feasible or necessary to measure the complete outcomes set at once. When time or resources are limited, we encourage users of the outcomes set to start with regular assessments of the outcomes in tier 1. Data collection may be expanded to the health outcomes in tiers 2 and 3 at a later stage.

Feasibility of implementation in different healthcare systems was our foremost priority. Therefore, we recommend the use of widely accepted measurement instruments that are publicly available in multiple languages, and which can be administered during routine clinical practice. We have summarized the length of each instrument, availability and validity in multiple languages, and accessibility (Supplementary table 9) to assist with implementation.

National registries already collect outcome data on a regular basis. The World Bleeding Disorders Registry (WBDR) of the World Federation of Hemophilia promotes standardized patient data collection from treatment centers around the world [44] and may be used to start measuring health outcomes and risk-adjustment variables. An acceptable burden of outcome assessments for both PWH and health care providers is crucial for a broad acceptability and use of any standard set. We expect that e-health developments such as a PROMs mobile app or routine data collection from electronic medical records will greatly reduce the burden for both PWH and health care providers.

Future directions

Hemophilia care is in transition. Novel and potentially curative treatments will be increasingly available for PWH in the near future. This may have implications for the definition of hemophilia (e.g. cut-off points for baseline coagulation factor levels [45]) as well as for which health outcomes are the most relevant. Therefore, the currently presented definitions of the medical condition and health outcomes may need to be adapted in the future.

In addition, outcome measurement instruments must be continuously improved and adapted to health care developments. An enhanced version of the FISH (personal communication A. Srivastava) is aimed at reducing the ceiling effects that have been found for children and individuals with mild hemophilia.[24] Similarly, the Hemophilia Joint Health Score (HJHS) is currently under revision to enhance efficacy [46] and to further improve convergent and discriminant validity in adults.[47] PROBE is expanding country and language availability, implementing longitudinal data collection to improve detection of change over time and testing performance in new hemophilia populations. [48] It may be more contemporary than existing instruments, potentially replacing older instruments over time. Finally, PROMs such as the CHO-KLAT questionnaire are currently updated to increase sensitivity for detecting improvements in treatment burden of novel treatments, and to include outcomes that may become relevant in the future, such as caregiver and family burden.[33]

For all these reasons, we emphasize that the recommendations regarding the standard set of health outcomes and measurement instruments are dynamic entities, and that revisions should be scheduled biennially.

Conclusion

The presented international standard set of health outcomes that matter to PWH will form the basis for harmonized longitudinal monitoring and comparison of health outcomes. Broad implementation will enable a more personalized approach in hemophilia care within a framework of continuous improvement of treatment with increasing value for PWH.

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Supplement

Methods

Working groups descriptions

Four working groups of stakeholders were involved in the HaemoValue project: a Core group, a Steering Group, a Patients and Health Care Professionals Panel and an International Academic Council (Table 1). The core group comprised epidemiologists, hematologists and patient representatives (n=6), with the role of coordinating and facilitating the HaemoValue project. The steering group comprised leading experts in hemophilia with experience in the development of earlier outcomes sets, and patient representatives (n=12). The Patients and Health Care Professionals Panel consisted of 17 hemophilia care professionals of eight different disciplines (Table 1) and 15 patient representatives, including people with hemophilia, parents of children with hemophilia, female carriers of hemophilia, ensuring representation of the patient voice. Care was taken to ensure that members represented countries from each continent, both established and emerging countries. The International Academic council consisted of seven experts in value-based health care methodology and leading authorities in hemophilia assessment and care. Their role was to review the final set of health outcomes. Characteristics of members of the working groups, their professions and countries of origin are listed in Supplementary tables 1 and 2.

The Decision Group, a Dutch consultancy firm with an extensive track record in Value-Based Health care methodology coordinated and facilitated the HaemoValue project, together with the HaemoValue core team.

Supplementary table 1: Participants in working groups (in alphabetical order)

Name	Profession	Country of origin
Core group members		
Erna van Balen	PhD candidate clinical epidemiology	The Netherlands
Johanna van der Bom	Professor clinical epidemiology	The Netherlands
Marjon Cnossen	Pediatric hematologist	The Netherlands
Samantha Gouw	Pediatric hematologist	The Netherlands
Brian O'Mahony	PWH	Ireland
Cees Smit	PWH	The Netherlands
Steering group members		
Victor Blanchette	Pediatric hematologist	Canada
Donna Coffin / Glenn Pierce	Director of research WFH	Canada
Gerard Dolan	Hematologist	UK
Kathelijn Fischer	Pediatric hematologist	The Netherlands
Deb Gue	Nursing specialist	Canada
Alfonso Iorio	Hematologist	Canada
Shannon Jackson	Hematologist	Canada
Barbara Konkle	Hematologist	USA
Diane Nugent	Pediatric hematologist	USA
Jamie O'Hara	PWH	UK
Mark Skinner	PWH	USA
Alok Srivastava	Hematologist	India
Patients and Health Care Professionals Panel members		
Brian Feldman	MD - Orthopaedic specialist	Canada
Cesar Garrido	Father of PWH	Venezuela
David Page	PWH	Canada
Declan Noone	PWH	Ireland
Deon York	PWH	New Zealand
Annamma Kurien	Hematologist	India
Ed Kuebler	Social worker	United States of America
Fendi Valdez	PWH	Dominican Republic
Frederica Cassis	Psychologist	Brazil
Ilmar Kruis	PWH	The Netherlands
Johnny Mahlangu	Hematologist	South Africa
Judy Ann David	Rehabilitation specialist	India
Khalid Habaybeh	Nurse	Saudi Arabia
Lotte Haverman	Psychologist	The Netherlands
Mariette Driessens	Carrier of hemophilia	The Netherlands
Marlène Beijlevelt	Nursing specialist	The Netherlands
Mathieu Jackson	PWH	Canada
Pamela Narayan	Physiotherapist	India
Pamela Wilton	Mother of PWH, carrier	Canada
Paul McLaughlin	Physiotherapist	UK
Pedro Jardim	PWH	Brazil
Petra Buckova	Psychologist	Czech Republic

Supplementary table 1: Participants in working groups (in alphabetical order) (Continued)

Name	Profession	Country of origin
Radek Kaczmarek	PWH	Poland
Randall Curtis	PWH	United States of America
Rungrote Natesirinilkul	Hematologist	Thailand
R. Sathyanarayanan	PWH	India
Sheldon Simson	PWH	Suriname
Suely Rezende	Hematologist	Brazil
Sulochana Badagabettu	Nurse	India
Susan Cutter	Social worker	United States of America
Suzie Peterson	Nurse	South Africa
Yasu Nishida	PWH	Japan
International Academic Council		
Mike Makris	Hematologist	United Kingdom
Pia Petrini	Pediatric hematologist	Sweden
Kate Khair	Nursing specialist	United Kingdom
Piet de Kleijn	Physiotherapist	The Netherlands
Rezan Abdul-Kadir	Gynaecologist	United Kingdom
Leonard Friedman	Expert public health	United States of America
Roberto Solinis Nuño	Expert in value-based health care	Spain

PWH: person with hemophilia

Supplementary table 2: Characteristics of the Patients and Health Care Professionals Panel

Demographic characteristics (Table 2a), professional characteristics (Table 2b) and clinical characteristics (Table 2c). Data are available for 22 of 35 participants.

Table 2a: Demographic characteristics of participants

	PWH, carriers, parents (n=11)	Health care providers (n=11)
Sex (male/female), N	10 / 1	3 / 8
Mean age (range)	46.2 (29-67)	49.8 (35-60)
Active in NMO, N		
Yes	10	11
No	1	0

NMO: National Member Organization

Table 2b: Professional characteristics (hemophilia health care providers only)

	Health care providers (n=11)
Years of experience, mean	19.3
Participant's profession	
Hematologist	1
Hematology laboratory analyst	1
Nurse	3
Nurse practitioner	1
Physiotherapist	1
Psychologist	2
Social worker	1
Pediatric rheumatologist	1
Hemophilia team members	
Adult/Pediatric hematologist	8
Nurse	10
Physiotherapist	8
Psychologist	10
Social worker	6
Orthopaedic specialist	8
Rehabilitation specialist	1
Clinical geneticist	4
Primary care / General medicine	2
Obstetrics & Gynaecology	2
Other*	4
Patient population cared for	
Adults only	2
Children only	2
Adults and children	7

*Other team members included: epidemiologist, genetic counsellor, a hematopathologist, microbiologist, nurse practitioner, dentist, oral surgeon, gastroenterologist

Table 2c. Characteristics of persons with hemophilia, carriers and parents of child with hemophilia

	PWH / carriers / parents (n=11)
PWH / carrier	
PWH	9
Carrier	1
Parent of PWH	1
Highest completed education level	
Primary	0
Lower secondary	0
Upper secondary	0
Tertiary	11
Hemophilia type	
A	7
B	4
Hemophilia severity	
Mild	0
Moderate	1
Severe	9
Not applicable (carrier)	1
Access to home treatment	
Yes	8
No	2
Not applicable (no treatment required)	1
Type of treatment*	
DDAVP / desmopressin**	0
Coagulation factor	9
Not applicable (no treatment required)	1
Receiving treatment from comprehensive treatment center	
Yes	8
No	0
Unsure	2
No treatment required	1
Access to coagulation factor treatment	
Always available	9
Sometimes available	1
Not available	0
No treatment required	1
Past or current HIV/HCV infection	
Yes	4
No	7

*For one person the type of treatment is missing

**There were no participants being treated with DDAVP since people with mild hemophilia were not on the panel.

Literature search

A systematic literature search was performed to collect an extensive list of health outcomes and risk-adjustment variables. In addition, longlists of outcomes from previous or ongoing projects (CoreHEM,[1] the Value Framework,[2] PROBE,[3] published ICHOM standard sets) and from clinical and value-based health care practice were used.

The literature search was performed in Pubmed using date limits of July 1st 2017 to August 28, 2018, building on the CoreHem literature search that included literature published until July, 2017. Excluded were case reports, commentaries or editorials, and economic evaluations of hemophilia treatment, because they were not expected to contain true health outcomes. Search terms are listed below.

On November 16, 2018 a secondary literature search with the same characteristics was conducted on health outcomes specific for females with hemophilia, when it was agreed that the medical condition also included females. The search term 'women with hemophilia' was added to the search criteria.

Search terms

Two search strategies were performed to capture every possible health outcome in hemophilia.

1) Focus on hemophilia (major MESH heading and/or word in title)

((“Hemophilia A”[majr] OR “Hemophilia B”[majr] OR “hemophilia”[ti] OR “haemophilia”[ti] OR hemophili*[ti] OR haemophili*[ti] OR hemofili*[ti] OR haemofili*[ti] OR “Haemophilia”[Journal]) AND (“Self Efficacy”[Mesh] OR “self efficacy”[tw] OR “Patient Compliance”[mesh] OR “Medication Adherence”[mesh] OR “adherence”[tw] OR “compliance”[tw] OR “concordance”[tw] OR “sleep quality”[tw] OR “quality of sleep”[tw] OR “target joint”[tw] OR “target joints”[tw] OR “Accidental Falls”[Mesh] OR “falls”[tw] OR “fall”[tw] OR “Drug-Related Side Effects and Adverse Reactions”[Mesh] OR “adverse event”[tw] OR “adverse events”[tw] OR “Injection Site Reaction”[Mesh] OR “Injection Site Reaction”[tw] OR “Injection Site Reactions”[tw] OR “infusion site reaction”[tw] OR “infusion site reactions”[tw] OR “liver toxicity”[tw] OR “hepatotoxicity”[tw] OR “Chemical and Drug Induced Liver Injury”[Mesh] OR “inhibitor development”[tw] OR “Factor VIII/antagonists and inhibitors”[Mesh] OR “mortality”[Subheading] OR “Mortality”[Mesh] OR “mortality”[tw] OR “cause of death”[tw] OR “age of death”[tw] OR “bleeds”[tw] OR “factor activity level”[tw] OR “factor activity levels”[tw] OR “Pain”[mesh] OR “pain”[tw] OR “discomfort”[tw] OR “Health”[mesh] OR “wellbeing”[tw] OR “well being”[tw] OR “Mental Health”[mesh] OR “mental health”[tw] OR “anxiety”[tw] OR “depression”[tw] OR “coping”[tw] OR “worry”[tw] OR “Anxiety”[mesh] OR “Depression”[mesh] OR “Adaptation, Psychological”[Mesh] OR “vitality”[tw] OR “tiredness”[tw] OR “fatigue”[tw] OR “contentment”[tw] OR “happiness”[tw] OR “elation”[tw] OR “exhilaration”[tw] OR “Fatigue”[mesh] OR “Happiness”[Mesh] OR “social functioning”[tw] OR “Self Concept”[Mesh] OR “Social Identification”[Mesh] OR “Social belonging”[tw] OR “feelings of inequality”[tw] OR “feeling of inequality”[tw] OR “sexual intimacy”[tw] OR “sexual functioning”[tw] OR “sexual functioning”[tw] OR “Sexual Behavior”[mesh] OR “Sexual Dysfunction, Physiological”[Mesh] OR “Sexual Dysfunctions, Psychological”[Mesh] OR “physical functioning”[tw] OR “Exercise”[mesh] OR “exercise”[tw] OR “exercises”[tw] OR “exercising”[tw] OR “physical activity”[tw] OR “physical activities”[tw] OR “Sports”[mesh] OR “sport”[tw] OR “sports”[tw] OR “sexual activity”[tw] OR “Mobility Limitation”[Mesh] OR “Mobility Limitation”[tw] OR “joint function”[tw] OR “Joints/physiopathology”[mesh] OR “Range of Motion, Articular”[mesh] OR “role functioning”[tw] OR “Independent Living”[Mesh] OR “Independence”[tw] OR “Dependency (Psychology)”[Mesh] OR “Dependency”[tw]

OR "Activities of Daily Living"[Mesh] OR "Activities of Daily Living"[tw] OR "Social Participation"[tw] OR "Educational Status"[Mesh] OR "education attainment"[tw] OR "educational attainment"[tw] OR "education choice"[tw] OR "educational choice"[tw] OR "education achievement"[tw] OR "educational achievement"[tw] OR "Career Choice"[Mesh] OR "Career Choice"[tw] OR "Absenteeism"[Mesh] OR "Absenteeism"[tw] OR "family life"[tw] OR "family decision"[tw] OR "family decisions"[tw] OR "paternity decision"[tw] OR "paternity decisions"[tw] OR "Reproductive Behavior"[Mesh] OR "reproductive decision"[tw] OR "reproductive decisions"[tw] OR "Child Care"[Mesh] OR "Child Care"[tw] OR "burden"[tw] OR "risk aversion"[tw] OR "risk avoidance"[tw] OR "risk taking behavior"[tw] OR "risk taking behaviors"[tw] OR "risk taking behaviour"[tw] OR "risk taking behaviours"[tw] OR "Hospitalization"[mesh] OR "Hospitalization"[tw] OR "Hospitalisation"[tw] OR "Length of Stay"[tw] OR "Patient Admission"[tw] OR "Patient Discharge"[tw] OR "Patient Handoff"[tw] OR "Patient Readmission"[tw] OR "Patient Transfer"[tw] OR "Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "economics"[Subheading] OR "cost"[tw] OR "costs"[tw]) NOT ("editorial"[ptyp] OR "comment"[ptyp] OR "case reports"[ptyp] OR "editorial"[ti] OR "comment"[ti] OR "case report"[ti])) AND ("2017/07/01"[PDAT] : "3000/12/31"[PDAT]) AND (english[la] OR dutch[la]) NOT (("acquired hemophilia"[ti] OR "acquired haemophilia"[ti]) NOT ("hereditary hemophilia"[ti] OR "hereditary haemophilia"[ti] OR "congenital hemophilia"[ti] OR "congenital haemophilia"[ti]))

2) Strategy focused on outcomes, but not those already identified in previous projects, since July 1st, 2017

(((("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh] OR "hemophilia"[tw] OR "haemophilia"[tw] OR hemophili*[tw] OR haemophili*[tw] OR hemofili*[tw] OR haemofili*[tw] OR "Haemophilia"[Journal]) AND ("Outcome Assessment (Health Care)"[Mesh] OR outcome*[tw] OR "PROM"[tw] OR "PROMs"[tw] OR "PRO"[tw]) NOT ("editorial"[ptyp] OR "comment"[ptyp] OR "case reports"[ptyp] OR "editorial"[ti] OR "comment"[ti] OR "case report"[ti]) AND ("2017/07/01"[PDAT] : "3000/12/31"[PDAT]) AND (english[la] OR dutch[la]) NOT (("acquired hemophilia"[ti] OR "acquired haemophilia"[ti]) NOT ("hereditary hemophilia"[ti] OR "hereditary haemophilia"[ti] OR "congenital hemophilia"[ti] OR "congenital haemophilia"[ti]))) NOT (("Hemophilia A"[Mesh] OR "Hemophilia B"[Mesh] OR "hemophilia"[tw] OR "haemophilia"[tw] OR hemophili*[tw] OR haemophili*[tw] OR hemofili*[tw] OR haemofili*[tw] OR "Haemophilia"[Journal]) AND ("Self Efficacy"[Mesh] OR "self efficacy"[tw] OR "Patient Compliance"[mesh] OR "Medication Adherence"[mesh] OR "adherence"[tw] OR "compliance"[tw] OR "concordance"[tw] OR "sleep quality"[tw] OR "quality of sleep"[tw] OR "target joint"[tw] OR "target joints"[tw] OR "Accidental Falls"[Mesh] OR "falls"[tw] OR "fall"[tw] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh] OR "adverse event"[tw] OR "adverse events"[tw] OR "Injection Site Reaction"[Mesh] OR "Injection Site Reaction"[tw] OR "Injection Site Reactions"[tw] OR "infusion site reaction"[tw] OR "infusion site reactions"[tw] OR "liver toxicity"[tw] OR "hepatotoxicity"[tw] OR "Chemical and Drug Induced Liver Injury"[Mesh] OR "inhibitor development"[tw] OR "Factor VIII/antagonists and inhibitors"[Mesh] OR "mortality"[Subheading] OR "Mortality"[Mesh] OR "mortality"[tw] OR "cause of death"[tw] OR "age of death"[tw] OR "bleeds"[tw] OR "factor activity level"[tw] OR "factor activity levels"[tw] OR "Pain"[mesh] OR "pain"[tw] OR "discomfort"[tw] OR "Health"[mesh] OR "wellbeing"[tw] OR "well being"[tw] OR "Mental Health"[mesh] OR "mental health"[tw] OR "anxiety"[tw] OR "depression"[tw] OR "coping"[tw] OR "worry"[tw] OR "Anxiety"[mesh] OR "Depression"[mesh] OR "Adaptation, Psychological"[Mesh] OR "vitality"[tw] OR "tiredness"[tw] OR "fatigue"[tw] OR "contentment"[tw] OR "happiness"[tw] OR "elation"[tw] OR "exhilaration"[tw] OR "Fatigue"[mesh] OR "Happiness"[Mesh] OR "social functioning"[tw] OR "Self Concept"[Mesh] OR "Social Identification"[Mesh] OR "Social belonging"[tw] OR "feelings of inequality"[tw] OR "feeling of inequality"[tw] OR "sexual intimacy"[tw] OR "sexual functioning"[tw] OR "sexual functioning"[tw] OR "Sexual Behavior"[mesh] OR "Sexual Dysfunction, Physiological"[Mesh] OR "Sexual Dysfunctions, Psychological"[Mesh] OR "physical functioning"[tw] OR "Exercise"[mesh] OR "exercise"[tw] OR "exercises"[tw] OR

"exercising"[tw] OR "physical activity"[tw] OR "physical activities"[tw] OR "Sports"[mesh] OR "sport"[tw] OR "sports"[tw] OR "sexual activity"[tw] OR "Mobility Limitation"[Mesh] OR "Mobility Limitation"[tw] OR "joint function"[tw] OR "Joints/physiopathology"[mesh] OR "Range of Motion, Articular"[mesh] OR "role functioning"[tw] OR "Independent Living"[Mesh] OR "Independence"[tw] OR "Dependency (Psychology)"[Mesh] OR "Dependency"[tw] OR "Activities of Daily Living"[Mesh] OR "Activities of Daily Living"[tw] OR "Social Participation"[tw] OR "Educational Status"[Mesh] OR "education attainment"[tw] OR "educational attainment"[tw] OR "education choice"[tw] OR "educational choice"[tw] OR "education achievement"[tw] OR "educational achievement"[tw] OR "Career Choice"[Mesh] OR "Career Choice"[tw] OR "Absenteeism"[Mesh] OR "Absenteeism"[tw] OR "family life"[tw] OR "family decision"[tw] OR "family decisions"[tw] OR "paternity decision"[tw] OR "paternity decisions"[tw] OR "Reproductive Behavior"[Mesh] OR "reproductive decision"[tw] OR "reproductive decisions"[tw] OR "Child Care"[Mesh] OR "Child Care"[tw] OR "burden"[tw] OR "risk aversion"[tw] OR "risk avoidance"[tw] OR "risk taking behavior"[tw] OR "risk taking behaviors"[tw] OR "risk taking behaviour"[tw] OR "risk taking behaviours"[tw] OR "Hospitalization"[mesh] OR "Hospitalization"[tw] OR "Hospitalisation"[tw] OR "Length of Stay"[tw] OR "Patient Admission"[tw] OR "Patient Discharge"[tw] OR "Patient Handoff"[tw] OR "Patient Readmission"[tw] OR "Patient Transfer"[tw] OR "Costs and Cost Analysis"[Mesh] OR "Economics"[Mesh] OR "economics"[Subheading] OR "cost"[tw] OR "costs"[tw]) NOT ("editorial"[ptyp] OR "comment"[ptyp] OR "case reports"[ptyp] OR "editorial"[ti] OR "comment"[ti] OR "case report"[ti]) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT]) AND (english[la] OR dutch[la]) NOT (("acquired hemophilia"[ti] OR "acquired haemophilia"[ti]) NOT ("hereditary hemophilia"[ti] OR "hereditary haemophilia"[ti] OR "congenital hemophilia"[ti] OR "congenital haemophilia"[ti])))))

Definition of hemophilia

In preparation for the steering group consensus meetings, the core group drafted two alternative definitions of the medical condition hemophilia; one based on the ISTH definition ("All people (m/f) with a congenital deficiency of coagulation factor VIII or IX with plasma levels of factor VIII/IX of < 40IU/dl") and one based on clinical bleeding phenotype ("All people with an increased bleeding tendency, regardless of whether the deficiency is found in primary or secondary hemostasis").

In addition, potential meaningful patient subgroups were proposed based on four different criteria:

1) based on age:
   - infants and toddlers <4 years of age for whom treatment management and monitoring is the responsibility of the parent(s),
   - children >4 and <18 years for whom treatment management and monitoring is increasingly becoming a shared responsibility between children and parent(s),
   - adults: people >18 years for whom treatment management and monitoring is patient's own responsibility,
   - older adults: People >55 years who have conditions in addition to hemophilia that require treatment, or with conditions for which treatment is affected by hemophilia.
2) based on hemophilia severity (mild, moderate, severe),
3) based on access to treatment and / or coagulation factor replacement therapy (good access, limited access, no access [4]), and

4) based on clinical bleeding phenotype
- mild: People with non-spontaneous bleeds and low bleeding frequency (including non-severe hemophilia);
- severe: People with spontaneous, frequent or major bleed(s) (including severe hemophilia).

Health outcomes overview

The process of selecting the final set of health outcomes was iterative. An initial longlist was compiled through a literature search, earlier outcomes initiatives [1-3], ICHOM standard sets [5] and clinical practice.
Duplicate outcomes and all indicators that did not represent true health outcomes were removed and similar health outcomes were merged. For example, process indicators (e.g. adherence to guidelines and protocols), structural indicators (e.g. staff certification) and cost indicators (e.g. cost of coagulation factor) are not considered health outcomes.[6] Additional outcomes identified during the web-based meeting were added to the longlist.

Risk-adjustment variables

Definitions were written for all risk-adjustment variables remaining on the shortlist selected by the Steering Group. After selection of the final set of risk-adjustment variables, instructions on how and when to measure them were drafted and reviewed by the Steering Group.

Selection of measurement instruments

For clinical outcomes, a data dictionary with measurement instructions including frequency and timing was created.

For patient-reported outcomes and outcomes requiring scoring instruments, appropriate outcome measurement instruments were identified. Both hemophilia-specific instruments as well as generic PROMIS item banks were selected.

First, based on the health outcomes' definitions, uni- or multidimensionality of each health outcome was assessed.[7] Each health outcome was separated into one or more distinct constructs to be measured. For each construct appropriate outcome measurement instruments were selected.

Supplementary table 3: Scoring system for health outcomes measurement: fit of tool with outcomes of interest, time to complete instrument, and availability of instrument.

Criterion	++	+	+/-	-	?
Fit with outcome	(sub)scale covers outcome	(sub)scale covers outcome, but cannot be used separately	(sub)scale measures related construct, but does not fit with outcome	(sub)scale does not fit with outcome	Cannot be assessed
Time to complete, based on number of items	Less than 5 minutes	6 to 10 minutes	11 to 20 minutes	More than 20 minutes	Cannot be assessed
Availability	Free to use and publicly available	Free to use, available on request or after registration	For purchase	Not available	Cannot be assessed

Selection of hemophilia-specific instruments was primarily based on the instrument's content's fit with the construct of the health outcome definition. Then,; the psychometric quality of the instrument (as reported in previous systematic reviews [8-10]); the number of validated translations available (as reported in systematic reviews); and the availability and accessibility of the instrument (copyright, user fees) were used as secondary selection criteria. For two of the health outcomes (Ability to engage in normal daily activities and Sustainability of physical function, clinician-reported instruments were selected to supplement the patient-reported outcome measurement instruments. PROMIS item banks were selected based on their fit with the outcome construct and definition. Instruments were semi-formally scored on these criteria on a 4-point scale (-, +/-, +, ++) (Supplementary Table 3).

PROMIS item banks were selected from the Health Measures website (http://healthmeasures.net) based on the identified constructs. The number of available translations was extracted from the website.

Web-based meetings and voting process

A kick-off in-person Steering Group meeting was held in Dublin, Ireland, on July 19th 2018. The Decision Group provided an educational session on value-based health care principles and a presentation of the project protocol.

A nominal consensus process was followed with iterative discussions. A series of web-based meetings was held to reach consensus on the definition, health outcomes and risk adjustment variables. Prior to each meeting, panel members prepared individual assignments, whereby participants were asked to comment on definitions of health outcomes or risk-adjustment variables, or to select or rank health outcomes and risk-adjustment variables. A 10-point scoring system was used for some assignments, with 10 being the highest score and 1 the lowest. Assignments were to be submitted before each meeting. Results from the preparatory assignments were presented at each meeting for review and discussion. The purpose of the discussions was not to reach consensus on an absolute ranking of outcomes and risk adjustment variables. Instead, the ranking results served to facilitate qualitative discussions during the web-based meetings. The goal of these discussions was to confirm the voting results and to reach consensus. Any disagreements were discussed until consensus was reached. Consensus was considered reached when no new questions and discussion points were raised and all group members agreed with the conclusions of each session.

If consensus was not reached, the topic was added to the agenda of the next meeting and reviewed again. After each meeting, overviews of what was decided were distributed and all participants were explicitly asked whether they agreed with the decisions.

Table 4 shows the dates of the meetings with the different panels, meeting objectives, the number of completed assignments and meeting attendance.

Supplementary table 4: Overview of HaemoValue project meetings

Meeting dates	Working group	Meeting objectives	N of completed assignments (N patient representatives/N health care professionals)	Meeting attendance (N patient representatives/N health care professionals)
July 19, 2018	A	Introduce HaemoValue project Value-Based Health Care education Define medical condition	n.a.	4/10
1) Oct 15, 2018	A	Define medical condition and patient group Discuss longlist of health outcomes	5/10	5/8
2) Dec 20, 2018	A	Discuss shortlist of health outcomes Discuss longlist of risk-adjustment variables	3/10	3/10
3) Jan 21, 2019	B	Review and discuss shortlist of health outcomes	12/10	20
4) Feb 12, 2019	A	Review shortlist health outcomes and definitions Discuss Shortlist risk-adjustment variables	4/15	2/10
5) Mar 11, 2019	B	Review and discuss shortlist of risk-adjustment variables	9/8	10/10
6) May 6, 2019	B	Finalize international set of health outcomes Select most relevant risk-adjustment variables	8/8	2/8
7) May 20, 2019	A	Discuss final international set of health outcomes and definitions Discuss final list of risk-adjustment variables	5/15	2/11
8) May 27, 2019	C	Review of HaemoValue process and methodology Review of prefinal international set of health outcomes Comment on value of international standard set of health outcomes	n.a.	5
9) Jun 17, 2019	B	Review final international set of health outcomes and risk-adjustment variables	n.a.	6/10

A: core/steering group; B: Patients and Health Care Professionals Panel; C: International Academic Council; n.a.: not applicable; N: Number. For meetings 2 to 9, participants were asked to complete one pre-meeting assignment for each meeting, for meetings 4 and 7, participants were asked to complete two assignments.

1) Steering Group meeting 15 October 2018

In preparation for the meeting, Steering Group participants received the following preparatory assignments:

1) the two alternative definitions of the medical condition hemophilia
2) the longlist of all identified potential health outcomes: Participants were requested to submit responses to the following questions:
   a) Are the short descriptions of outcomes clear and valid?
   b) Are any outcomes missing from the longlist?

During the meeting, the two definitions were discussed. After the meeting, steering group members participated in two consecutive voting rounds.
- Voting round 1: what are the three most important health outcomes per subtier on the basis of the relevance to patients and the possibility of medical teams to act upon? Outcomes that were selected at least once moved to the second round of voting. Subsequently, the health outcomes that were not selected but that were considered important from both a patient- and value-based health care perspective were included in the second voting round.
- Voting round 2: Score the remaining health outcomes on a 10-point scale on the basis of three parameters:

1) Degree to which care activities influence the health outcomes.
2) Extent of the impact of the health outcome on patients.
3) Number of patients for whom the health outcome is relevant.

The 15 highest-ranking health outcomes per tier were compiled in an initial shortlist of 45 health outcomes.

2) Steering Group meeting 20 December 2018

The shortlist of 45 health outcomes was reviewed and discussed at the second steering group meeting, along with the longlist of all potential risk-adjustment variables. Participants were asked to add any relevant risk-adjustment variables to the longlist.

3) Patients and Health Care Professionals Panel meeting 21 January 2019

The Decision Group provided a brief educational session on value-based health care principles and an introduction to HaemoValue.
The shortlist of 45 health outcomes was sent to the Patients and Health Care Professionals Panel.

Preparatory assignments:

1) Select the five most important outcomes per tier from the shortlist.
2) Add any missing outcomes

The results of the Patients and Health Care Professionals Panel voting and those of the steering group voting were combined, resulting in a final shortlist.

4) Steering Group meeting 12 February 2019

Preparatory assignments:

1) Which risk-adjustment variables affect the health outcomes most, using a 10-point scoring system?
2) Comments on the health outcomes definitions drafted by the core group?
   Based on the steering group scoring of the risk-adjustment variables, the core group created a shortlist of risk-adjustment variables that was discussed during the meeting. The shortlist was sent to the Patients and Health Care Professionals Panel.

5) Patients and Health Care Professionals Panel meeting 11 March 2019

Preparatory assignments:

1) Select and rank the 5 most important health outcomes per tier.
2) Identify any risk-adjustment variables that were important and not included in the shortlist.

The health outcomes ranking and short list of risk-adjustment variables were discussed at the Patients and Health Care Professionals Panel meeting. Any missing risk-adjustment variables were added.

6) Patients and Health Care Professionals Panel meeting 6 May 2019

Preparatory assignments:

1) Do you agree with the definitions of the health outcomes proposed by the Steering Group?
2) Double check whether the health outcomes that were not selected in the first round were indeed not relevant enough to be included in the final outcomes set?
3) Select the 10 most important risk-adjustment variables from the shortlist.

7) Steering Group meeting 20 May 2019

Preparatory assignments:

1) Scored the quality of the definitions of the health outcomes on the shortlist, using a 10-point scoring system.
2) Rank the 5 most important health outcomes.
3) Do you agree with the proposed definitions of the risk-adjustment variables?
4) Select the ten most important risk-adjustment variables.

At the meeting the final international set of health outcomes and definitions and the final list of risk-adjustment variables were discussed. Any adjustments were made.

8) External review by independent International Academic Council

The Academic Council met by videoconference on May 27, 2019. Prior to the meeting, members received documentation outlining the goal of the project, panels involved and the process of international health outcomes set development. They reviewed an executive summary with the proposed definition of the medical condition hemophilia, the preliminary health outcomes set and the preliminary risk-adjustment variables set. The International Academic Council was asked to reflect on the process and the content of the health outcomes set development during the web-based meeting. The result of the meeting was a summary of recommendations for the Steering Group on all decision areas.

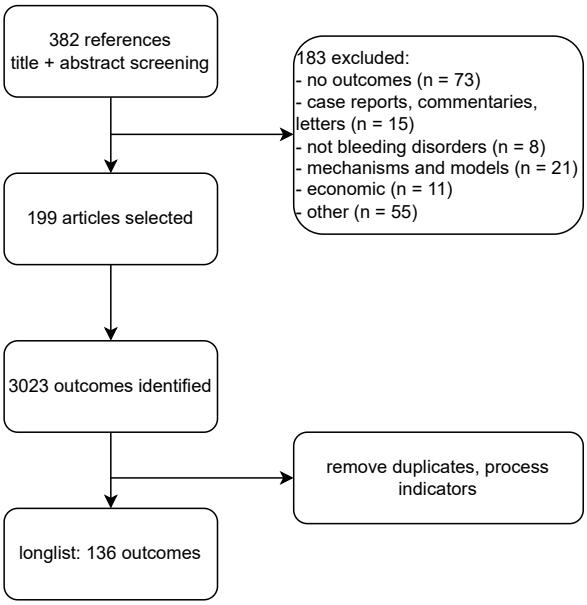
9) Steering group meeting, 17 June, 2019

At the final steering group meeting the final international standard set of health outcomes and risk-adjustment variables were reviewed as well as the comments of the International Academic Council.

Results

Literature search

Supplementary figure 1 shows the flowchart of the systematic literature search that aimed to identify health outcomes and risk adjustment variables. 199 references were initially included.[1-3, 11-206] Three references with outcomes for women were added later.[207-209]



Supplementary figure 1: Flowchart of systematic literature search

Definition of hemophilia

Consensus was reached about the definition of the medical condition hemophilia during the third steering group meeting.

Health outcomes

Preliminary definitions were used for the voting process. After voting, final definitions for the remaining health outcomes were written. Definitions were modified until consensus was reached. Tables 5 and 6 show the longlist and shortlist of health outcomes and their descriptions and definitions.

Supplementary table 5: Longlist of 136 health outcomes with draft explanatory descriptions, arranged by tier and subtier

ID	Outcome	Description
Tier 1: Health status achieved or retained		
Subtier 1.1: Survival		
1	**Cure**	The person is cured from hemophilia and does not require any further treatment
2	**Survival rate**	Survival among people with hemophilia within a certain time period
3	**Mortality rate**	Mortality among people with hemophilia within a certain time period
4	**Impact of disease on life expectancy**	The change in life expectancy for a person that could be attributed to hemophilia
5	**Life threatening complications**	Complications that threaten a person with hemophilia's life
6	**Life threatening bleeding episodes**	Bleeding episodes that threaten a person with hemophilia's life
Subtier 1.2: Degree of health or recovery		
7	**Change in treatment burden**	The change of the impact of the treatment burden (increased/decreased) on a person with hemophilia
8	Extent of recovery	The extent of recovery after a bleeding episode
9	Changes in vital signs	The change (improvement/deterioration) in the body's life-sustaining functions
10	**Physical health**	The ability to perform the basic actions (i.e. mobility, strength, and endurance) that are essential for maintaining independence and carrying out more complex activities
11	**Ability to return to work**	Ability to continue the same work after sick leave
12	Ability to engage in physical activities	The ability of a person with hemophilia to engage in physical activities
13	Extent of return to physical activities	The extent of engagement in similar physical activities as prior to the hemophilia-related event
14	Ability to engage in activities that are essential to live independently*	The ability to participate in activities that are essential to live independently
15	**Ability to engage in normal daily activities**	The ability to engage in activities of daily living
16	**Interference of pain with activities**	The change in the execution of daily activities caused by pain
17	**Mobility**	The mobility and range of motion of a person with hemophilia
18	Severity of bleeding episode	The severity of the bleeding episode
19	Response to treatment	The person with hemophilia's response on disease activity as a result of treatment
20	**Changes in functional status**	The change (improved/impaired) in functional capacity to perform functions of daily living
21	**Functional status achieved**	The ability to function in daily life
22	Alteration in target joints	The change of the appearance/disappearance of target joints, the number of target joints, and the target joint bleeding rate
23	Number of affected joints	The number of joints that are affected due to joint bleeding episodes

Supplementary table 5: *(Continued)*

ID	Outcome	Description
24	**Degree of hemophiliac arthropathy**	The extent of the joint disease due to recurrent bleeding into the joint
25	**Frequency of bleeding episodes requiring treatment**	The number of bleeding episodes that require treatment within a certain time period
26	**Frequency of bleeding episodes**	The number of bleeding episodes within a certain time period
27	Number of bleeding episodes	The total number of bleeding episodes
28	Changes in joint functional status	The change (improved/impaired) in joint functional capacity to perform functions of daily living
29	**Joint functional status achieved**	The ability of the joint to function in daily life
30	Frequency of joint bleeding	The number of joint bleeding episodes within a certain time period
31	Number of joint bleeding episodes	The total number of joint bleeding episodes
32	Total number of exposure days	Total number of days in which the patient is exposed to FVIII/FIX
33	**Frequency of injection/factor use**	The number of injections/consumptions within a certain time period
Tier 2: Process of recovery		
Subtier 2.1: Time to recovery and time to return to normal activities		
34	**Time to diagnosis**	The time from birth to diagnosis of hemophilia by hematologist
35	Time between the need for treatment and the start of treatment†	The time between the need for treatment and the start of the treatment
36	**Time to achievement of functional status**	Recovery time to achieve the functional status as prior to the bleeding episode
37	Time to response	The time between the bleeding episode and the response to the treatment
38	**Time to stop the bleed**	The time between the bleeding episode and the stop of bleeding
39	**Time to return to physical activities**	The time to return to being physically active
40	**Time to return to work**	The time between hemophilia-related stop with work and return to work
41	**Duration of factor expression**	Number of months/years of factor expression after gene therapy
42	Duration of vector-neutralizing response	The length of time a patient's body maintains an immune response to the viral vector that is used in gene therapy
43	**Time needed to achieve complete or partial ITI success**	The time between start of ITI and eradication of FVIII/FIX inhibitor
Subtier 2.2: Disutility of care or treatment process (e.g., diagnostic errors, ineffective care, treatment-related discomfort, complications, adverse events)		
44	Pain	The duration of general pain
45	**Chronic pain**	Persistent/chronic pain intensity and duration
46	**Acute pain**	Acute pain frequency, intensity, quality and duration
47	**Joint pain/arthralgia**	The pain frequency, intensity, quality and duration in a specific joint or joints
48	Pain or discomfort induced by treatment	Interference of treatment-related pain/discomfort on daily life/activities of daily living

Supplementary table 5: *(Continued)*

ID	Outcome	Description
49	**Side effects of treatment**	The occurrence of a secondary, typically undesired effect of a drug or medical treatment
50	**Complications direct due to disease**	Complications that could directly be attributed to the patient having hemophilia
51	Complications due to treatment (medical)	Complications that could be attributed to medical treatment activities
52	Allergic / hypersensitivity reactions	Allergic reaction to treatment
53	**Complications due to treatment (medical and non-medical)‡**	Complications (medical and non-medical) that could be attributed to medical treatment activities
54	Secondary complications	Complications that occur as result of primary complication
55	Duration of immune tolerance	Time during which immune tolerance is achieved (i.e. the inhibitor is eradicated)
56	Inhibitor development§	Presence of antibodies against factor VIII or IX
57	Other mental illnesses	Conditions, except from depression and anxiety, which causes serious disorder in a person with hemophilia's behaviour and thinking
58	Anxiety	General anxiety of persons with hemophilia
59	**Anxiety specific to events (e.g. having bleeding episodes)**	The anxiety of a person with hemophilia about occurrence of specific hemophilia- related events
60	**Depression**	Specific mental illness that is associated with feelings of severe despondency and rejection
61	Chronic inflammation of joints	Persistent/chronic inflammation of joint
62	**Development of hemophilia-related comorbidities¶**	The development of hemophilia-related comorbidities
63	Fracture	Broken bone
64	Risk of bone fracture	Hemophilia-related increased risk for bone fracture
65	Risk of falling	The increased risk of falling
66	**Inconvenience of prophylactic treatment**	Inconvenience of prophylactic treatment for person with hemophilia
67	**Infections (all-cause)**	The contracting of an infection
68	Transfusion transmitted infections	The contracting of an infection that is transmitted during transfusion
69	Risk of infections	Hemophilia-related increased risk of infection
70	**Total length of inpatient or outpatient stay (days)**	Total number of inpatient or outpatient days
71	**Number of emergency department visits**	Number of emergency visits due to hemophilia-related events
72	**Number of inpatient and outpatient visits**	Total number of inpatient and outpatient visits due to any hemophilia-related events
73	Number of unscheduled doctor's office visits	Number of unscheduled doctor's office visits due to any hemophilia-related events
74	**Number of days lost (work or school)**	Number of days lost from work or school because of hemophilia-related activities
75	Readmissions	Number of readmissions of persons with hemophilia
76	**Need for mobility aids**	Person with hemophilia who need a cane or a stick to walk
77	Progression of arthropathy	Worsening of the joint arthropathy
78	Cardiovascular risk	Risk of cardiovascular disease

Supplementary table 5: *(Continued)*

ID	Outcome	Description
Tier 3: Sustainability of health		
Subtier 3.1: Sustainability of health or recovery and nature of recurrences		
79	**Sustainability of functional status**	The sustainability of a person with hemophilia's ability to function in daily life
80	**Joint functional level maintained**	The maintained ability of the joint to function in daily life
81	**Impact on daily life of the therapy**	The impact of hemophilia-related treatment on the person's daily life encompassing physical, mental, and social health status
82	**General health / Quality of life**	The person with hemophilia's state of physical, mental, and social well-being
83	General health perception	The person with hemophilia's perception about his/her state of physical, mental, and social well-being
84	Body functioning	The sustainability of a person with hemophilia's body functioning
85	Body structure	The sustainability of a person with hemophilia's body structure
86	**Body image**	How a person with hemophilia sees himself/herself when looking in the mirror or picturing himself/herself in mind
87	**Vitality**	The vitality of a person with hemophilia
88	**Feeling of normalcy in daily life/ identification as person with hemophilia**	The person with hemophilia's feeling of being normal
89	Extent of being autonomous	The extent of being autonomous
90	**Perceived disease control**	The person with hemophilia's perception about his/her control over the disease
91	**Self-management**	A person with hemophilia's ability of taking responsibility for one's own behaviour and well-being
92	Self-efficacy	A person with hemophilia's motivated attitude towards a disease and its treatment, a capacity towards adequate judgment with regard to therapeutic interventions and demonstration of adherence to prescribed therapy
93	Self esteem	Level of self-confidence of a person with hemophilia
94	Ability to self-care	A person with hemophilia's ability to self-care
95	Ability to maintain basic self-care	A person with hemophilia's ability to maintain basic self-care
96	Interference with engaging in normal daily living	The change in daily life activities due to preoccupation with self-care practicalities
97	Ability to live independently	A person with hemophilia's ability to live independently
98	**Emotional functioning**	The awareness, expression and regulation of emotions
99	**Social functioning**	The interactions of a person with hemophilia with their environment and the ability to fulfil his/her role within such environments, such as work, social activities, and relationships with partners and family
100	Role functioning	The capacity of a person with hemophilia to perform activities typical to his/her specific age and particular social responsibility
101	Ability to participate in working life	A person with hemophilia's ability to participate in working life

Supplementary table 5: *(Continued)*

ID	Outcome	Description
102	**Effect of disease on education/ employment and employment-related issues**	The impact of hemophilia on the person's ability to achieve the same academic/employment results as when someone did not have hemophilia
103	**Securing appropriate employment**	The ability of a person with hemophilia to secure employment that is appropriate to his/her condition
104	School functioning	The capacity of a person with hemophilia to attend school, achieve academic results and engage in social relationships
105	Impact on academic achievement	The impact of having hemophilia on the person's academic achievement
106	Time lost from work/school	Time lost from work/school attainment due to hemophilia-related events
107	Change in work productivity	The change in work productivity due to hemophilia-related events
108	Confidence in ability to participate in sports	The confidence of a person with hemophilia in his/her ability to participate in sports
109	Attitude towards future	The attitude of a person with hemophilia towards the future
110	**Anxiety about financial aspects of the disease****	A person with hemophilia's anxiety that is related to the financial burden of hemophilia-related treatment and his/her financial security.
111	Anxiety about financial security	A person with hemophilia's anxiety about his/her financial security that is influenced by the person's hemophilia
112	**Impact on family life**	The impact of having hemophilia on pursuing a family life, including but not limited to childbearing, romantic/sexual relationships and marriage
113	Impact on residency	The impact of having hemophilia on a person's residential location
114	Impact on sexual health/intimacy	The impact of having hemophilia on a person's sexual health and intimacy
115	Sexual functioning	The extent of being able to experience sexual pleasures and satisfaction when desired
116	Impact of paternity	The impact of having hemophilia on the number of children conceived
117	Change in caregiver burden	The change in a caregiver burden that is attributed to changes in functional status of a person with hemophilia
118	**Disease impact on caregivers and/or partners††**	The impact of hemophilia on the caregiver and/or partner of a person with hemophilia
119	Impact on child care	The impact of having a child with hemophilia and the ability to find and maintain child care
120	Perceived family functioning of parent of children with hemophilia	The perceived family functioning from the perspective of the parent of a child with hemophilia
121	Perceived stress of parent of children with hemophilia	The perceived stress of the parent of a child with hemophilia
122	Need for reoperation/revision	The need for hemophilia-related reoperation/revision
123	**Recurrences of bleeding episodes**	Recurrences of bleeding episodes
124	Inhibitor recurrence	Development of inhibitor after first inhibitor was eradicated
125	**Mental health**	The psychological well-being or absence of mental illnesses

Supplementary table 5: *(Continued)*

ID	Outcome	Description
126	Worrying	The extent of worrying of a person with hemophilia
127	**Needle fear**	Fear of needles
128	Sleep	The quality and amount of sleep of a person with hemophilia
129	Tiredness/fatigue	General feeling of being tired
130	**Heavy menstrual bleeding‡‡**	Interference of heavy menstrual bleeding with a person with hemophilia's daily life
Subtier 3.2: Long-term consequences of therapy (e.g., care-induced illnesses)		
131	**Development of comorbidities on the long-term**	Occurrence of other diseases
132	Long-term - immune response to gene therapy	Reduced effectiveness of treatment as a result of an immune response against the gene therapy
133	Incidence of tumour development	Tumour development that is related to hemophilia-treatment
134	**Long-term venous access**	Worsening venous access due to many infusions in the same location
135	**Loss of mobility**	The loss of mobility due to inadequate alignment of prosthesis
136	**Susceptibility to infection**	A treatment-induced increased risk to attract an infection
137	**Frustration**	Frustration of a person with hemophilia that is directly or indirectly related to having the disease

Health outcomes in **bold** were the 71 health outcomes selected used for the second round of steering group voting.

*The original health outcome was 'Ability to engage in activities of daily living', but it was considered too similar to the outcome 'Ability to engage in normal daily activities'

†The original outcome was 'Time between birth and first and second joint surgery', but this was modified into 'Time between the need for treatment and the start of treatment' because it was considered more useful.

‡The original outcome was 'Complications due to treatment (non-medically induced; adverse events)', but this was modified into 'Complications due to treatment (medical and non-medical)' because it was not considered relevant to distinguish medical and non-medical complications.

§The outcome 'inhibitor development' was moved to subtier 3.2 prior to the second voting round.

¶The original outcome 'Comorbidities' was modified into 'Development of hemophilia-related co-morbidities' to make it more descriptive.

**The original outcome 'Anxiety about financial burden of treatment' was modified into 'Anxiety about financial aspects of the disease' to make it more descriptive.

††The original outcome 'Disease impact on partners' was broadened to 'Disease impact on caregivers and/or partners'.

‡‡The outcome 'Heavy menstrual bleeding' was added after the first steering group voting round.

Supplementary table 6: Shortlist of health outcomes with preliminary definitions

ID	Tier	Health outcome	Preliminary definition
1	I	Cure	A complete cure for hemophilia, consisting of a factor level >40%, measured twice resulting in a normal or near-normal bleeding tendency
2	I	Survival rate	The number / percentage of patients still alive after a certain time period
3	I	Mortality rate	The number / percentage of people that have died after a certain time period
4	I	Impact of disease on life expectancy	Decrease in number of years a person is expected to live due to hemophilia compared to an age-matched reference population
5	I	Life threatening complications	Occurrence of 1) fatal bleeding, 2) any intra-cranial, neck-throat, gastro-intestinal bleeding or 3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells, in a patient (per all patients), and any adverse events due to hemophilia regardless of the availability of treatment, that are potentially lethal
6	I	Major bleeding episodes	Occurrence of 1) fatal bleeding, 2) any intra-cranial, neck-throat, gastro-intestinal bleeding 3) bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells in a patient, per patient population (cumulative incidence)
7	I	Physical health	The ability and degree to perform the basic actions (i.e. mobility, strength, and endurance) that are essential for maintaining independency and carrying out activities (e.g. sports)
8	I	Ability to engage in activities that are essential to live independently	Carrying out daily routine: Carrying out simple or complex and coordinated actions in order to plan, manage and complete the requirements of day-to-day procedures or duties, such as budgeting time and making plans for separate activities throughout the day
9	I	Ability to engage in normal daily activities	Functional ability of individuals with hemophilia to perform activities of daily living (eating, bathing, dressing, chair transfer, squatting, walking pattern, stair climbing, running)
10	I	Functional status achieved	The degree of functional status, defined as the endurance, strength, and mobility of the body and body structures
11	I	Frequency of bleeding episodes	Mean total number of bleeds of any type per patient per year: annualized bleeding rate (including major/minor bleeds, joint/muscle/soft tissue/mucosal bleeds) as assessed clinically or with imaging studies, CNS bleeding assessed clinically and with imaging studies, or patient-reported bleeds or clinician-suspected bleed
12	II	Time to diagnosis	The time from initial symptoms until diagnosis of a bleed
13	II	Time between the need for treatment and the start of treatment	Time duration between onset of bleeding as assessed by patient, and administration of hemophilia treatment (clotting factor products, desmopressin)
14	II	Time to achievement of functional status	The time from the start of bleeding symptoms until achieving the functional status as prior to the bleed
15	II	Time to stop the bleed	The duration of time to pain relief, followed by complete resolution of symptoms

Supplementary table 6 (Continued)

ID	Tier	Health outcome	Preliminary definition
16	II	Chronic pain	The degree of chronic pain: a patient has chronic pain when they report pain for more than three months. Pain may be intermittent or continuous, and may be of variable intensity over this time. This is pain that is not associated with an acute bleeding episode
17	II	Acute pain	Degree of acute pain: Acute pain is a type of pain that typically lasts less than 3 to 6 months, or pain that is directly related to soft tissue damage such as a bleed. It is of short duration but it gradually resolves as the bleed resolves. Acute pain is distinct from chronic pain and is relatively more sharp and severe. Alternatively, pain may be assessed by cause of the pain: venous access, joint or muscle bleeding, post-operative pain
18	II	Joint pain/arthralgia	Degree of chronic pain in joints, which is a result of past bleeds. Sensation of unpleasant feeling indicating potential or actual damage to one or more joints. It includes: sensations of generalized or localized pain in joint(s), stabbing pain, burning pain, dull pain, aching pain; impairments such as myalgia, analgesia and hyperalgesia
19	II	Complications direct from disease	Complications that are due to an increased bleeding tendency: musculoskeletal complications, excessive bleeding (during or after surgical procedures, bleeding after trauma, post-partum hemorrhage), compartment syndrome, pseudo-tumors, iron deficiency. Excluded complications are those due to treatment (see ID #20: complications due to treatment)
20	II	Complications due to treatment (medical and non-medical)	Any health complication that is caused by administration of treatment: inhibitor development and treatment-related infections, other infection-related complications, thrombosis complications of medication (complications from medical perspective). It includes also difficult venous access, infections or thrombosis from central venous access devices (CVADs) as well as clogging of port-a-catheters (complications from patient perspective)
21	II	Number of days lost (work or school)	Number of extra days a person is absent from work or school due to hemophilia (because of a bleed, hospital admission, outpatient visit, picking up medication). Excluded are days of absence for other reasons
22	II	Need for mobility aids	Patient-reported use of any device designed to assist walking or otherwise improve the mobility of people with a mobility impairment, e.g. walking cane, walker, wheelchair at any time. It does not include mobility aids that are used temporarily, e.g. because of a bleed
23	II	Recurrences of bleeding episodes	Rebleed into a muscle/joint, defined as any bleed that occurs at the same location as the original bleed, >72 hours after stopping the treatment for the initial bleed
24	II	Inhibitor development	The development of alloantibodies to FVIII or FIX that neutralize the function of infused clotting factor concentrates. Considered relevant if documented on two separate occasions within a 1-4 week period and a level of >0.6 BU/mL . For inhibitors to be considered clinically significant, they should be associated with < 66% recovery of the particular product
25	III	Sustainability of functional status	The change in functional status as defined in ID #10 (functional status achieved), per year

Supplementary table 6 (Continued)

ID	Tier	Health outcome	Preliminary definition
26	III	Joint functional level maintained	The degree of joint function, as defined as the joint strength, endurance, and range of motion
27	III	Impact on daily life of the therapy	The burden of treatment, defined as the extra work and time it requires a person with hemophilia to order, pick up, transport and store clotting factor, including the need for a fridge, the need to prepare the medication before use and administering the injection. May also include registering and remembering administrations. The burden of treatment may also be financial if patients need to pay for part or all of their treatment
28	III	General health / Quality of life	Quality of life is health-related quality of life in this setting. HRQOL is the functional effect of a medical condition and/ or its consequent therapy upon a patient. HRQOL is thus subjective and multidimensional, encompassing physical and occupational function, psychological state, social interaction and somatic sensation
29	III	Effect of disease on education/employment and employment-related issues	The degree to which hemophilia limits a person to engage in all aspects of work, as an occupation, trade, profession or other form of employment, for payment, as an employee, full or part time, or self-employed, such as seeking employment and getting a job, doing the required tasks of the job, attending work on time as required, supervising other workers or being supervised, and performing required tasks alone or in groups. The effect on education may be due to two mechanisms: 1) frequent bleeding episodes leading to diminished ability to take advantage of academic opportunities, in part because of school absenteeism, and 2) factors that limit or interfere with physical functioning having an effect by reducing the ability to complete schoolwork and participate in school-related activities
30	III	Securing appropriate employment	Whether someone with hemophilia has a job to maintain himself
31	III	Disease-related anxiety	The degree of anxiety, such as a feeling of worry, nervousness, or unease about something with an uncertain outcome, for example the cost of hemophilia treatment, fear of falling or disease progression
32	III	Impact on family life	The impact of having hemophilia on pursuing a family life, including but not limited to childbearing, romantic/sexual relationships, marriage and passing the condition on to offspring
33	III	Disease impact on caregivers and/or significant others	Degree of burden of care, emotional, physical, practical and mental wellbeing on caregiver and / or significant others of the person with hemophilia
34	III	Mental health	Degree of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community

Supplementary table 6 (Continued)

ID	Tier	Health outcome	Preliminary definition
35	III	Social functioning	Complex interpersonal interactions, as defined by WHO: the degree of a person to maintain and manage interactions with other people, in a contextually and socially appropriate manner, such as by regulating emotions and impulses, controlling verbal and physical aggression, acting independently in social interactions, and acting in accordance with social rules and conventions, when for example playing, studying or working with others

Outcomes that were removed from initial shortlist: Mortality rate; Securing appropriate employment.
Outcome that was added: Major bleeding episodes
Outcomes that were combined: 'Survival rate' was combined with 'Impact of disease on life expectancy'; 'Physical health' and 'Ability to engage in activities that are essential to live independently' were combined with 'Ability to engage in normal daily activities'; 'Time to stop the bleed' was combined with 'Time to achievement of functional status'; 'Joint pain' was combined with 'Chronic pain'; 'Inhibitor development' was combined with 'Complications due to treatment'; 'Sustainability of joint functional level' was combined with 'Sustainability of functional status'.

Risk-adjustment variables

Table 7 shows the longlist of risk-adjustment variables. We recommend to measure risk-adjustment variables as described in Table 8.

Supplementary table 7: Longlist of potential risk-adjustment variables with explanatory descriptions.

#ID	Patient initial condition	Description
1	**Age at first joint bleed**	Age at first confirmed joint bleed
2	**Severity of hemophilia**	The amount of clotting factor that is Missing from a person's blood
3	Type of hemophilia	Whether the gene mutation is related to factor VIII/IX
4	Hemophilia in family	Whether family members also have hemophilia
5	**Comorbidities**	The presence of diseases in addition to hemophilia
6	**HIV infection**	Whether the person with hemophilia is infected with HIV
7	**HCV infection**	Whether the person with hemophilia is infected with HCV
8	**Psychological well-being**	Whether a person with hemophilia has mental health disorders (including depression)
9	**Body Mass Index (BMI) / obesity**	The Body Mass Index of a person
10	**Bleeding frequency**	Number of spontaneous bleeds in the past year or in a specified number of consecutive months
11	Spontaneous bleed in the past 12 months	Whether or not patient had at least one spontaneous bleed in the last 12 months
12	Previous treatment with factor	How many times has the person been exposed to coagulation factor replacement therapy
13	**Inhibitor status**	Whether or not an inhibitor is present that provokes an immune response to treatment with clotting factor concentrates
14	Bleeding location	Whether the bleeding episode is in a joint, muscle, etc.

Supplementary table 7 (Continued)

#ID	Patient initial condition	Description
15	Performance status	Whether a person with hemophilia reports to be limited in certain activities
16	Joint specific surgical history	History of previous joint surgery (e.g. joint replacements)
17	**Degree of arthropathy / arthritis**	The degree of joint damage
18	Pain medication use	Use of (over-the-counter) pain medicine or strong pain medicine
19	Total number of medications prescribed	Total number of medications prescribed
20	Adherence to medication	Whether the person with hemophilia adheres to its prescribed medication
21	**Bleeding phenotype**	The combination of the type and severity of bleeding episodes
22	Frailty stage	Frailty profile of older adults
23	Cognitive impairment	Whether any cognitive impairment exists
24	Hearing or vision impairment	Decreased vision or hearing
25	**Availability of and access to treatment (financial / supply)**	Whether persons with hemophilia (PWH) have access to and can afford coagulation factor
26	**Involvement of health care professional in management of hemophilia**	Whether hemophilia is managed by a specialized hemophilia team (e.g. hematologist, nurse, physiotherapist, general practitioner (GP)/ family doctor , psychologist etc) and level of care received
27	Responsible person for managing hemophilia	Who is responsible for managing hemophilia (e.g. FVIII administration)? For instance: parent, partner, family member, self-care by PWH
28	Treatment location	Whether patient is treated at home or receives care in care facilities
29	Discharge destination	Where does a person with hemophilia go to after discharge (e.g. home, nursing home)
30	Frequency of HTC visit	Number of visits to hemophilia treatment center in the past year
31	**Person with hemophilia's knowledge about the disease**	The person with hemophilia's knowledge about hemophilia and knowledge about management of the disease
32	**Health literacy***	The degree to which individuals have the capacity to understand health information adequately
33	Caregivers knowledge about the disease	The caregiver of a person with hemophilia's knowledge about hemophilia and management of the disease
34	**Date of birth**	Age, based on date of birth
35	Age at diagnosis	Age at confirmed diagnosis of hemophilia
36	Age at first encounter with team	First referral to hemophilia treatment center
37	**Gender**	Gender at birth
38	Country of origin	Country where the person was born
39	Ethnicity	Ethnic origin
40	Ethnicity parents*	The ethnic origin of the biological parents of the person with hemophilia
41	Religiosity*	Whether a person has religious feelings or beliefs
42	Diet*	A special course to which a person restricts themselves (including experimental nutrition models)
43	Physical activity level*	The extent to which the person with hemophilia is physically active
44	Residency/distance to treatment center	Distance from a person with hemophilia's residency to the hemophilia treatment center (HTC) where the PWH receives comprehensive assessment and care

Supplementary table 7 (Continued)

#ID	Patient initial condition	Description
45	Country of residence	Country where the person lives
46	Education level	Highest level of education completed
47	Parent education	Highest level of education completed by the parents of a person with hemophilia
48	Income level	The annual income of the person with hemophilia (before tax)
49	Work status	Is the person with hemophilia employed? (fulltime or parttime) Does the person receive work-related benefits
50	Social support / network	Does the person with hemophilia have support by significant others and/or caregivers
51	Marital status	The relationship status
52	Housing condition	Whether a person with hemophilia lives alone, together with his/her family, in a nursing home or other facility, or does not have a house
53	**Insurance status**	What type of health care insurance does the person with hemophilia have? To what extent does the person with hemophilia have to pay for his/her treatment?
54	Family's socio-economic status	The economic and sociological class of the family of a person with hemophilia
55	**Individual socio-economic status**	An individual's economic and sociological class
56	Parity	Parity greater than 0
57	Perception of disease control	Perceived degree of control of hemophilia by caregiver and/or PWH
58	Physical activity	Whether patient is physically active
59	Smoking status	Whether a person with hemophilia smokes more than 1 tobacco product a week
60	Alcohol use	Whether a person with hemophilia uses more than 1 alcoholic beverage a day
61	Drug use*	Whether a person with hemophilia consumes substances (including alcohol) or drugs in amounts or with methods which are harmful to themselves or others

Risk-adjustment variables indicated with * were added after steering group discussions. The risk-adjustment variables 'obstetric history' and 'multiple gestations' were removed from the longlist. Risk-adjustment variables indicated in **bold** were selected for the shortlist.

Supplementary table 8: Measurement of risk-adjustment variables

Risk-adjustment variable	Description	Response options	Timing	Data source
Age	Month and year of birth	MM/YYYY	Baseline	Patient-reported
Gender	Gender at birth	0 = male 1 = female 2 = other, please specify 999 = undisclosed	Baseline	Administrative
Availability of and access to treatment	Amount of coagulation factor (in IU) available per capita per patient, and type of product used (standard or extended half-life)	- IU/capita/patient - type of product (SHL, EHL)	Baseline	Administrative
Individual socio-economic status (in adult persons with hemophilia)	Patient's socioeconomic status, or that of their family (children). Education level according to ISCED may be used as a surrogate	0 = Low 1 = Middle 2 = High	Baseline	Administrative
Severity of hemophilia	Plasma levels of factor VIII (FVIII) or IX (FIX) activity	0 = Mild (5-40 IU/dl) 1 = Moderate (1-< 5 IU/dl) 2 = Severe (<1 IU/dl)	Baseline	Administrative (lab) / clinical
Psychological well-being	Degree of psychological functioning, assessed by generic mental health questionnaire	Calculated score	Baseline and annually	Patient-reported
Inhibitor status	Current or past inhibitor: clinically relevant inhibitor defined as an inhibitor that is documented on two separate occasions within a 1–4 week period and with a positive titer (cut-off) according to the local laboratory using the Nijmegen modification of the Bethesda assay.	0 = Never inhibitor 1 = Past inhibitor, but disappeared spontaneously or as a result of treatment 2 = Current inhibitor 999 = Unknown	Baseline and annually	Administrative (lab) / clinical
Degree of joint damage	Patient's degree of joint damage due to recurrent bleeding in the joint. As a surrogate, patient-reported range of motion may be used.	Numerical	Baseline and annually	Clinical or patient-reported

Supplementary table 8: Measurement of risk-adjustment variables *(Continued)*

Risk-adjustment variable	Description	Response options	Timing	Data source
Comorbidities	Have you been told by a doctor that you have any of the following? Based upon the Self-administered Comorbidity Questionnaire[210]	0 = I have no other diseases 1 = Heart disease (e.g. angina, heart attack, heart failure) 2 = High blood pressure 3 = Poor circulation (resulting in leg pain) 4 = Lung disease (e.g. asthma, chronic bronchitis, emphysema) 5 = Diabetes 6 = Kidney disease 7 = Liver disease 8 = Problems caused by stroke 9 = Disease of the nervous system (e.g. Parkinson's disease, multiple sclerosis) 10 = Malignant neoplasms/cancer (within the last 5 years) 11 = Depression 12 = Arthritis 13 = HIV 14 = Hepatitis C 15 = Thrombosis (venous thromboembolism, pulmonary embolism) 15 = Other, please specify	Baseline and annually	Clinical

Supplementary table 8: Measurement of risk-adjustment variables *(Continued)*

Risk-adjustment variable	Description	Response options	Timing	Data source
Health literacy	Health literacy is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.	0 = Illiterate 1 = Functional or basic literacy 2 = Communicative/ interactive literacy 3 = Critical literacy	Baseline	Clinical
Involvement of comprehensive hemophilia care team	Indicate which hemophilia care professionals are involved in the comprehensive hemophilia care team.	0 = Hematologist 1 = Nurse 2 = Physiotherapist 3 = Psychologist 4 = Social worker 5 = Orthopedic specialist 6 = Rehabilitation specialist 7 = Clinical geneticist 8 = Other, specify	Baseline and ongoing	Patient-reported

Selection of measurement instruments

Supplementary table 9 summarizes the scoring of the hemophilia-specific measurement instruments, both patient-reported as well as clinical outcome assessment instruments. The core group scored instruments on fit with outcome, psychometric quality, number of translations, time to complete and availability / accessibility.

Supplementary table 9: Overview of potential hemophilia-specific measurement instruments

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct - cross-cultural validity				
Ability to engage in normal daily activities											
Adults - patient-reported											
HAL: use of transportation*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	3 items	++	++
HAL: self-care*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	5 items	++	++
HAL: household tasks*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	6 items	++	++
Haemo-QoL-A: physical functioning	+	+++	++	+++	++ (total scale)	+	++ (total scale)	32	11 items	+	+
Haemo-QoL-A: role functioning	+/-	+++	++	+++	++ (total scale)	+	++ (total scale)	32	14 items	+	+
Hemofilia-QoL: physical health	+/?	+++	+	+++	NIA	-	NIA	9	16 items	+	?
Haem-A-QoL: physical health	+/?	++	+	NIA	NIA	+	NIA	57	5 items	++	+
Haem-A-QoL: sports / leisure	+/?	++	+	NIA	NIA	+	NIA	57	5 items	++	+
PROBE (difficulties with daily activities)	+	+	+	+	NIA	+	++	58	1 item	++	+
Children - patient-reported											
PedHAL: use of transportation*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	3 items	++	++
PedHAL: self-care*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	5 items	++	++

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct - cross-cultural validity				
PedHAL: household tasks*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	6 items	++	++
Haemo-QoL: physical health	+/?	- (4-7 years) + (8-16 years)	+ (8-16 years)	+++	? (total scale)	- (total scale)	NIA	28	8-12 domains/ 21-77 items	-	+
Haemo-QoL: sport and school	+/?	- (4-12 years) + (13-16 years)	? (4-7 years) + (8-16 years)	+++	? (total scale)	- (total scale)	NIA	28	8-12 domains/ 21-77 items	-	+
CHO-KLAT	+	?	+++	+++		+++	NIA	20	1 (35 items)	+/-	+
Haemo-QoL index	+	?	+	NIA	---	+	NIA	6	1 item	++	+
'Toddler questionnaire': physical functioning	+/?	++	NIA	+++	NIA	+	NIA	?	?	? (-)	?
Adults - clinician-reported											
FISH*	+	n.a.	+	n.a.	n.a.	++	n.a.	n.a.	n.a.	+/-	++
Accelerometer	-	n.a.	NIA	n.a.	n.a.	+/-	n.a.	n.a.	n.a.	n.a.	+/-
Six minute walk test	-	n.a.	NIA	n.a.	n.a.	+/-	n.a.	n.a.	n.a.	+	++
Timed up and go test	-	n.a.	NIA	n.a.	n.a.	++	n.a.	n.a.	n.a.	++	++
Children - clinician-reported				n.a.							

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct - cross-cultural validity				
FISH*	+	n.a.	+	n.a.	n.a.	++	n.a.	n.a.	n.a.	+/-	++
Accelerometer	-	n.a.	n.a.	n.a.	n.a.	+/-	n.a.	n.a.	n.a.	n.a.	+/-
Six minute walk test	-	n.a.	n.a.	n.a.	n.a.	+/-	n.a.	n.a.	n.a.	+	++
Chronic pain											
Adults											
Hemofilia-QoL: pain	+/?	+++	+	+++	n.a.	+	NIA	9	2 items	++	?
PROBE chronic pain*	+	+	+	+	n.a.	+	NIA	22	3 items	++	+
Children											
PROBE chronic pain*	+	+	+	+	n.a.	+	NIA	22	3 items	++	+
Sustainability of physical functioning											
Adults - patient-reported											
HAL: lying down / sitting / kneeling / standing*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	8 items	++	++
HAL: functions of the legs*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	9 items	++	++
HAL: functions of the arms*	++	? (total scale)	? (total scale)	++ (total scale)	? (total scale)	+/- (total scale)	? (total scale)	9	4 items	++	++
Hemofilia-QoL: joint damage	+/?	+++	+	+++	NIA	-	NIA	9	3 items	++	?

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct - cross-cultural validity				
Haemo-QoL-A: physical functioning	+/-	+++	++	+++	NIA	+	NIA	32	11 items	+	+
Haem-A-QoL: physical health	+/-	++	+	NIA	NIA	+	NIA	32	5 items	++	+
Adults - clinician-reported											
WFH physical examination score (Gilbert)	++	n.a.	n.a.	n.a.	n.a.	+/-	n.a	n.a	n.a	-	++
Colorado physical examination scale	++	n.a.	n.a.	n.a.	n.a.	n.a.	n.a	n.a	n.a	? (-)	++
Petrini joint score	++	n.a.	n.a.	n.a.	n.a.	n.a.	n.a	n.a	n.a	? (-)	++
Hemophilia Joint Health Score (HJHS)*	++	n.a.	n.a.	n.a.	n.a.	++	n.a	7	n.a	-	++
Colorado Adult Joint Assessment Scale (CAJAS)	++	?	+	+	n.a.	?	n.a.	n.a.	9 items, 6 joints	-	++
Children - patient-reported											

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct - cross-cultural validity				
PedHAL: sitting / kneeling / standing*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	10 items	+	++
PedHAL: functions of the legs*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	11 items	+	++
PedHAL: functions of the arms*	++	? (total scale)	? (total scale)	+ (total scale)	NIA	? (total scale)	NIA	4	6 items	++	++
CHO-KLAT	-	?	+++	+++	NIA	+++	NIA	20	1 (35 items)	+/-	+
Haemo-QoL: physical health	+/-	- (4-7 years) + (8-16 years)	+ (8-16 years)	+++	? (total scale)	- (total scale)	NIA	28	8-12 domains/ 21-77 items	-	+
'Toddler questionnaire' (physical functioning)	+/-	++		+++	NIA	+	NIA	?	?	? (-)	?
Children - clinician-reported											
WFH physical examination score (Gilbert)	++	n.a.	n.a.	n.a.	n.a.	+/-	n.a	n.a	n.a	-	++

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct -cross-cultural validity				
Colorado physical examination scale	++	n.a.	n.a.	n.a.	n.a.	+/-	n.a	n.a	n.a	? (-)	++
Petrini joint score	++	n.a.	n.a.	n.a.	n.a.	++	n.a	n.a	n.a	? (-)	++
Hemophilia Joint Health Score (HJHS) *	++	+	n.a.	n.a.	+	+/-	n.a.	7	n.a	-	++
Social functioning											
Adults											
Hemofilia-QoL: social support	+ / ?	+++	+	+++	NIA	+	NIA	9	3 items	++	?
Haemo-QoL-A: role functioning*	++	+++	++	+++	NIA	+	NIA	32	14 items	+	+
Haem-A-QoL: family planning	+/- ?	++	+	NIA	NIA	+	NIA	57	4 items	++	+
Haem-A-QoL: relationship / partner	+/- ?	++	+	NIA	NIA	+	NIA		3 items	++	
Children											
CHO-KLAT*	+	?	+++	+++	NIA	+++	NIA	20	1 (35 items)	? (-)	+
'Toddler questionnaire' (social functioning)	+ / ?	NIA	NIA	NIA	NIA	NIA	NIA	NIA	NIA	NIA	?

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct -cross-cultural validity				
Haemo-QoL: family	+/?	-	+(8-16 years)	+++	NIA	-(4-12 years) +(13-16 years)	NIA	NIA	8-12 domains/ 21-77 items	-	+
Haemo-QoL: friends	+/?	?(4-7 years) +(8-12 years) -(13-16 years)	+(8-16 years)	+++	NIA	?(4-12 years) -(13-16 years)	NIA	NIA	8-12 domains/ 21-77 items	-	+
Haemo-QoL: others	+/?	-(4-7 years) +98-16 years)	+(8-16 years)	+++	NIA	+(4-7 years) ?(8-16 years)	NIA	NIA	8-12 domains/ 21-77 items	-	+
Mental health											
Adults											
Hemofilia-QoL: emotional functioning	+/?	+++	+	+++	+	+	NIA	9	5 items	++	?
Hemofilia-QoL: mental health	+/?	+++	+	+++	+	+	NIA	9	4 items	++	?
Haemo-QoL-A: emotional impact*	+	+++	+++	+++	NIA	+	NIA	32	11 items	+	+
Haem-A-QoL : feelings	+/?	++	+	NIA	NIA	+	NIA	57	4 items	++	+
Haem-A-QoL: view	+/?	++	+	NIA	NIA	+	NIA	57	5 items	++	
Haem-A-QoL: dealing	+/?	--	+	NIA	NIA	+	NIA	57	3 items	++	
Hemophilia Well-Being Index	+/-	+++	++	+++	+++	+	NIA	3	11 domains	?(-)	+
Children											
CHO-KLAT*	+	?	+++	+++	NIA	+++	NIA	20	1 (35 items)	?(-)	+

Supplementary table 9 (Continued)

	Fit with outcome	Psychometric characteristics						N validated translations	N domains and items	Time to complete	Availability/ accessibility
		Internal consistency	Test-retest reliability	Content validity	Construct - structural validity	Construct - hypothesis testing	Construct -cross-cultural validity				
Haemo-QoL: feeling	+/?	+	+	+++	NIA	- (4-12 years) + (13-16)	NIA	28	8-12 domains/ 21-77 items	-	+
Haemo-QoL: view	+/?	- (4- 7 years) + (8-16 years)	+	+++	NIA	- (4-12 years) + (13-16)	NIA	28	8-12 domains/ 21-77 items	-	+

n.a.: not applicable. * indicates the recommended health outcome measurement instrument.

4 point score for fit of outcome was: ++ tools fits well with definition of outcome, + tool fits reasonably well, but may measure more domains, +/- tool measures related construct, but does not fit with outcome and - tool does not fit with outcome.

For psychometric properties: +++ or – – – strong evidence positive/negative result, ++ or – – moderate evidence positive/negative result, + or – limited evidence positive/negative result, +/- conflicting evidence, ? unknown due to poor methodological quality, n.a. measurement property not applicable for measurement tool, NIA = no information available [8-10].

4 point score time to complete was ++ less than 5 minutes, + 6 to 10 minutes, +/- 11 to 20 minutes and – more than 20 minutes.

4 point score for availability and accessibility was ++ free to use and publicly available, + free to use, available on request / after registration, +/- for purchase and - not available for use.

Responsiveness: Evidence on responsiveness was missing for outcome assessment instruments in the domain of activities and participation and hemophilia-specific health related quality of life questionnaires. [9, 10] For hemophilia-specific instruments of joint health overall responsiveness was +/- for the WFH (- in children/na in adults), ++ for the CPE (+ in children/+ in adults), + for PJS (not available in children/not available in adults), unknown for the HJHS (unknown in children/unknown in adults)[8] and ? for CAJAS.[211]

Additional information recommended instruments

Hemophilia Activities List (HAL)

The Hemophilia Activities List contains seven domains with 42 items. The domains are Lying/sitting/kneeling/standing (8 items), Functions of the legs (9 items), Functions of the arms (4 items), Use of transportation (3 items), Self-care (5 items), Household tasks (6 items), Leisure activities and sports (7 items). Domains can be administered separately. All domains except Leisure activities and sports were considered for HaemoValue appraisal. https://elearning.wfh.org/resource/haemophilia-activities-list-hal/

Pediatric Hemophilia Activities List (PedHAL)

The Pediatric Hemophilia Activities List contains seven domains with 53 items. The domains are Sitting/kneeling/standing (10 items), Functions of the legs (11 items), Functions of the arms (6 items), Use of transportation (3 items), Self-care (9 items), Household tasks (3 items), Leisure activities and sports (11 items). All domains except Leisure activities and sports were considered for HaemoValue appraisal.
https://elearning.wfh.org/resource/haemophilia-activities-list-pediatric-pedhal/

Functional Independence Score in Hemophilia (FISH)

The Functional Independence Score in Hemophilia is a performance-based tool to assess an individual's functional ability. Eight activities of daily living are assessed: eating, grooming, dressing, chair transfer, squatting, walking, step climbing, and running.
https://elearning.wfh.org/resource/functional-independence-score-in-hemophilia-fish/

Hemophilia Joint Health Score (HJHS)

The Hemophilia Joint Health Score assesses joint health in people with hemophilia.
It measures functional impairment of the six main joints (ankles, knees and elbows).
http://ipsg.ca/update/hemophilia-joint-health-score-toolkit-web-site

PROBE

The PROBE questionnaire consists of four parts: part 1 contains demographic data, part 2 contains patient-reported outcomes (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 comorbid diseases), part 3 contains questions about clinical characteristics of hemophilia and part 4 contains the EQ-5D-5L. The patient-reported outcome portion of the questionnaire is part 2, which is summarized in a numerical score spanning from 0 to 1. For the HaemoValue appraisal, questions from part 2 have been considered. https://probestudy.org/contact_us

CHO-KLAT

The Canadian Hemophilia Outcomes – Kids' Life Assessment Tool (CHO-KLAT) is a hemophilia-specific instrument that measures several aspects of quality of life in children. The CHO-KLAT is currently being updated to make it more sensitive to capture burden of treatment. https://eprovide.mapi-trust.org/instruments/canadian-hemophilia-outcomes-kids-life-assessment-tool

Haemo-QoL-A

Haemo-QoL-A consists of 41 items in six domains. The domains are Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns. The domains Physical functioning and Role functioning were considered for HaemoValue appraisal.https://eprovide.mapi-trust.org/instruments/hemophila-specific-quality-of-life-questionnaire-for-adults

PROMIS item banks

PROMIS item banks are large collections of items measuring the same construct. Short forms with different lengths (4, 6 or 8 items) are also available. http://www.healthmeasures.net/index.php?Itemid=992

References

Available in the online Supplement

CHAPTER 6

Validation of PROMIS Profile-29 in adults with hemophilia in the Netherlands

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J Thromb Haemost. 2021;19:2687–2701.

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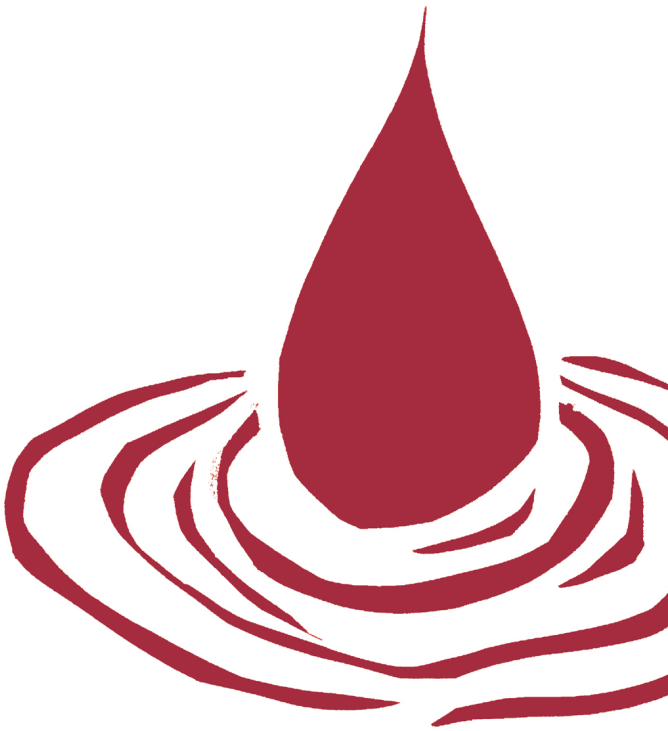

Abstract

Background

The PROMIS Profile-29 questionnaire is widely used worldwide, but it has not yet been validated in the Netherlands, nor in persons with hemophilia. The aim of this study was to validate the Dutch-Flemish version of the PROMIS-29 Profile v2.01 in adults with hemophilia.

Methods

Dutch males with hemophilia (all severities) completed questionnaires that contained socio-demographic and clinical characteristics, the PROMIS-29, RAND-36, and the Hemophilia Activities List (HAL). Structural validity of each subscale was assessed with Confirmatory Factor Analysis (CFA). Internal consistency was calculated for each subscale with sufficient model fit in CFA. Construct validity was assessed by testing hypotheses about 1) correlations of each PROMIS-29 subscale with corresponding scales of RAND-36 and domains of HAL, and 2) mean differences in T-scores between subgroups with different hemophilia severities, self-reported joint impairment, and hiv infection status. We considered ≥75 percent of data in accordance with the hypotheses evidence for construct validity.

Results

In total, 770 persons with hemophilia participated in this cross-sectional study. CFA revealed sufficient structural validity for five subscales: Physical Function, Depression, Sleep Disturbance, Ability to Participate in Social Roles and Activities and Pain Interference. Internal consistency was high and Cronbach's alpha ranged from 0.79 for Sleep Disturbance to 0.96 for Pain Interference. Differences between clinical subgroups were in the expected direction. Construct validity was confirmed for Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, and Pain Intensity.

Conclusion

This study revealed sufficient evidence for structural validity, internal consistency, and construct validity for most PROMIS Profile-29 subscales among people with hemophilia in the Netherlands.

Introduction

The congenital bleeding disorder hemophilia causes recurrent bleeds into joints and muscles due to a deficiency in coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). The condition predominantly affects males and is classified into mild (0.05-0.40 IU/mL), moderate (0.01-0.05 IU/mL) and severe (<0.01 IU/mL) hemophilia, depending on the activity of factor VIII or IX. Individuals with severe hemophilia often suffer from spontaneous bleeds into joints and muscles, while those with mild hemophilia typically bleed when triggered by trauma or surgery.[1] Treatment consists of coagulation factor replacement by intravenous injection to treat bleeds (episodic treatment) or to prevent bleeds (prophylaxis, defined as regular administration of an hemostatic agent, usually administered intravenously or subcutaneously). Recently, non-factor replacement products have been marketed and gene therapy is currently under study.[1]

Early forms of treatment had devastating effects on the hemophilia community: through contaminated plasma-derived blood products, many patients were infected with hiv in the 1980s and / or hepatitis C (HCV) before the 1990s.[2] The availability of treatment has resulted in a near-normal life expectancy and improved outcomes,[3] but a potential side-effect of factor replacement therapy is the development of neutralizing antibodies ('inhibitors') against the infused coagulation factor. Regular prophylaxis with factor replacement products is not effective in patients with inhibitors, and since recently, prophylaxis with non-factor replacement products helps reduce the burden of bleeding.[1] In addition, joint damage (hemophilic arthropathy), pain and disability are still relatively common, especially among older males affected by severe hemophilia, due to recurrent joint bleeding. Large differences in joint status and pain exist between individuals. It is important to measure and monitor these outcomes in persons with hemophilia in order to personalize health care.

Patient-reported outcomes (PROs) are any aspect of a patient's health that come directly from the patient without interpretation of the patient's responses by a physician or anyone else.[4] In hemophilia, PROs have been measured with hemophilia-specific instruments such as the Hemophilia Activities List (HAL),[5, 6] Haemo-QoL-A [7] and Hemofilia-QoL [8] as well as with generic instruments such as the RAND-36 [9] or EQ-5D. Two systematic reviews reported that the measurement properties of hemophilia-specific instruments have not been studied sufficiently, in particular structural validity, responsiveness and hypothesis-testing.[10, 11] Whether to use disease-specific or generic tools for hemophilia PROs depends on the goal of measuring such outcomes.

An alternative approach to measuring patient-reported outcomes is to use generic instruments based on Item Response Theory (IRT), which has several advantages over other generic instruments. First, instruments using IRT-based scoring take the difficulty of items into account, thereby providing more valid and reliable scores.[12] Second, IRT-based item banks, consisting of large sets of questions, can be used as short forms of

any length (consisting of the best performing items from an item bank) or as computerized adaptive tests (CAT). In a CAT, the computer selects relevant questions based on the answer to the previous question, resulting in even more efficient and precise, but comprehensive assessment of a construct of interest. The use of patient-reported outcome measures (PROMs) in clinical practice is increasing. Using different PROMS for different patients and implementing many different PROMs in electronic health records may pose a burden on researchers and clinicians. Therefore, the availability of valid and precise generic PROMs for domains that are relevant across medical conditions (such as pain, fatigue, physical function) would be highly beneficial.

The Patient-Reported Outcomes Measurement Information System (PROMIS®), developed in the United States, is the most extensively validated measurement system of item banks in the world.[13-15] PROMIS profiles have been developed that consist of a collection of short forms derived from IRT-based item banks, covering seven patient-relevant domains. Profiles offer quick assessment of several domains of health-related quality of life (HRQoL).[16] Available profiles are the Profile-29, Profile-43 and Profile-57, which measure seven domains with 4, 6 or 8 items, respectively.[16] As a generic tool, PROMIS-29 has the advantage of making results comparable across diseases and the general population.[12]

Before using an instrument in a new population or language, it should be validated [4] by assessing its measurement properties. The measurement properties can be divided into three domains: validity (content validity, construct validity, hypotheses-testing), reliability (internal consistency, measurement error and test-retest reliability) and responsiveness.[17] A hierarchy of measurement properties can be defined.[18] Content validity is considered the most important measurement property, defined as the degree to which the content of an instrument is an adequate reflection of the construct to be measured.[18] It can be assessed in a qualitative study in which the relevance, comprehensiveness and comprehensibility of the items of a PROM are assessed, for example by cognitive debriefing in the target population.[19] The next measurement properties that should be evaluated are structural validity and internal consistency.[17] Structural validity is the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured [18] and is assessed with confirmatory factor analysis.[4] Internal consistency is the degree of interrelatedness of items [18] as assessed with Cronbach's alpha.[4] Finally, other measurement properties are to be evaluated, such as test-retest reliability (the extent to which scores are stable over time in stable participants), construct validity (the degree to which the scores of an instrument are consistent with formulated hypotheses about relationships to scores of other instruments, or differences between relevant groups, based on the assumption that the instrument validly measures the construct to be measured), and responsiveness (the ability of an instrument to detect a change of the construct over time).

Item banks that underlie the PROMIS Profiles were translated into Dutch and showed sufficient linguistic, content and conceptual equivalence.[20] A next step is to evaluate the measurement properties of the item banks and their derivative short forms. PROMIS Profiles have been validated in several countries and in a number of conditions,[21-23] but not yet in hemophilia.

Therefore, this study aimed to validate the Dutch-Flemish version of the PROMIS-29 Profile v2.01 ('PROMIS-29') in Dutch adults with hemophilia by assessing its structural validity, internal consistency, and construct (convergent and discriminative) validity.

Methods

Data were collected as part of the Dutch nation-wide 'Hemophilia in the Netherlands 6' study (HiN-6). HiN-6 is the latest in a series of six cross-sectional studies that have been conducted since 1972.[3, 24, 25] Approval was obtained from the Medical Ethical Committee at Leiden University Medical Center, the Netherlands (registration number NL59114.058.17).

Participants and procedures

All adult males with mild, moderate or severe congenital hemophilia A or B with levels of Factor VIII of IX <0.40 IU/mL registered at one of the six Dutch hemophilia treatment centers were invited by letter to participate between June 2018 and July 2019.

Participants received a questionnaire through a secure e-mail link or in hard copy, depending on their preference. Answers were stored in the Castor Electronic Data Capture system.[26] Clinical characteristics were collected from electronic medical records. Participants signed written informed consent for extraction of data from electronic medical records, but this was not required for participation in the questionnaire.

Measures

Self-reported sociodemographic and clinical data collected through the questionnaire were: age, education level (categorized in ISCED levels [27]), and perceived impairment in joint function. Joint impairment was assessed with a single question that was used in previous HiN surveys. Joint impairment was defined as 'do you have any chronic joint problems due to hemophilia' (yes / no). Clinical characteristics collected from electronic medical records were type and severity of hemophilia, treatment type (prophylaxis, episodic), inhibitor status, and hiv and HCV status. Clinical characteristics were taken from medical records if the participant had signed written informed consent for use of these data. If medical record data were not available, self-reported data from the questionnaire were used. Hemophilia severity was known for all responders and non-responders.

Dutch-Flemish PROMIS-29 Profile v2.01

PROMIS Profiles are derived from full PROMIS item banks that were developed in the U.S. general population and patient groups.[13] PROMIS Profiles were shown to be reliable and correlate highly with full item banks.[16] The PROMIS-29 Profile v2.01 (PROMIS-29) measures seven domains of health-related quality of life (HRQoL) that are often considered important by patients:[16] Physical Function; Anxiety; Depression; Fatigue; Sleep Disturbance; Ability to Participate in Social Roles and Activities; and Pain Interference. Each domain is measured with four items. The PROMIS-29 also contains a single item on Pain Intensity, resulting in a total of 29 items. Each item is scored from 1 to 5; a higher score indicates a higher degree of the construct being measured. For the subscales Physical Function and Ability to Participate in Social Roles and Activities this means that a higher score indicates better HRQoL, while for the other subscales a higher score indicates worse HRQoL.[16] Domain scores were calculated as T-scores using the Health Measures Scoring Service,[28] resulting in a normalized score with a mean of 50 and a standard deviation of 10 in the reference population (the US general population). T-scores were only calculated for a domain if at least one item of that domain was completed; T-scores were considered missing if none of the items was completed.

RAND-36

RAND-36 version 1 is a generic measure that assesses health status using 36 items. It consists of eight health concepts with multi-item scales: Physical functioning (10 items); Social functioning (2 items); Role limitations caused by physical health problems (4 items); Role limitations caused by emotional problems (3 items); Emotional well-being (5 items); Pain (2 items); General health perceptions (5 items); Energy / Fatigue (4 items); and an additional single item measuring Change in perceived health during the past 12 months.[29] Items were scored on a three to six point Likert scale. As per the standard scoring instructions, subscale scores were calculated if a participant had completed at least half of the items of that subscale.[30] If fewer than half of the items were completed, subscale scores were considered missing. Subscale scores were converted to a 0-100 point scale.[9] A higher score indicates a better health status. The RAND-36 was reported to have good internal consistency and discriminative validity in the Dutch general population [31] and in several hemophilia populations.[32, 33]

Hemophilia Activities List (HAL)

The HAL version 2.0 is a hemophilia-specific instrument, developed in the Netherlands, that measures self-perceived functional abilities in adults due to hemophilia, in the previous month. It consists of 42 items in seven subdomains: Lying / sitting / kneeling / standing (8 items), Functions of the legs (9 items), Functions of the arms (4 items), Use of transportation (3 items), Self-care (5 items), Household tasks (6 items), Leisure activities and sports (7 items). Items are scored on a 6-point Likert scale.[5, 6] Scores

were calculated according to the standard instructions (i.e. a domain score was calculated if less than half of the items were missing) and converted to a 0-100 point scale, with a higher score indicating better functional status. The HAL has sufficient content validity and construct validity but its structural validity is not known.[11]

Statistical analyses

Descriptive statistics (means, standard deviations (SD), N) were used to describe participant characteristics. Mean scores, SDs, the proportion of best and worst scores and percentage of missing scores for each domain or subscale were described for all measures. If proportions of best and worst scores were >30 percent, these were considered substantial ceiling or floor effects, respectively.[21]

Structural validity, internal consistency and construct validity were investigated as defined by the COSMIN taxonomy[18] and reported according to the COSMIN reporting guideline for studies on measurement properties.[34] A sample size of at least 100 participants is considered adequate for these analyses.[35]

Structural validity was assessed with confirmatory factor analysis (CFA) for each PROMIS domain separately. Model parameters were estimated with the Weighted Least Square Mean and Variance Adjusted Estimators (WLSMV) for ordinal data.[36] Model fit was assessed using the Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI) and the Root Mean Squared Error of Approximation (RMSEA). Model fit was considered sufficient if CFI or TLI were >0.95, or RMSEA<0.06.[37] Internal consistency was calculated for each domain with sufficient model fit and considered sufficient if Cronbach's alpha was ≥0.70.[37]

Hypotheses were formulated a priori for construct validity (convergent and discriminative) for each domain. We considered ≥ 75 percent of results in accordance with the hypotheses evidence for construct validity.[37] Convergent validity was assessed with Pearson's correlations. We expected strong correlations ($r \geq 0.70$ or $r \geq -0.70$) between similar subscales of PROMIS-29 with RAND-36 subscales and HAL domains, based on published literature [38-40] and expert judgment (authors EvB and SG), as shown in Table 1. All other correlations were expected to be ≤ 0.60.

Discriminative validity was assessed by comparing mean T-scores between relevant clinical groups. Clinical subgroups were defined based on: hemophilia severity (mild compared to severe hemophilia); self-reported joint impairment in one or more of the six main joints (left and right ankles, knees, elbows; no / yes) and hiv infection (no / yes). Mean differences between mild and severe hemophilia were adjusted for age, mean differences between absent and present joint impairment were adjusted for age and severity using UNIANOVA. The comparison of mean T-scores for individuals with and without hiv were restricted to those born in 1985 or earlier, because the risk of hiv infection was considered negligible for younger patients.

Table 1: Hypotheses for construct validity (convergent and discriminative)

	Convergent validity		Discriminative validity		
PROMIS-29 subscale	Pearson's r ≥0.70	Pearson's r ≤0.60	MID	Δ T-score ≥ MID	Δ T-score < MID
Physical function	RAND-36 Physical Functioning HAL LSKS HAL Legs HAL Arms HAL Transportation HAL Household	All other RAND-36 subscales (n=8) All other HAL domains (n=2)	2.0	Mild - severe hemophilia No - yes joint impairment	No - yes hiv infection
Anxiety	RAND-36 Emotional well-being	All other RAND-36 subscales (n=8) All HAL domains	-2.3	n.a.	Mild - severe hemophilia No - yes joint impairment No - yes hiv infection
Depression	RAND-36 Emotional well-being	All other RAND-36 subscales (n=8) All HAL domains	-3.0	n.a	Mild - severe hemophilia No - yes joint impairment No - yes hiv infection
Fatigue	RAND-36 Energy / Fatigue	All other RAND-36 subscales (n=8) All HAL domains	-2.0	No - yes hiv infection	Mild - severe hemophilia No - yes joint impairment
Sleep Disturbance	n.a.	All RAND-36 subscales All HAL domains	-1.0	n.a	Mild - severe hemophilia No - yes joint impairment No - yes hiv infection
Ability to Participate in Social Roles and Activities	RAND-36 Social Functioning RAND-36 Role limitations – physical RAND-36 Role limitations - emotional HAL Household HAL Leisure and Sports	All other RAND-36 subscales (n=6) All other HAL domains (n=5)	1.0	No - yes joint impairment	Mild - severe hemophilia No - yes hiv infection

Table 1 (Continued)

	Convergent validity		Discriminative validity		
Pain Interference	RAND-36 Physical Functioning	All other RAND-36 subscales (n=7)	-2.0	Mild - severe hemophilia	No - yes hiv infection
	RAND-36 Pain	All other HAL domains (n=3)		No - yes joint impairment	
	HAL LSKS				
	HAL Legs				
	HAL Transportation				
	HAL Household				
Pain Intensity	RAND-36 Pain	All other RAND-36 subscales (n=8)	-1.0	Mild - severe hemophilia	No - yes hiv infection
		All HAL domains		No - yes joint impairment	

MID: Minimal important difference; HAL: Hemophilia Activities List; LSKS: Lying / sitting / kneeling / standing; n.a: not applicable

The following differences in mean T-scores were considered relevant differences between groups, based on published minimally important differences or changes for other patient groups (MID): ≥ 2 for Physical function,[41] ≥ -2.3 for Anxiety,[42] ≥ -3.0 for Depression,[42] ≥ -2 for Fatigue,[43] ≥ -1 for Sleep Disturbance,[43] ≥ 1 for Ability to Participate in Social Roles and Activities,[43] ≥ -2.0 for Pain Interference,[44] and ≥ -1 for Pain Intensity.[45] Because the MID is specific for each domain, a difference of, for example, 2 points may be a relevant difference in one domain, but not in another. Based on literature [46, 47] and clinical experience (authors SG, MD), we expected to find the following relevant differences: between mild and severe hemophilia and between absent and present joint impairment for Physical Function; between not hiv-infected and hiv-infected for Fatigue; between absent and present joint impairment for Ability to Participate in Social Roles and Activities; between mild and severe and between absent and present joint impairment for Pain Interference and for Pain Intensity (Table 1).
All analyses were performed with IBM SPSS version 25, except for Confirmatory Factor Analysis, which was performed in R, version 3.6.1 (package 'lavaan').

Results

Participants

Of 1746 Dutch adults with hemophilia who were invited to participate, 808 completed the questionnaires partially or in full (response 46.3 percent). The final sample for analysis consisted of 770 participants for whom one or more PROMIS-29 T-scores were calculated. For 598 of 770 participants (77.7 percent) clinical data from electronic medical records were available. Mean age was 48.9 (SD 17.2) years. Half of the participants (49.9 percent) had mild hemophilia, 15.6 percent had moderate and 34.5 percent had severe hemophilia, which is representative of the total Dutch hemophilia population (55.8, 13.2 and 30.1 percent, respectively). Clinical and socio-demographic characteristics are shown in Table 2.

Table 2: Participant characteristics (n = 770)

Clinical characteristics		
Hemophilia severity*	**N**	**%**
Mild	384	49.9
Moderate	120	15.6
Severe	266	34.5
Type of hemophilia	**N**	**%**
Hemophilia A	669	86.9
Hemophilia B	92	11.9
No hemophilia*	3	0.4
Unknown†	6	0.7
Prophylaxis (severe hemophilia)	**N**	**%**
Yes	233	87.6

Table 2: Participant characteristics (n = 770) (Continued)

Clinical characteristics		
No	30	11.3
Missing	3	1.1
Hiv infection	**N**	**%**
Yes	22	2.9
No	721	93.6
Unknown	27	3.5
HCV infection	**N**	**%**
Never infected	418	54.3
Past infection	231	30.0
Current infection	8	1.0
Past or current infection‡	2	0.6
Unknown	111	14.4
Inhibitor	**N**	**%**
Never	637	82.7
Past	68	8.8
Current	12	1.6
Unknown§	53	6.9
Joint impairment¶	**N**	**%**
Yes	338	43.9
No	379	49.2
Unknown	53	6.9
Demographic characteristics	**Mean**	**SD**
Age in years††	48.9	17.2
Education‡‡	**N**	**%**
Primary education	44	5.7
Secondary education	397	51.6
Tertiary education	298	38.7
Missing / prefer not to say	31	4.0

Clinical characteristics were taken from electronic medical records if participant had provided informed consent for extraction of data. If electronic medical record data were not available and participants did not complete the questions, status is unknown. Hemophilia severity was available from electronic medical records for all eligible persons (responders and non-responders)

* Three participants indicated on the questionnaire that they no longer had hemophilia, which might be because of a liver transplant (n=1) or participation in a gene therapy trial, but the exact reason is unknown.

† Five participants did not know their type of hemophilia (A or B), and one person skipped this question. Medical record data was missing for these individuals.

‡ Five individuals had a past or current HCV infection, but current infection status could not be established.

§ Inhibitor data from the medical record were not available for 53 participants because they did not provide informed consent for extraction of data.

¶ Joint impairment was self-reported chronic joint impairment in any joint (yes / no).

†† For three participants, age was missing and no electronic medical record was available.

‡‡ Education level was categorized according to ISCED levels: Primary education (ISCED level 1), Secondary education ISCED levels 2 and 3), Tertiary education (ISCED levels 6 and 7).

Description of measures

Table 3 shows mean, minimum and maximum scores, standard deviations, floor and ceiling effects and percentage of missing scores of all measures from the questionnaires. Mean T-scores for PROMIS-29 were better than the U.S. general population average for all subscales except Physical function, which was worse (48.9). Distributions of all PROMIS-29 domain scores were skewed toward better scores, i.e. scores >50 for the subscales Physical Function and Ability to Participate in Social Roles and Activities, and <50 for all other subscales (Figure 1). Five of seven PROMIS-29 subscales and Pain Intensity showed substantial ceiling effects of >30 percent patients with the best scores, while this was the case for five of eight RAND subscales and for all HAL-domains. PROMIS-29 had fewer missing answers than RAND-36 and HAL.

Structural validity

PROMIS-29 showed sufficient CFA model fit (CFI or TLI >0.95, or RMSEA<0.06) for Physical Function (CFI 0.95, TLI 0.85, RMSEA 0.13), Depression (CFI 1.00, TLI 0.99, RMSEA 0.02), Sleep Disturbance CFI 0.94, TLI 0.82, RMSEA 0.05), Ability to Participate in Social Roles and Activities (CFI 1.00, TLI 1.00, RMSEA 0.00) and Pain Interference (CFI 0.99, TLI 0.98, RMSEA 0.05). The subscales Anxiety and Fatigue did not show sufficient model fit (Table 4).

Internal consistency

Internal consistency was sufficient (Cronbach's alphas ≥0.70) for all five PROMIS-29 subscales with sufficient model fit in CFA. For four of them, Cronbach's alphas were ≥0.90: Physical function, Depression, Ability to Participate in Social Roles and Activities, and Pain Interference (Table 4). No Cronbach's alphas were calculated for Anxiety and Fatigue, because model fit was not sufficient.

Table 3: Characteristics of PROMIS-29, RAND-36 and HAL for adult men with hemophilia

	N*	Mean (SD)†	Range (min-max)	Worst score (%)‡	Best score (%)‡	Missing (%)§
PROMIS-29						
Physical Function	765	48.9 (9.6)	22.9-56.9	1.3	**51.9**	0.6
Anxiety	744	48.0 (8.2)	40.3-81.4	0.1	**43.2**	3.4
Depression	744	46.4 (7.8)	41.0-79.3	0.3	**59.1**	3.4
Fatigue	738	46.6 (9.6)	33.7-75.8	0.5	21.0	4.2
Sleep Disturbance	738	46.5 (7.9)	32.0-73.3	0.3	5.6	4.2
Ability to Participate in Social Roles and Activities	729	54.2 (8.9)	27.5-64.2	0.6	**30.6**	5.3
Pain Interference	726	49.6 (9.0)	41.6-75.6	0.6	**47.4**	5.7
Pain Intensity	724	2.4 (2.5)	0-10	0.1	**31.6**	6.0
RAND-36						
Physical functioning	734	77.9 (27.4)	0-100	0.8	**31.9**	2.3
Social functioning	705	83.5 (20.7)	0-100	0.5	**43.0**	8.4
Role limitations - physical	710	76.5 (37.5)	0-100	13.1	**61.7**	7.7
Role limitations - emotional	702	84.9 (31.6)	0-100	8.1	**71.8**	8.7
Emotional well-being	698	77.2 (15.6)	0-100	0.1	3.6	9.2
Energy / Fatigue	698	64.7 (17.8)	0-100	0.3	1.2	9.1
Pain	698	77.4 (22.5)	0-100	0.5	**31.6**	9.0
General health perceptions	694	64.5 (22.3)	0-100	0.6	4.3	0.0
Change in health	763	50.4 (19.8)	0-100	2.7	4.8	0.9
HAL						
Lying / sitting / kneeling / standing	709	77.6 (26.5)	7.5-100	0.0	**37.3**	7.1
Functions of the legs	694	74.0 (31.3)	0-100	1.6	**38.8**	9.1
Functions of the arms	688	83.9 (24.5)	0-100	0.6	**50.9**	10.3
Use of transportation	680	85.8 (24.7)	0-100	0.4	**55.6**	11.6
Self-care	681	90.8 (18.3)	5-100	0.0	**59.0**	11.4
Household tasks	647	87.4 (21.8)	0-100	0.4	**51.7**	12.5
Leisure activities and sports	614	82.0 (24.9)	0-100	0.5	**39.1**	13.1

* The number of participants for whom a score could be computed as described in the methods section.
† Higher scores on RAND-36 and HAL indicate better health status and better physical functioning, higher scores on PROMIS-29 indicate more of the construct being measured (e.g. more Physical Function and Ability to Participate in Social Roles and Activities, or more Anxiety, Depression, Fatigue, Sleep Disturbance and Pain)
‡ Worst and best possible scores were calculated if at least one item had been completed. Floor and ceiling effects are defined as the percentage of participants with the worst and the best scores possible. Floor and ceiling effects are considered present if >30 percent (in **bold**).
§ Percentage of participants for whom all items on a domain are missing.

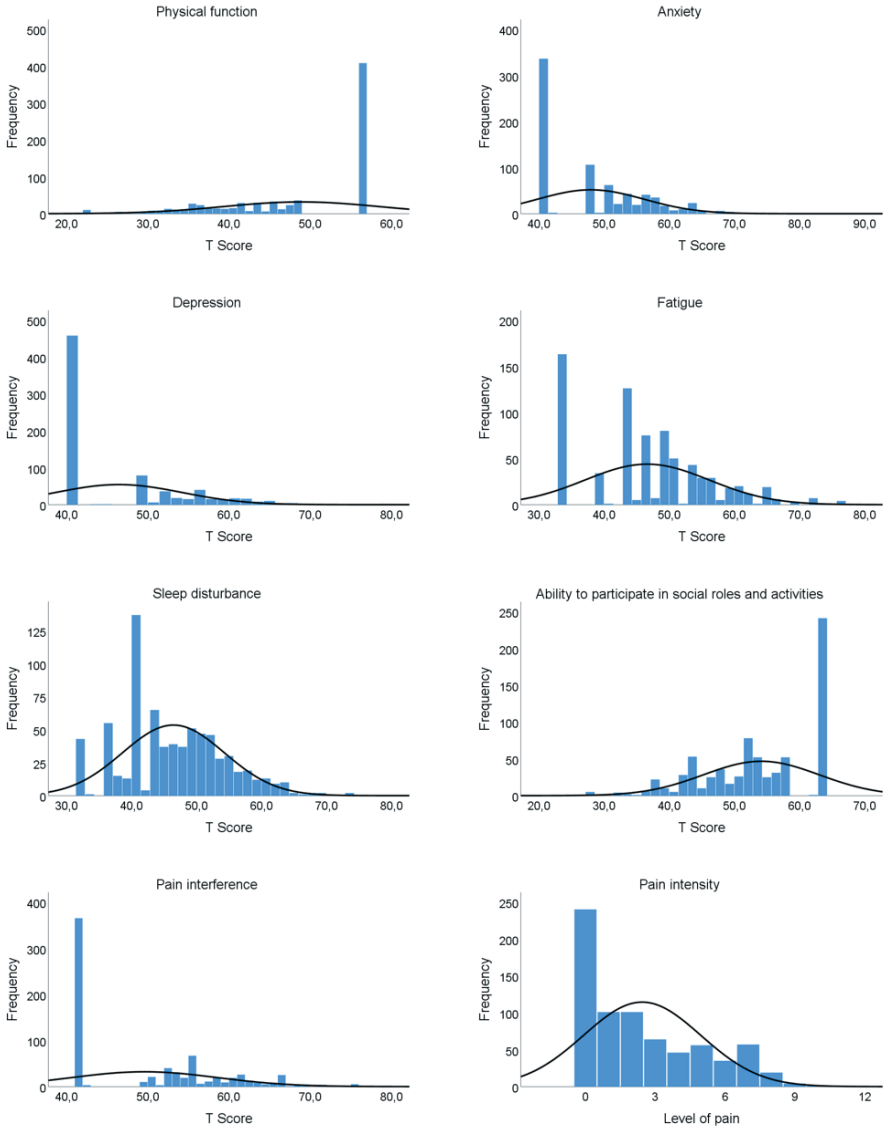

Figure 1: Distribution of T-scores on PROMIS-29 subscales

Frequencies of T-scores for each PROMIS-domain, and level of pain for Pain Intensity. The black curve indicates the normal distribution based on the frequencies. A higher score indicates more of the construct being measured.

Table 4: Structural validity and internal consistency of PROMIS-29

	N	CFI	TLI	RMSEA	Cronbach's alpha
PROMIS-29					
Physical function	752	**0.95**	0.85	0.13	0.94
Anxiety	735	0.88	0.63	0.15	-
Depression	727	**1.00**	**0.99**	**0.02**	0.93
Fatigue	728	0.85	0.56	0.24	-
Sleep Disturbance	713	0.94	0.82	**0.05**	0.79
Ability to Participate in Social Roles and Activities	717	**1.00**	**1.00**	**0.00**	0.93
Pain Interference	715	**0.99**	**0.98**	**0.05**	0.96

CFI: comparative fit index, TLI: Tucker-Lewis Index, RMSEA: root mean square error of approximation, Sufficient fit, indicated in **bold**: CFI or TLI >0.95, or RMSEA<0.06. Good internal consistency is defined as Cronbach's alpha ≥0.70. Fit parameters were rounded to two decimal places.

Construct validity

Results for convergent validity are shown in Table 5. For the subscales Anxiety, Depression, Fatigue, Sleep Disturbance, and Pain Intensity all correlations were in accordance with the hypotheses for convergent validity. For the subscales Physical Function 12 out of 16 correlations were as hypothesized, while for Ability to Participate in Social Roles and Activities this was the case for 11 out of 16 correlations. Nine out of 16 correlations were in accordance with the hypotheses for Pain Interference.

Table 5: Pearson's r for correlations between RAND-36 and PROMIS-29 subscales (convergent validity)

		PROMIS-29							
		Physical function	Anxiety	Depression	Fatigue	Sleep Disturbance	Ability to participate	Pain Interference	Pain Intensity
RAND-36	Physical functioning	**0.91**	-0.31	-0.36	-0.37	-0.28	0.59	**-0.70**	-0.59
	Social functioning	0.52	-0.57	-0.60	-0.58	-0.42	**0.70**	-0.59	-0.53
	Role limitations – physical	0.63	-0.36	-0.40	-0.48	-0.32	**0.62**	-0.66	-0.57
	Role limitations - emotional	0.33	-0.48	-0.56	-0.44	-0.37	**0.50**	-0.37	-0.33
	Emotional well-being	0.28	**-0.74**	**-0.75**	-0.55	-0.50	0.56	-0.35	-0.33
	Energy / Fatigue	0.40	-0.55	-0.59	**-0.72**	-0.50	0.60	-0.46	-0.42
	Pain	0.63	-0.33	-0.38	-0.46	-0.31	0.55	**-0.82**	**-0.80**
	General health perceptions	0.59	-0.46	-0.47	-0.54	-0.43	0.62	-0.63	-0.55
	Change in health	0.29	-0.14	-0.16	-0.17	-0.11	0.27	-0.28	-0.28
HAL	Lying / sitting / kneeling / standing	**0.79**	-0.24	-0.27	-0.29	-0.28	0.53	**-0.63**	-0.53
	Functions of the legs	**0.85**	-0.23	-0.28	-0.28	-0.25	0.53	**-0.65**	-0.56
	Functions of the arms	**0.73**	-0.30	-0.31	-0.35	-0.28	0.56	-0.64	-0.54
	Use of transportation	**0.77**	-0.25	-0.30	-0.30	-0.25	0.54	**-0.58**	-0.48
	Self-care	0.66	-0.30	-0.32	-0.33	-0.27	0.54	-0.60	-0.53
	Household tasks	**0.80**	-0.31	-0.35	-0.36	-0.29	**0.60**	**-0.70**	-0.56
	Leisure activities and sports	0.80	-0.29	-0.34	-0.36	-0.29	**0.60**	-0.70	-0.57
Hypotheses confirmed (%)		75	100	100	100	100	69	56	100

Correlations in **bold** were expected to be ≥ 0.70 or ≥ -0.70. All other correlations were expected to be ≤0.60.

Table 6: Differences in mean PROMIS-29 T-scores for clinical subgroups (discriminative validity)

		Severe – mild hemophilia		Yes – no joint impairment		Yes – no hiv infection		Hypotheses confirmed (%)§
	MID	unadjusted (95% CI)	adjusted (95% CI)*	unadjusted (95% CI)	adjusted (95% CI)†	unadjusted (95% CI)	adjusted (95% CI)‡	
Physical function	2.0	**8.6 (7.0; 10.0)**	**10.2 (9.1; 11.4)**	**10.8 (9.6; 11.9)**	**6.1 (4.8; 7.4)**	10.5 (6.4; 14.6)	1.5 (-1.9; 4.8)	100
Anxiety	-2.3	-0.4 (-1.7; 0.9)	-0.8 (-2.1; 0.5)	-2.5 (-3.7; -1.3)	-2.7 (-4.2; -1.2)	-2.6 (-6.2; 1.0)	-1.7 (-5.8; 2.3)	67
Depression	-3.0	-1.7 (-2.9; -0.4)	-2.1 (-3.3; -0.8)	-2.7 (-3.9; -1.6)	-1.8 (-3.3; -0.4)	-3.4 (-6.7; -0.1)	-1.7 (-5.6; 2.2)	100
Fatigue	-2.0	-1.9 (-3.4; -0.3)	-2.2 (-3.7; -0.6)	-3.6 (-5.0; -2.1)	-3.5 (-5.3; -1.7)	**-4.7 (-8.8; -0.7)**	**-2.5 (-6.9; 1.9)**	33
Sleep Disturbance	-1.0	-1.2 (-2.5; 0.0)	-1.4 (-2.7; -0.2)	-2.2 (-3.3; -1.0)	-1.8 (-3.2: -0.3)	-3.7 (-7.0; -0.3)	-2.8 (-6.5; 1.0)	0
Ability to Participate in Social Roles and Activities	1.0	4.4 (3.0; 5.8)	5.4 (4.0; 6.7)	**5.7 (4.4; 7.0)**	**3.1 (1.6; 4.6)**	8.7 (5.0; 12.5)	3.5 (-0.2; 7.3)	33
Pain Interference	-2.0	**-6.0 (-7.4; -4.7)**	**-7.2 (-8.5; -5.8)**	**-8.2 (-9.4; -7.0)**	**-5.7 (-7.2; -4.3)**	-7.3 (-11.1; -3.5)	-0.9 (-4.7; 3.0)	100
Pain Intensity	-1.0	**-1.5 (-1.9; -1.2)**	**-1.8 (-2.1; -1.4)**	**-1.9 (-2.3; -1.6)**	**-1.4 (-1.8; -0.9)**	-1.9 (-2.9; -0.8)	-0.6 (-1.7; 0.5)	100

Differences in **bold** were hypothesized to be > MID. 95% CI: 95% confidence interval. For the subscales Physical Function and Ability to Participate in Social Roles and Activities a positive difference means that persons with mild hemophilia, no joint impairment or no hiv infection have more of these constructs than persons with severe hemophilia, joint impairment or hiv infection. For the other subscales negative differences indicate less of these constructs for persons with mild hemophilia, no joint impairment or no hiv infection.

* Adjusted for age.

† Adjusted for age and severity.

‡ Mean difference between individuals with severe hemophilia born in 1985 or earlier, with or without hiv.

§ Hypotheses confirmed for discriminative validity.

Unadjusted and adjusted differences in mean T-scores between clinical groups (discriminative validity) are shown in Table 6. All differences between groups were in the expected direction, i.e. participants with mild hemophilia, no joint damage and no hiv infection had better scores for all subscales. Adjusting for age resulted in a larger difference between mild and severe hemophilia, and adjusting for age and disease severity resulted in smaller differences between individuals with and without joint impairment. Finally, differences became smaller when hiv-infected participants were compared with non-infected participants with severe hemophilia born in or before 1985.

The evidence for discriminative validity was strongest for Physical Function, Depression, Pain Interference and Pain Intensity: all differences between subgroups were as hypothesized. For Anxiety, two of three differences between groups were as hypothesized, and for Fatigue and Ability to Participate in Social Roles and Activities one difference was as hypothesized. None of the differences between groups were in accordance with the hypotheses for Sleep Disturbance.

In total, six subscales showed evidence for construct validity (≥75 percent hypotheses confirmed): Physical Function, (79 percent), Anxiety (95 percent), Depression (100 percent), Fatigue (89 percent), Sleep Disturbance (84 percent) and Pain Intensity (100 percent). Two subscales did not meet the criterium for ≥75 percent of hypotheses confirmed: for Ability to Participate in Social Roles and Activities and Pain Interference 63 percent of hypotheses were confirmed.
Table 7 summarizes the evidence for structural validity, internal consistency and construct validity.

Table 7: Summary of the evidence for structural validity, internal consistency and construct validity (convergent and discriminative)

PROMIS-29 subscale	Structural validity	Internal consistency	Construct validity
Physical function	+	+	+
Anxiety	-	0	+
Depression	+	+	+
Fatigue	-	0	+
Sleep Disturbance	+	+	+
Ability to Participate in Social Roles and Activities	+	+	-
Pain Interference	+	+	-
Pain Intensity	n/a	n/a	+

+ indicates evidence for the measurement property according to pre-specified criteria; - indicates that the evidence for the measurement property did not meet pre-specified criteria; 0: not assessed because of limited structural validity; n/a: measurement property not applicable (1 item)

Discussion

This study is the first validation of the Dutch-Flemish version of the PROMIS Profile-29, as well as the first validation of this Profile among persons with hemophilia. Using consensus-based standards for evaluating validity, we aimed to assess structural validity, internal consistency and construct validity of the PROMIS-29 Profile v2.01 in Dutch adults with hemophilia. In a representative sample of the Dutch hemophilia population, our analyses showed sufficient evidence for structural validity and internal consistency for five of seven subscales and sufficient evidence for construct validity for five subscales and for Pain Intensity.

In the confirmatory factor analysis, model fit was not sufficient for Anxiety and Fatigue, potentially indicating a lack of unidimensionality,[48] i.e. that these subscales may measure more than one construct for people with hemophilia. An explanation may be that CFA modelling assumes a normal distribution of the data. Our results, however, showed skewed distributions for all subscales. This may have influenced fit statistics. [48] In contrast to our findings, a previous validation of PROMIS-29 among kidney transplant recipients found excellent structural validity for all subscales,[23] even with similarly skewed distributions.

We found evidence for sufficient internal consistency for five subscales, with Cronbach's alphas >0.90 for the subscales Physical Function, Depression, Ability to Participate in Social Roles and Activities, and Pain Interference. Consistent with our findings, two previous studies in kidney transplant recipients and populations with rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus reported similarly high Cronbach's alphas for all subscales.[21, 23]

Overall, the subscales Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance and Pain Intensity showed evidence for construct validity (i.e. >75 percent of results in accordance with the hypotheses). Fewer hypotheses were confirmed for the subscales Ability to Participate in Social Roles and Activities and Pain Interference (63 percent).

Correlations lower than the expected 0.70 were found for Ability to Participate in Social Roles and Activities with the RAND-36 Role limitations caused by physical or emotional health problems (0.62 and 0.50, respectively). The hypothesis for the former correlation was based on a Dutch study among 30 abdominal surgery patients that reported a correlation of 0.72 between the SF-36 subscale Role limitations caused by physical health problems and the 8-item PROMIS Ability to Participate in Social Roles and Activities short form.[40] Though the correlation we report is below the 0.70 threshold, it is of the same order of magnitude and the difference may be due to random variation or to differences in the underlying constructs being measured.

Lower correlations were also found between PROMIS-29 Ability to Participate in Social Roles and Activities with HAL Household tasks (0.60) and Leisure and sports

(0.60). This may mean that these constructs differ more than anticipated, resulting in fewer hypotheses for convergent validity confirmed. Indeed, HAL subscales measure several aspects of self-perceived functional ability, while PROMIS Ability to Participate in Social Roles and Activities measures participation.

Some subscales that were not expected to correlate highly with RAND-36 and HAL (i.e. expected to be ≤ 0.60) showed correlations above the threshold of 0.60. This was the case for the correlation between Physical Function with RAND-36 Pain (0.63), RAND-36 Role limitations caused by physical health problems (0.63) and HAL Self-care (0.66), and for Ability to Participate in Social Roles and Activities with RAND-36 General health perceptions (0.62), and for Pain Interference with RAND-36 Role limitations caused by physical health problems (-0.66), with RAND-36 General health perceptions (-0.63) and with HAL Functions of the arms (-0.64). We used a relatively low expected correlation of ≤ 0.60 between subscales that do not measure the same construct to distinguish them from the correlations ≥ 0.70 expected between subscales that measure the same construct, but this resulted in fewer hypotheses confirmed (especially for Ability to Participate in Social Roles and Activities and Pain Interference), and thus lower evidence of construct validity. This strict criterium may have led to quite conservative conclusions.

Also interesting is that most correlations between Pain Interference and HAL subscales were of similar strength, between -0.58 and -0.66. Though below the 0.70 threshold, the subscales perceived functional ability (HAL) [5, 6] and Pain Interference with functional ability (PROMIS) [16] may measure similar constructs after all.

We found unexpected differences larger than the MID for some subscales. For example, differences between all clinical groups were larger than expected for Sleep Disturbance. Sleep Disturbance is not routinely studied in hemophilia, but a qualitative study reported that pain may affect sleep disturbance.[49] Persons with severe hemophilia, joint impairment and hiv are more likely to experience pain due to recurrent bleeding, which may explain part of the observed differences. However, confidence intervals of the observed differences were wide. Also, the correlation between PROMIS-29 Sleep Disturbance and RAND-36 pain was low (-0.31), making a substantial influence of pain on sleep disturbance less likely. Differences between mild and severe hemophilia and for different hiv infection status were also larger than expected for Ability to Participate in Social Roles and Activities, while we only expected to find differences for joint impairment. Since effective treatment is available, persons with severe hemophilia should be able to lead near-normal lives, and for this reason were expected to have similar levels of social participation as individuals with mild hemophilia. Our results indicate that this may not be the case. Indeed, hemophilia is reported to have a negative impact on employment and education,[50] and may also have affected the Ability to Participate in Social Roles and Activities. Individuals with hiv infection may have a more severe bleeding phenotype than those without hiv: persons with a more severe bleeding phenotype may have received more plasma-derived treatment products in

the past, and contracted hiv as a result, compared to persons with severe hemophilia with a milder bleeding phenotype. A more severe bleeding phenotype may also have resulted in more joint impairment and lower participation. Unfortunately, we did not have reliable information on bleeding phenotype and were therefore unable to correct for this confounder. It should be noted that the number of individuals with hiv was small (n=22), resulting in less reliable estimates of T-scores in this subgroup.

A potential limitation of this study is that the response rate of the HiN-6 study was limited (46.3 percent). This may have led to some bias. First, fewer people had only primary education (5.7 percent) and more had secondary education (51.6 percent) compared to the general Dutch population (21 and 40 percent, respectively).[51] If people with a higher education were better able to manage their hemophilia, this could have resulted in higher scores on PROMIS subscales. This may, in part, explain our finding that mean scores on many PROMIS-29 subscales were higher than the general population average of 50. Second, persons with more health-related problems due to hemophilia may have been more likely to participate because they were more motivated to complete a questionnaire about their health. This would have resulted in low scores. However, our results showed large proportions of participants with the highest scores on several subscales, indicating few health problems. Therefore, we believe selection bias due to health problems was unlikely to have impacted the findings of this study.

Content validity of PROMIS-29 was reported to be good in several other populations.[13, 14] Our results also provide some evidence for content validity of PROMIS-29 among persons with hemophilia: the number of missing answers was low, which may indicate that items were relevant to participants.[52] On the other hand, PROMIS-29 showed large proportions of best scores for most subscales, which may indicate a lack of content validity: best scores may indicate that items were not relevant to measure the domain for this population and that more 'difficult' items may be missing.[52] The large proportion of best scores on most subscales (except Fatigue and Sleep Disturbance) leads to a loss in measurement precision in well-functioning individuals. The 4-item short forms that comprise PROMIS-29 may therefore not be optimal for persons with hemophilia. Because PROMIS item banks are IRT-based, they are flexible and another selection of items can be considered. For example, a longer or a custom short form with more 'difficult' items from the item bank or a Computerized Adaptive Test may solve these ceiling effects and still yield comparable results.[12] Unfortunately, Dutch CATs were not available yet at the time of our study, but have become available recently.[53, 54]

In our study, five subscales met all criteria for structural validity and internal consistency and five and Pain Intensity met all the criteria for hypotheses-testing for construct validity. Small changes in the methods regarding the cut-offs of correlations and the percentage of hypotheses confirmed may have had profound effects on the conclusions.

Other studies that validated PROMIS-29 in different populations did not formulate hypotheses for construct validity, which may lead to less transparent and less consistent

interpretation of the results.[21-23] Yet, hypothesis-testing for construct validity depends on sufficient knowledge about the constructs being measured with all subscales. However, limited literature was available that quantified correlations with other instruments or differences between groups. Despite the lack of explicit hypotheses in other studies, the magnitude of differences between relevant subgroups is similar.[21-23] This indicates generalizability across diseases.

Ideally, PROMs are used that measure the most relevant outcomes for a specific population. A consensus-based standard set of relevant outcomes for persons with hemophilia was published recently,[55] along with recommendations for instruments to measure these outcomes. The set included the five patient-reported outcomes Ability to engage in normal daily activities, Chronic pain, Sustainability of physical functioning, Social functioning, and Mental health. The latter four can be measured with the PROMIS Profile-29 subscales that were validated in the current study: Pain Interference and Pain Intensity; Physical function; Ability to Participate in Social Roles and Activities; and Anxiety and Depression, respectively. For an even more comprehensive assessment, Social functioning may be measured with the PROMIS domain Self-efficacy for managing social interactions, and Mental health with the subscales General Life Satisfaction and Positive Affect. Ability to engage in normal daily activities may be measured with PROMIS Self-efficacy for Managing Chronic Conditions - Managing Daily Activities. PROMIS item banks or short forms for these subscales may be validated for comprehensive assessment of the standard set of outcomes for hemophilia. The standard set of outcomes did not include the domains fatigue and sleep disturbance, which may not need to be prioritized for measurement, though they may still be important in some patients or certain situations.

Which tools to use (disease-specific or generic) depends on the goal of measuring outcomes and the type of outcomes. Some outcomes, such as degree of hemophilic arthropathy, are disease-specific and need to be assessed with disease-specific instruments. Functional outcomes such as those measured with PROMIS item banks (e.g. physical function, fatigue) are of a more generic nature. For clinical care aimed at improving outcomes, generic tools may be the most suitable, while in other cases disease-specific tools may be necessary. Still, in many cases, a combination of generic tools where possible, supplemented with disease-specific tools where needed, may be the most suitable for comprehensive measurement of all outcomes that are relevant for hemophilia.

Conclusion

This study found sufficient evidence for structural validity, internal consistency and construct validity of the PROMIS-29 subscales Physical Function, Depression and Sleep Disturbance in adult persons with hemophilia in the Netherlands. Construct validity

was also sufficient for Anxiety, Fatigue and Pain Intensity. These results indicate that PROMIS short forms that measure these domains may be used in hemophilia populations. Future studies should explore whether the use of custom short forms or CAT can solve observed ceiling effects.

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CHAPTER 7

Socio-economic participation of persons with hemophilia: results from the sixth Hemophilia in the Netherlands study

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Res Pract Thromb Haemost. 2022;6:e12741

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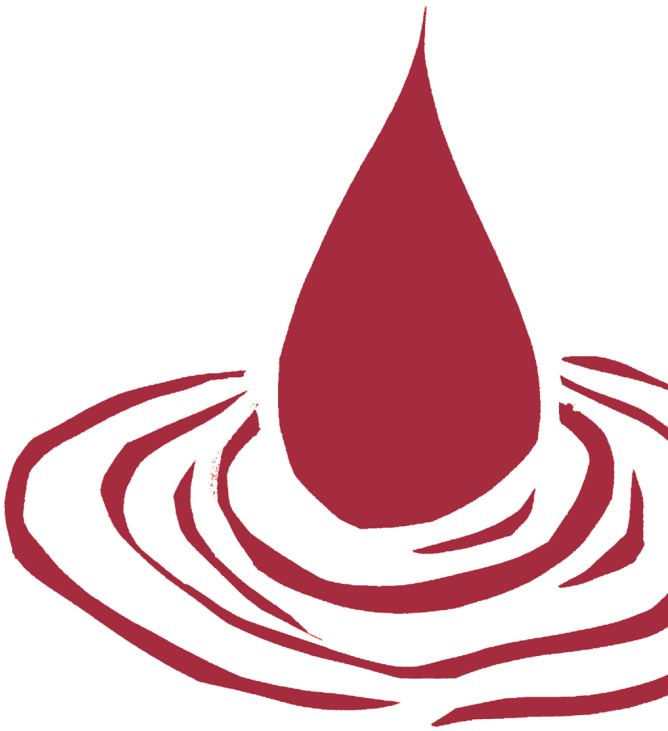

Abstract

Background

Treatment availability and comprehensive care have resulted in improved clinical outcomes for persons with hemophilia. Recent data on socio-economic participation in the Netherlands are lacking. This study assessed participation in education, in the labor market and social participation for persons with hemophilia compared with the general male population.

Methods

Dutch adults and children (5-75 years) of all hemophilia severities (n = 1009) participated in a questionnaire study that included socio-demographic, occupational and educational variables. Clinical characteristics were extracted from electronic medical records. General population data were extracted from Statistics Netherlands. Social participation was assessed with the PROMIS Ability to Participate in Social Roles and Activities short form, with a minimal important difference (MID) set at 1.0.

Results

Data from 906 adults and children were analysed. Participation in education of 20-24 year-olds was 68% (general male population: 53%). Educational attainment was higher compared to Dutch males, especially for severe hemophilia. Absenteeism from school was more common than in the general population. The employment-to-population ratio and occupational disability were worse for severe hemophilia than in the general population (64.3% vs. 73.2% and 14.7% vs. 4.8%, respectively), but similar for non-severe hemophilia. Unemployment was 5.4% (general male population: 3.4%). Absenteeism from work was less common (38% vs. 45.2%). Mean PROMIS score was similar to or higher than in the general population (54.2; SD 8.9 vs. 50; SD 10).

Conclusion

Socio-economic participation of persons with non-severe hemophilia was similar to the general male population. Some participation outcomes for persons with severe hemophilia were reduced.

Introduction

The X-linked congenital bleeding disorder hemophilia is characterized by an increased bleeding tendency due to a deficiency of functional coagulation factor VIII (hemophilia A) or IX (hemophilia B). It is classified into severe (<0.01 IU/mL FVIII or FIX), moderate (0.01-0.05 IU/mL FVIII or FIX) or mild (0.05-0.40 IU/mL FVIII or FIX) hemophilia. Bleeding occurs spontaneously in joints and muscles in persons with severe hemophilia, or when triggered by major trauma or surgery in persons with mild or moderate hemophilia.[1] In the long term, recurrent bleeding causes irreversible joint damage, which may lead to disability.[1]

Treatment first became available in high-income countries in the late 1960s. Modern treatment mostly consists of intravenous infusion of factor VIII or IX replacement products: 2-3 times a week as prophylaxis for severe hemophilia, or as treatment of bleeds in mild and moderate hemophilia ('on-demand'). The majority of persons with severe hemophilia receive prophylaxis since the mid-1980s.[2] A potential side effect of these products is the development of neutralizing antibodies ('inhibitors'). Also, blood-borne pathogens were transmitted through plasma-derived treatment products, such as HIV between 1980-1985 and hepatitis C until the early 1990s.[3] Non-factor replacement hemostatic agents have been marketed in the past few years as alternative prophylactic treatment.[1]

Hemophilia care in the Netherlands is organized in six comprehensive hemophilia treatment centers (HTCs) distributed over nine locations across the country according to the European principles of Hemophilia Care.[4-6]Bleeding rates, joint impairment, consequences of comorbidities, life expectancy and several aspects of health-related quality of life have improved tremendously in the Netherlands since the 1970s.[2, 7] No recent data are available for socio-economic participation in the Netherlands, even though the ability to participate in daily life is among the most important health outcomes for persons with hemophilia.[8, 9] Insight into socio-economic participation will help to evaluate the effects of comprehensive care over time.[9]

Several recent studies from other high-income countries suggested negative impacts of hemophilia on employment and disability rates,[10-13] absenteeism from work or school,[10, 14, 15] perceived impact on education or career,[12, 13] and social functioning.[11] Dutch young adults with non-severe hemophilia were more likely to have paid employment than those with severe hemophilia.[16] Among persons with severe hemophilia A in five European countries, lifelong prophylaxis and high therapy adherence led to reduced activity impairment and work productivity loss, while frequent bleeds and pain were associated with increased activity impairment and work productivity loss.[17]

Few studies have examined the 'gap' in socio-economic participation between persons with different severities of hemophilia and the general population. Furthermore, participation outcomes are often not reported in a standardized manner, i.e., using internationally recognized indicators that allow for comparison across settings. For example, the most important indicators labor market participation are the unemployment rate

and the employment-to-population ratio.[18] Absenteeism from work and occupational disability are indicators of temporary and (semi-)permanent limitations on the labor market, and as such reflect the health status of a population.[19]
The aim of the current study was to assess participation of the Dutch hemophilia population, focused on participation in education and the labor market, and social participation, and to compare these outcomes with the general male population using standardized indicators.

Methods

Study design

The Hemophilia in the Netherlands (HiN) studies are a series of cross-sectional studies that provide a comprehensive evaluation of the medical, psychosocial and socio-economic situation of the Dutch hemophilia population since 1972.[15, 20-22] The sixth edition, HiN-6, was conducted in 2018-2019. Approval was obtained from the Medical Ethics Committee at Leiden University Medical Center, the Netherlands.

Participants and procedures

All Dutch male adults and children with mild, moderate or severe congenital hemophilia A or B (<40 IU/mL coagulation factor VIII / IX) receiving treatment from one of six Dutch hemophilia treatment centers were invited by letter to participate between June 2018 and July 2019. Excluded were females with hemophilia, persons with acquired hemophilia and non-hemophilic individuals with reduced FVIII levels due to Von Willebrand Disease. Individuals between 5-75 years were included in the analyses.

Individuals who agreed to participate received a comprehensive questionnaire (hard copy or electronic; captured with the Castor Electronic Data Capture system.[23]). Participants were reminded during their regular outpatient clinic appointment and two reminders were sent by email. Three questionnaire versions were available: children aged 0-11 (completed by parents), teenagers aged 12-17, and adults of 18 years and older. Clinical characteristics were extracted from medical records if the participant (or parents) had signed written informed consent. If the participant did not consent, only self-reported data from the questionnaire were used. Hemophilia severity was known for all responders and non-responders.

Data collected

The questionnaire contained clinical and socio-demographic questions: chronic joint problems due to hemophilia (defined as 'do you have any chronic joint problems due to hemophilia' (yes / no)), current and highest completed education level, work status, time missed from work or school in the past year and the perceived impact of hemophilia

on education and career (yes / no and an open-ended question). Social participation was assessed with the PROMIS-29 Profile v2.01 Ability to Participate in Social Roles and Activities.[24] In brief, PROMIS short forms are based on Item Response Theory, which provides valid and reliable results that can be compared across populations.[25] The ability to participate is measured with four items, each scored from 1 to 5; a higher score indicates better social participation.[26]
The following clinical characteristics were collected: date of birth, type of hemophilia (A or B), severity of hemophilia based on factor VIII or factor IX activity (severe: <0.01 IU/mL; moderate: 0.01– 0.05 IU/mL; or mild >0.05–0.40 IU/mL), prophylaxis use (yes / no), inhibitor status (current / past / never), HIV infection (yes / no) and hcv status (currently / past / never infected).

Outcomes and definitions

Three types of outcomes were assessed in partially overlapping populations: educational outcomes, labor market participation and the ability to participate in social roles and activities.

Educational outcomes were assessed according to the International Standard Classification of Education (ISCED).[27, 28] The following educational outcomes were assessed: 1) participation in education, defined as the proportions of 15-19 and 20-24 year-olds enrolled in formal education; 2) educational attainment, defined as the percentage of the population aged 15-75 that completed at least upper secondary education (ISCED level 3), which is the Dutch minimally required qualification considered sufficient to enter the labor market;[29] 3) absenteeism from school due to hemophilia, defined as the number of days missed from school in the past 12 months due to hemophilia (bleeds or outpatient clinic visits) for individuals aged 5 years and older enrolled in formal education.

Labor market participation was assessed using internationally recognized labor market indicators.[18, 19] The study population for labor market outcomes consisted of individuals aged 15-75 years. Participants were either part of the labor force (individuals with paid employment and individuals without paid employment but actively looking for work) or the non-labor force (fulltime students, retirees, individuals with an occupational disability, unpaid employment).[30] The following outcomes were reported: 1) the employment-to-population ratio, defined as the proportion with paid employment for at least one hour a week (including self-employed persons) [18, 30] relative to the study population; 2) unemployment, defined as the proportion of the labor force without paid employment who were available for the labor market and actively looking for work;[30] 3) occupational disability, defined as the proportion of the study population being unable to obtain or maintain paid employment due to an illness or disability (with ≥ 80% disability considered fully occupationally disabled according to Dutch law;[19, 30]) 4) the proportion of individuals working fulltime (i.e. ≥36 hours a week) among

employed persons; 5) absenteeism from work, defined as the total number of days missed from work, and the number of days missed from work due to hemophilia (bleeds or outpatient clinic visits) in the past 12 months for individuals with paid employment and 6) perceived impact of hemophilia on education or career.

The ability to participate in social roles and activities was assessed for adults (≥18 years) by calculating T-scores for the PROMIS-29 Ability to Participate in Social Roles and Activities domain using the Health Measures Scoring Service.[31] T-scores are a normalized score with a population mean of 50 and a standard deviation (SD) on 10 in the reference population (the U.S. general population).

Data analysis and comparisons

Educational outcomes and labor market indicators were compared to aggregate-level data from the Dutch general male population when possible, as specified below.

Descriptive statistics (N, %, median, interquartile range (IQR)) were mainly used, categorized according to disease severity. Educational outcomes and labor market participation were presented as percentages with 95% confidence intervals (CI) and stratified by hemophilia severity, type and inhibitor status. If confidence intervals for our estimates did not include the estimate for the general population, we consider our estimate to be different from the general male population. The employment-to-population ratio was also stratified by 10-year age groups. The number of days of absenteeism was reported as medians with the interquartile range (IQR). The ability to participate in social roles and activities was presented as mean and median T-scores with IQR, stratified by hemophilia severity.

Participation in education was compared to Organization for Economic Co-operation and Development (OECD) aggregate data in 2018 (combined for males and females, as data for males are not available).[32] Educational attainment was compared to data at the aggregate level from Statistics Netherlands in 2019.[33] Children aged 5-18 years were assumed to be in compulsory education. The only data available for comparisons of school absenteeism was the proportion of Dutch boys in grades 8 (13-14 years old) and 10 (15-16 years old) who reported at least one day of school absenteeism in 2015.[34]

The employment-to-population ratio and occupational disability were compared to aggregate data of the general male population aged 15-75 years in 2018, stratified by age group, extracted from Statistics Netherlands.[35] Absenteeism from work was compared to data from Statistics Netherlands in 2018).[36]

The impact of hemophilia on career or education and the Ability to Participate in Social Roles and Activities were assessed for adults in three age groups: those born before the introduction of coagulation factor products (born before 1971), those born before the introduction of pathogen inactivation and removal techniques (1971-1992) and those born after the introduction of such techniques (1993 or later). T-scores were

plotted by age group and hemophilia severity. The minimal important difference (MID) was 1; a difference of ≥1 was considered clinically relevant.[37]
Analyses were performed in IBM SPSS Statistics for Windows, Version 25.0.

Results

Study population

In total, 2192 adults and children with hemophilia were invited to participate; 1009 of them completed the questionnaire in part or in full (response 46%). Of these 1009 individuals, 906 were between 5-75 years old (84 children 5-11 years old, 57 adolescents 12-17 years old and 765 adults) and included in the current analysis. Medical record data were available for 665 of 906 individuals (73.4%). Of all participants, 86.4% had hemophilia A and 339 participants had severe hemophilia (37.4%). Individuals with severe hemophilia were younger (median age 36 years, IQR 20-54) than individuals with moderate (median age 40 years, IQR 25-57.5) and mild hemophilia (median age 48 years, IQR 27-61, Table 1).

Educational outcomes

Educational outcomes are summarized in Table 2. Participation in education was 96% (CI: 92-100) for 15-19 year-olds and 68.1% (CI: 57-79) for 20-24 year-olds, compared to 92% and 53% in the general population, respectively. One third (33.8%) of individuals enrolled in education also had fulltime or parttime work or was self-employed, and another 3.8% was actively looking for work.

Information on educational attainment was missing for 63 individuals. Of 731 remaining participants, 557 (76.2%; CI: 73.1-79.3), had completed at least upper secondary education (ISCED level 3), compared to 72.8% in the general male population. Educational attainment was similar across severities and types of hemophilia (Table 2 and Supplementary Table 1a and 1b).

Data for school absenteeism due to hemophilia were available for 154 of 263 persons aged 5-75 years who were enrolled in formal education; part of the absenteeism data were missing due to a routing error in the first electronic version of the questionnaire, which was corrected after six months. Overall, 69.5% (CI: 63.6-75.3) reported absenteeism due to hemophilia in the past 12 months (Table 2), compared to 37.8% of Dutch boys in grades 8 and 10. The number of days of absenteeism due to hemophilia was higher among individuals with severe hemophilia (median 2 days, IQR 0.9-4.8) than among those with moderate (median 1 day, IQR 0.2-3) and mild hemophilia (median 0.8, IQR 0-2).

Table 1: Characteristics of persons with hemophilia aged 5-75 years

	Total (n = 906)	Severe (n = 339)	Moderate (n = 133)	Mild (n = 434)
Age (median, IQR)	43.0 (21-59)	36 (20-54)	40 (25-57.5)	48 (27-61)
Type of hemophilia	N (%)	N (%)	N (%)	N (%)
Hemophilia A	783 (86.4)	294 (86.7)	113 (85.0)	376 (87.2)
Hemophilia B	113 (12.5)	45 (13.3)	19 (14.3)	49 (11.4)
Missing	10 (1.1)	-	1 (0.8)	9 (2.5)
Treatment modality				
Prophylaxis	327 (36.0)	303 (89.4)	21 (15.8)	2 (0.5)
No prophylaxis	553 (61.0)	28 (8.3)	111 (83.5)	414 (95.4)
Missing	27 (3.0)	8 (2.4)	1 (0.8)	18 (4.2)
Hepatitis C infection*				
Never infected	557 (61.5)	166 (49.0)	81 (60.9)	310 (71.4)
Past infection	226 (24.9)	142 (41.9)	38 (28.6)	46 (10.6)
Current infection	7 (0.8)	5 (1.5)	0 (0)	2 (0.5)
Missing	116 (12.8)	26 (7.7)	14 (10.5)	76 (17.5)
HIV positive				
No	853 (94.2)	314 (92.6)	129 (97.0)	410 (94.5)
Yes	21 (2.3)	21 (6.2)	0 (0)	0 (0)
Missing	32 (3.5)	4 (1.2)	4 (3.0)	24 (5.5)
Inhibitor status†				
Never	732 (80.8)	269 (79.4)	113 (85.0)	350 (80.6)
Past	85 (9.4)	51 (15.0)	14 (10.5)	20 (4.6)
Current	14 (1.5)	4 (1.2)	2 (1.5)	8 (1.8)
Missing	73 (8.1)	13 (3.8)	4 (3.0)	56 (12.9)
Joint impairment‡				
No	478 (52.8)	102 (30.1)	67 (50.4)	309 (71.2)
Yes	327 (36.1)	205 (60.5)	54 (40.6)	68 (15.7)
Missing	101 (11.1)	32 (9.4)	12 (9.0)	57 (13.1)

Information on ethnicity was not collected, as this is not allowed under Dutch law.

* Two individuals with severe hemophilia had a past or current hcv infection, but current status could not be established.

† Two individuals with severe hemophilia had a past or current inhibitor, but current status could not be established.

‡ Joint impairment is self-reported joint impairment in any joint (yes / no).

Table 2: Educational outcomes for persons with hemophilia and the general male population

	Participation in education, % (95% CI)*		Educational attainment (% with ISCED ≥ 3 (95% CI)†	Absenteeism from school‡	
	15-19 years	20-24 years		% with absenteeism	Median days (IQR)
General male population	92	53	72.8	37.8	n.a.
HiN-6	96 (90-100)§	**68.1 (57-79)¶**	**76.2 (73.1-79.3**)	**69.5 (63.6-75.3**)	1.0 (0-3.3)
Severe	-	-	**78.7 (73.6-83.7)**	**80 (70-90)**	2.0 (0.9-4.8)
Moderate	-	-	72.2 (64.0-80.4)	77 (22-140)	1.0 (0.2-3)
Mild	-	-	75.8 (71.3-80.2)	**54 (38-70)**	0.8 (0-2)

Outcomes that are different from the general population are indicated in **bold**.

n.a. = not available

* 263 individuals were enrolled in formal education, i.e. ISCED level 1 and higher; 151 of them were between 5 and 18 years old and in compulsory education. One third (33.8%) of individuals enrolled in education also had fulltime or parttime work or was self-employed, and another 3.8% was actively looking for work. General population data are from the Organization for Economic Co-operation and Development (OECD) for males and females combined.[32]

† Highest completed education level of the hemophilia population and general male population aged 15-75 years. Educational attainment was missing for 63 individuals (8%) with hemophilia and for 1.6% of individuals in the general population. General population data are from Statistics Netherlands.[33]

‡ Due to hemophilia for all individuals aged 15-75 and enrolled in formal education of any type or level, or absenteeism from school for any illness for Dutch boys in grades 8 and 10 without hemophilia.[34]

§ Education status was unknown for 2 of 46 individuals. Participation in education was not stratified by severity because of low numbers (n = 18 for mild hemophilia, n = 4 for moderate hemophilia and n = 24 for severe hemophilia)

¶ Education status was unknown for 1 of 72 individuals. Participation in education was not stratified by severity because of low numbers (n = 28 for mild hemophilia, n = 12 for moderate hemophilia and n = 32 for severe hemophilia)

Labor market participation

The analysis population consisted of 794 individuals aged 15-75 years. Information on labor market status was missing for 24 individuals. Of the remaining 770 individuals, 379 had mild hemophilia, 119 had moderate hemophilia and 272 had severe hemophilia (Supplementary table 2a); 555 were in the labor force (of whom 30 were unemployed) and 215 were not in the labor force (Figure 1); Of 525 individuals with paid employment, 89 were also enrolled in education.

The employment-to-population ratio of the hemophilia population was 525/770 = 68.2% (CI: 64.9-71.5), compared to 73.2% in the general male population (Table 3 and Figures 1 and 2). Persons with severe hemophilia had the lowest employment-to-population ratio: 64.3% (CI: 58.6-70.0). For moderate and mild hemophilia the employment-to-population ratio was similar to that of the general population (70.6%, CI: 62.4-78.8 and 70.2%, CI: 65.6-74.8, respectively, Supplementary table 2a and Supplementary figure 1). For almost 10-year age groups, the employment-to-population ratio followed the same pattern as the general population; however, it was consistently lower for persons with severe hemophilia than for mild and moderate hemophilia and the general population, except for the 15-25 year age group (Figure 3). The employment-to-population ratio for hemophilia A and B was 68.1% and 67%, respectively (Supplementary table 2b). Finally, the employment-to-population ratio for individuals with a current inhibitor was 41.7% (5 of 12).

Unemployment was 5.4% (CI: 3.5-7.3; 30 of 555), compared to 3.4% among the general male population. Unemployment was higher for severe hemophilia (6.9%) than for mild hemophilia (4.3%) (Table 3 and Supplementary Table 2a), but estimates are imprecise due to low numbers. Unemployment was 5.6% and 4.5% for hemophilia A and B, respectively (Supplementary table 2b).

Occupational disability was reported by 8.4% (CI: 6.5-10.4) of the population aged 15-75; higher than among the general male population (4.8%). This was mainly attributable to those with severe hemophilia, where 14.7% (CI: 10.5-18.9) reported an occupational disability (Table 3). Of 12 individuals with a current inhibitor, 2 had an occupational disability (17%). The majority of persons with an occupational disability (89%) were considered ≥ 80% occupationally disabled. Hemophilia was the cause of occupational disability for 34 of 65 individuals (52%). For another ten, a combination of hemophilia and hemophilia-related comorbidities (such as hcv and / or HIV infection) was the cause of occupational disability. Sixteen individuals had an occupational disability not related to hemophilia and for five the cause was not reported. Individuals with self-reported joint impairment were more likely to have an occupational disability than those without joint damage (14.3% with joint impairment vs. 3.4% without joint impairment).

Most persons with paid employment worked fulltime (71.4%; CI: 67.6-75.3), which is similar to the general male population (72%).

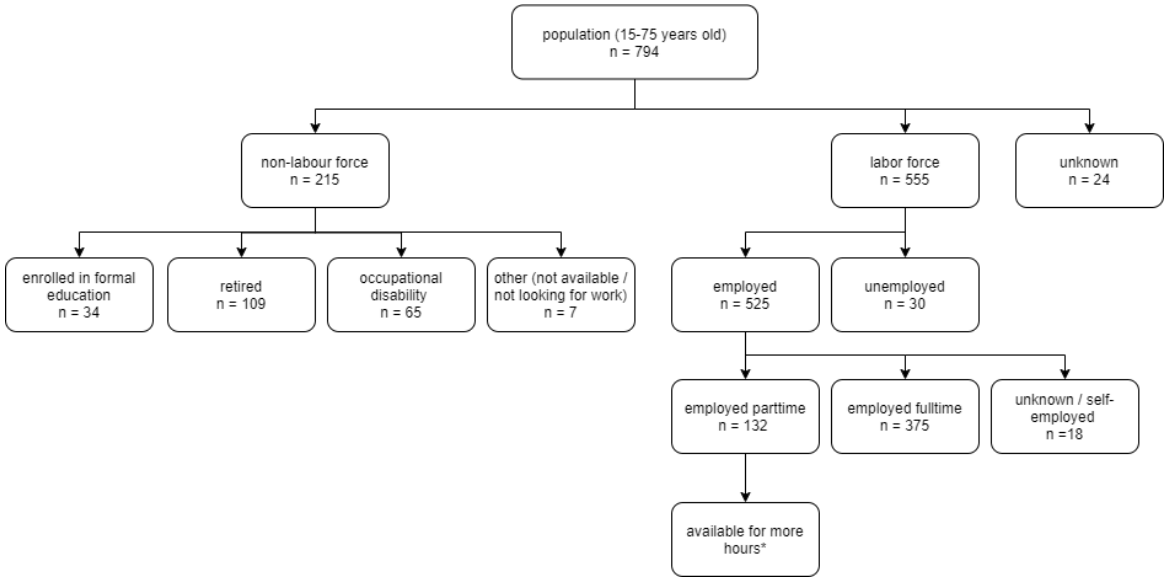

Figure 1: Distribution of the hemophilia population aged 15-75 in the labor force and the non-labor force. The labor force consists of individuals with paid employment > 1 hour / week and individuals who are legally unemployed. Persons in the non-labor force are not able to work or available for work because they are enrolled in (fulltime) education, retired, have an occupational disability or have unpaid employment.

*No data were available for the work availability of persons with a parttime job

Table 3: Comparison of labor market participation for persons with hemophilia and the general male population aged 15-75 years

	Labor market indicators			Limitations labor market			
	Employment-to-population ratio*	Unemployment†	% working fulltime‡	Occupational disability (%)§	% with work absenteeism (any reason)	% with work absenteeism (hemophilia)	Median days (IQR)
General male population¶	73.2	3.4	72	4.8	45.2	-	n.a.
HiN-6	**68.2 (64.9-71.5)**	**5.4 (3.5-7.3)**	71.4 (67.6-75.3)	**8.4 (6.5-10.4)**	**37.7 (31.4-43.9)**	19.7 (14.5-24.8)	0 (0-5)
Severe	**64.3 (58.6-70.0**)	6.9 (3.3-10.5)	66.9 (59.9-73.8)	**14.7 (10.5-18.9)**	42.6 (30.9-54.4)	25.0 (14.7-35.3)	0 (0-5)
Moderate	70.6 (62.4-78.8)	5.6 (0.8-10.4)	75 (65.7-84.3)	4.2 (0.6-7.8)	34.4 (17.9-50.8)	21.9 (7.6-36.2)	0 (0-4)
Mild	70.2 (65.6-74.8)	4.3 (1.9-6.7)	73.3 (68.0-78.6)	5.3 (3.0-7.5)	**35.9 (27.7-44.1)**	16.3 (9.9-22.6)	0 (0-4)

Outcomes that are different from the general population are indicated in **bold**.

n.a. = not available

* Defined as the proportion of the (male) population aged 15-75 years with paid employment for at least one hour a week.[18, 30]

† Proportion of the labor force (aged 15-75 years) without paid employment who were available for the labor market and actively looking for work.

‡ For another 18 individuals (3.4% of individuals with paid employment), fulltime / parttime status was unknown. Most of them were self-employed.

§ Defined as the proportion of the population aged 15-75 years being unable to obtain or maintain paid employment due to an illness or disability.[30]

¶ Aggregate-level data from the general male population from Statistics Netherlands.[35]

Data on absenteeism from work were available for 231 of 525 individuals with paid employment; data from the remaining individuals were missing due to a routing error in the electronic version of the questionnaire. Persons with hemophilia less often reported work absenteeism than the general male population (37.7%, CI: 31.4-43.9, general male population: 45.2%, Table 3). Almost twenty percent (19.7%) of persons with paid employment reported absenteeism from work due to hemophilia.

The number of days of absenteeism was skewed and ranged from 0 to 250 days (Supplementary Figure 2). The median number of days of absenteeism was 0 for all severities (IQR severe hemophilia: IQR 0-5 days, IQR mild / moderate hemophilia: 0-4 days (Table 3)).

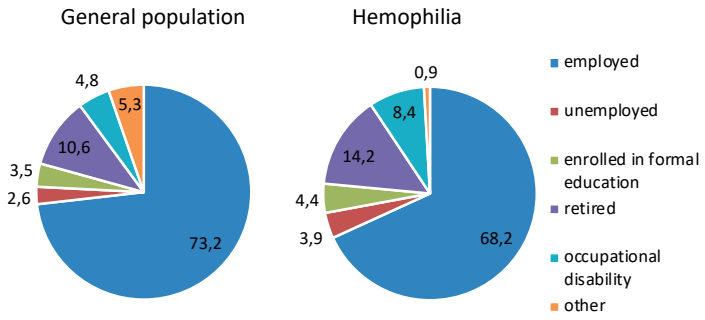

Figure 2: Labor market participation for the general population (left) and for persons with hemophilia (right)

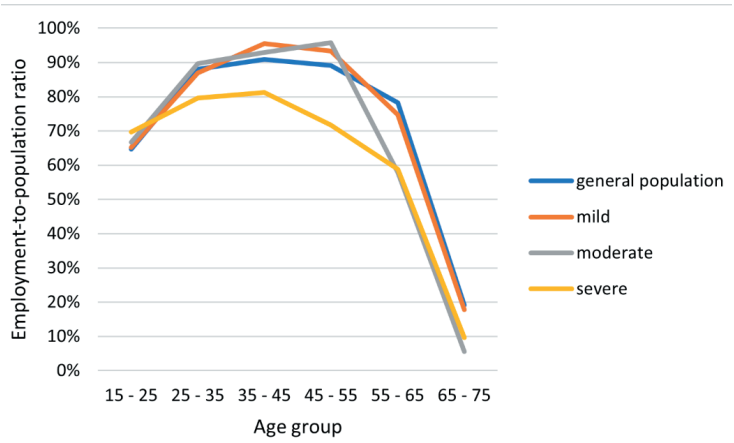

Figure 3: Employment-to-population ratio by hemophilia severity and 10-year age group

Perceived impact of hemophilia on career and education

Of 273 participants aged 15-75 years with severe hemophilia, 129 (47.3%) reported that hemophilia had affected their choice of education or career to some or to a large extent. This proportion was 35.6% for moderate hemophilia and 17.6% for mild hemophilia (Supplementary table 3). Among participants born in 1993 or later, 16.5% reported that hemophilia had affected this decision. For participants born between 1971-1992, this was 28.6% and for the group born in 1970 or earlier this was 36.1%. Frequently mentioned impacts in the open-ended question were choosing jobs that required little physical activity or that had a low injury risk.

Social participation

Persons with hemophilia had similar or better scores on the PROMIS Ability to Participate in Social Roles and Activities than the general population mean of 50, with differences larger than the MID (set at 1.0). The overall mean score was 54.2 (median 53.8; IQR: 48.0-64.2); for severe hemophilia the mean was 51.2 (median 51.8, IQR 44.2-58.2), for moderate hemophilia it was 56.4 (median 58.1; IQR: 51.7-64.2) and for mild hemophilia it was 55.5 (median 55.9; IQR: 50.1-64.2). The Ability to Participate in Social Roles and Activities declined with age in all severity groups; the negative association was more pronounced among those with severe hemophilia (Figure 4).

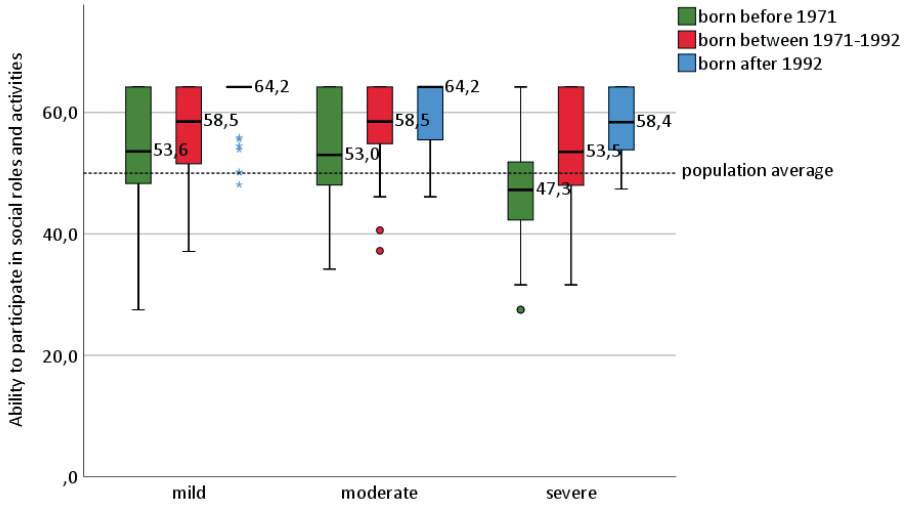

Figure 4: Median T-Scores on PROMIS Profile-29 Ability to participate in social roles and activities, by hemophilia severity and age group (≥18 years old)

Medians are shown as horizontal bars. Boxes indicate IQR, whiskers indicate range of T-scores

Discussion

This study assessed socio-economic participation in Dutch persons with hemophilia. To our knowledge, this is the first comprehensive report of nationwide participation in education, labor market participation and social participation of persons with hemophilia using internationally recognized socio-economic standards.

Participation in education and educational attainment of Dutch persons with hemophilia were similar to or higher than among the general population. Absenteeism from school was increased. The most important labor market indicators, i.e. the employment-to-population ratio, unemployment and occupational disability, were worse than in the general population, especially for individuals with severe hemophilia. Absenteeism from work and the ability to participate in social roles and activities were similar to or better than in the general population. However, the latter was worse for the oldest age group with severe hemophilia.

Most of our results corroborate those of previous reports. However, in contrast with other studies,[12, 13] occupational disability in HiN-6 was lower than reported in other studies,[12, 15] and fewer participants perceived a negative impact of hemophilia on their career or education.[12, 13] These differences may be explained by differences in population and study settings. For example, lower and upper-middle income countries may have higher disability rates than high-income countries such as the Netherlands due to suboptimal availability of treatment products.[12, 13] On the other hand, unemployment was higher in HiN-6 than in other studies and the general population.[10, 11] The reason for this is unknown, but unemployment rates are known to vary seasonally and according to economic developments.[38] Finally, school absenteeism was much higher than among Dutch boys, which may in part be due to regular hospital visits. However, data may not be comparable because of differences in age groups and reference year.

Occupational disability was almost twice as common. The employment-to-population ratio was five percentage points lower than in the general population, especially for severe hemophilia. This does not necessarily imply worse participation because it depends to a large degree on the size of the non-labor force.[18] Persons in the non-labor force are not necessarily inactive because of disease, but they may be enrolled in education or be retired. Our study showed large proportions of students and retirees, resulting in a larger non-labor force and thus a lower employment-to-population ratio.[18] Still, men with hemophilia have a better employment-to-population ratio than 45 to 75-year old men with a chronic disease (14%).[39]

Our findings of lower absenteeism from work may be explained by a healthy worker effect:[40] working individuals with hemophilia may be relatively healthy and therefore have low absenteeism.

The PROMIS T-scores for Ability to Participate was lower for individuals born before the introduction of prophylaxis, especially for severe hemophilia. This is consistent with

PROMIS short form scores of a recent Spanish study among patients with rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus.[41] However, we found higher participation rates than for rheumatic disease patients, who had mean scores of 26.2 (SD: 7.79). In our study, scores of younger persons with non-severe hemophilia were higher than in the general population. We cannot explain this finding. Further research is needed to study the determinants of the ability to participate. The differences in participation outcomes with the general population appear to be of the same order of magnitude as those reported in the HiN-5 survey conducted in 2001.[11] However, historic comparisons should be interpreted with caution because of changes in legislation (e.g. for occupational disability),[42] decreasing trends in absenteeism,[19] increasing education level in the general population and other labor market developments.[43] Therefore, rather than comparing indicators over time, it is more meaningful to compare socio-economic participation outcomes for persons with hemophilia with the general population in the same reference year.

This study has several limitations. First, the response rate was 46%. Despite this, the most important characteristics of responders were similar to those of non-responders in terms of hemophilia severity and age distribution:[2] 48% of persons in our sample had mild hemophilia, compared to 53.5% in the Dutch hemophilia population. We therefore consider our results generalizable to the full Dutch hemophilia population. Some selection based on education level or ethnicity is possible, as completing a comprehensive questionnaire is a cognitive task that requires sufficient Dutch language skills; individuals with a lower education level or limited ability to understand Dutch (i.e. immigrants) may therefore have been less likely to respond. This may have resulted in possible underrepresentation of these groups and overestimation of educational attainment. Under Dutch law, we were not allowed to collect information on ethnicity. On the other hand, those with higher education levels may have busier jobs and schedules, and less time to complete a questionnaire. This source of selection bias is inherent to questionnaire research and may be similar for the previous HiN survey as well as for the surveys conducted by Statistics Netherlands.

Second, we relied on self-reported clinical data for part of our sample because electronic medical record data were not available for 26.6% of participants. Self-reported clinical data may be less reliable, which may have resulted in some misclassification, for example for disease severity. However, low rates of misclassification were observed among those with complete data. Therefore, misclassification is unlikely to have affected our results.

Third, we were only able to compare outcomes to aggregate-level data from the general male population. This may have led to some confounding by age. To overcome this, we stratified our analyses by age groups when possible. However, within-stratum confounding cannot be ruled out completely.

Fourth, reliability of our estimates for unemployment may be limited due to low numbers, resulting in imprecise estimates. The same applies to the employment-to-population ratio and occupational disability for individuals with a current inhibitor. Comparisons with the general population should therefore be interpreted with caution.

Fifth, women with hemophilia were not included in HiN. Our results may therefore not be applicable to women with hemophilia. Finally, the data on work and school absenteeism are incomplete due to a routing error in the electronic version of the questionnaire that occurred until December 2018. This resulted in fewer participants responding to the questions about absenteeism, making our estimates of absenteeism less reliable. The missing data on absenteeism may be considered missing completely at random because missingness is not dependent on any other variable.[44]

The more favorable outcomes of younger compared with older participants and modest improvements since the previous nationwide study suggests beneficial effects of widespread prophylaxis. Hemophilia treatment is costly. However, treatment has also brought direct and indirect gains for persons with hemophilia and for society because of near-normal participation. Monitoring such outcomes in a standardized manner will help evaluate the long-term effects of comprehensive hemophilia care, including innovations in treatment. Such novel treatments were not yet available

at the time the survey was conducted and their effects on socio-economic outcomes could not be taken into account in this study.

In conclusion, educational outcomes and social participation were similar to or better than in the general population. Some labor market indicators were worse for severe hemophilia. Further research is needed to establish whether comprehensive care contributed to better participation.

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Supplement

Educational outcomes

Supplementary Table 1a: Highest completed education level of the hemophilia population and Dutch males aged 15-75 years, by hemophilia severity.

	Severe, n = 281 (%)	Moderate, n = 121 (%)	Mild, n = 392 (%)	HiN-6, n = 794 (%)	General male population (%)[1]
Primary education	14 (5.0)	10 (8.3)	15 (3.8)	39 (4.9)	8.3
Lower secondary education	40 (14.2)	22 (18.2)	73 (18.6)	135 (17.0)	18.5
Upper secondary education	105 (37.4)	31 (25.6)	120 (30.6)	256 (32.2)	39.0
Bachelor or equivalent	56 (19.9)	34 (28.1)	105 (26.8)	195 (24.6)	20.2
Master or equivalent	38 (13.5)	18 (14.9)	50 (12.8)	106 (13.4)	12.4
Prefer not to say/Missing	28 (10.0)	6 (5.0)	29 (7.4)	63 (8.0)	1.6

Primary education = ISCED level 1, lower secondary education = ISCED level 2, upper secondary education = ISCED level 3, bachelor or equivalent = ISCED level 6, master or equivalent = ISCED 7.

Supplementary Table 1b: Highest completed education level of the hemophilia population, by type of hemophilia.

	Hemophilia A, n = 690 (%)	Hemophilia B, n = 97 (%)
Primary education	33 (4.8)	5 (5.2)
Lower secondary education	118 (17.1)	15 (15.5)
Upper secondary education	228 (33.0)	28 (28.9)
Bachelor or equivalent	164 (23.8)	28 (28.9)
Master or equivalent	96 (13.9)	10 (10.3)
Prefer not to say/Missing	51 (7.3)	11 (11.3)

Primary education = ISCED level 1, lower secondary education = ISCED level 2, upper secondary education = ISCED level 3, bachelor or equivalent = ISCED level 6, master or equivalent = ISCED 7.

Labor market participation

Supplementary Table 2a: Labor market participation for persons with hemophilia and Dutch males aged 15-75

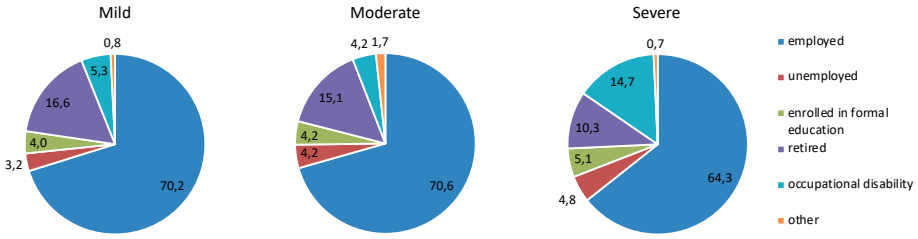
	Severe, n = 272	Moderate, n = 119	Mild, n = 379	Total*, n = 770	General male population
	(%)	(%)	(%)	(%)	(%)[2]
Labor force	188	89	278	555	
Paid employment†	175 (64.3)	84 (70.6)	266 (70.2)	525 (68.2)	73.2
Unemployed‡	13 (4.8)	5 (4.2)	12 (3.2)	30 (3.9)	2.6
Non-labor force	84	30	101	215	
Enrolled in formal education	14 (5.1)	5 (4.2)	15 (4.0)	34 (4.4)	3.5
Retired	28 (10.3)	18 (15.1)	63 (16.6)	109 (14.2)	10.6
Occupational disability§	40 (14.7)	5 (4.2)	20 (5.3)	65 (8.4)	4.8
Other¶	2 (0.7)	2 (1.7)	3 (0.8)	7 (0.9)	5.3

* For 24 individuals employment information was missing (13, 2 and 9 for mild, moderate and severe hemophilia, respectively).
† Paid employment refers to paid work for at least one hour per week (employment-to-population ratio). 89 of 525 working individuals were also enrolled in education.
‡ Percentage of the total population aged 15-75. Unemployment is also often reported as a percentage of the labor force: 3.4% of Dutch males in the labor force (6.9, 5.6 and 4.4 percent for severe, moderate and mild hemophilia, respectively).
§ 58 of 65 individuals with an occupational disability were classified as ≥80 percent disabled. For 4 individuals their disability percentage was unknown.
¶ Includes fulltime or parttime unpaid employment.

Supplementary Table 2b: Labor market participation by type of hemophilia*

	Hemophilia A, n = 668	Hemophilia B, n = 94
	(%)	(%)
Labor force	482	66
Paid employment	455 (68.1)	63 (67.0)
Unemployed†	27 (4.0)	3 (3.2)
Non-labor force	186	28
Enrolled in formal education	26 (3.9)	8 (8.5)
Retired	95 (14.2)	13 (13.8)
Occupational disability§	58 (8.7)	7 (7.4)
Other¶	7 (1.0)	0

* For 7 individuals type of hemophilia was unknown.
† 5.6% and 4.5% of the labor force with hemophilia A and hemophilia B were unemployed.

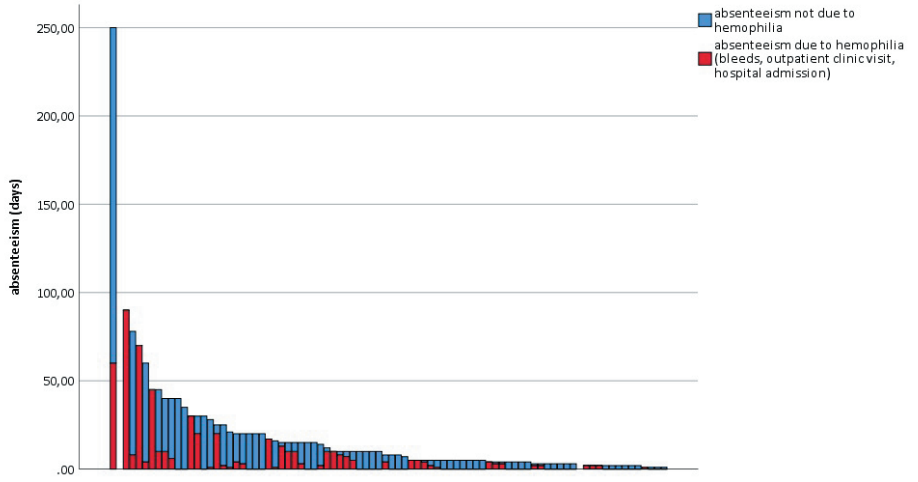


Supplementary figure 1: Labor market participation for persons with hemophilia and Dutch males aged 15-75

Impact of hemophilia

Supplementary Table 3: Impact of hemophilia on education or career for individuals aged 15-75

	Severe, n = 281	Moderate, n = 121	Mild, n = 392	Total n = 771
	(%)	(%)	(%)	(%)
No impact	136 (48.3)	74 (61.2)	305 (77.8)	515 (64.9)
Some or large impact	129 (45.9)	42 (34.7)	67 (17.1)	238 (30.0)
Do not know	8 (2.8)	2 (1.7)	8 (2.0)	18 (2.3)
Missing	8 (2.8)	3 (2.5)	12 (3.1)	23 (2.9)

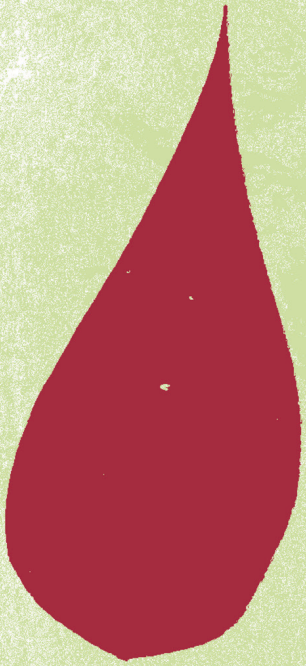


Supplementary Figure 2: Absenteeism from work due to hemophilia and other reasons (n = 231)

References

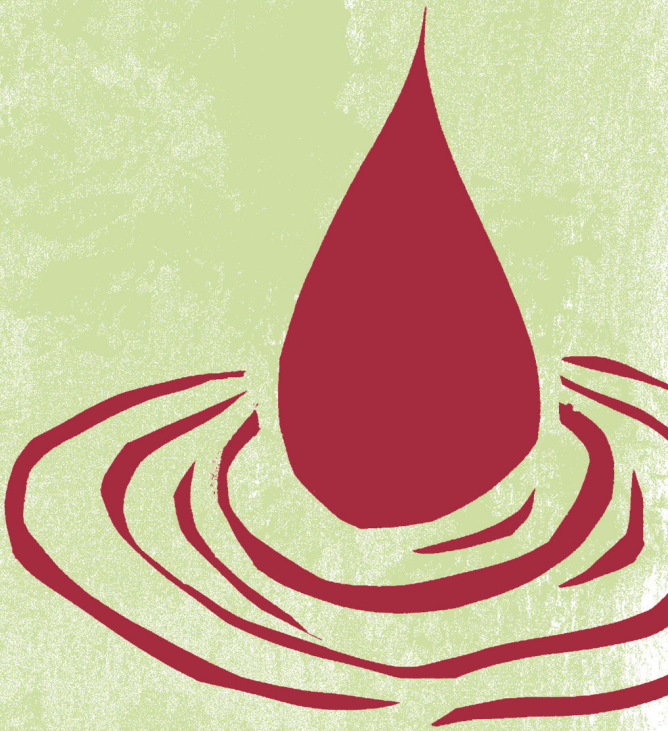
1 Statistics Netherlands (CBS). Bevolking; onderwijsniveau; geslacht, leeftijd en migratieachtergrond [Educational attainment]. Den Haag 2019.

2 Statistics Netherlands (CBS). Arbeidsdeelname; kerncijfers [labor participation; core figures]. Den Haag 2018.



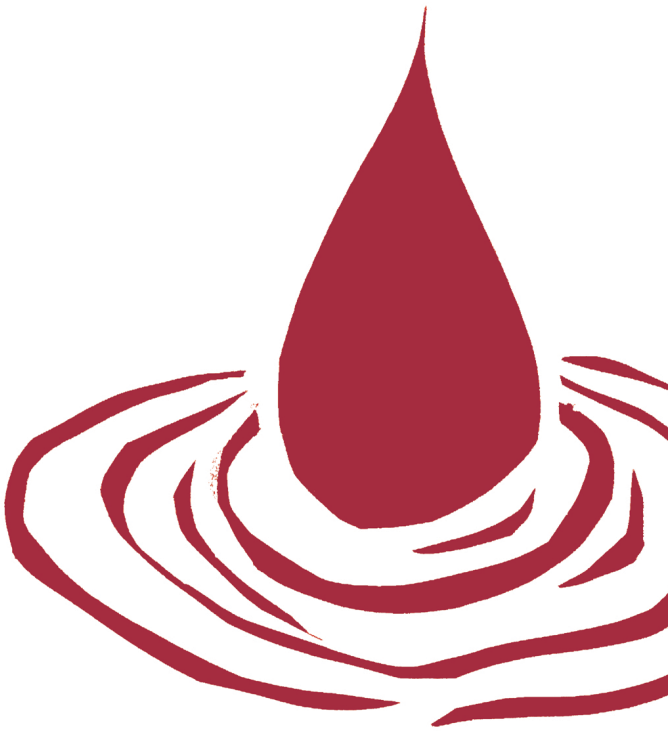
PART III

CONCLUSIONS



CHAPTER 8

Summary and general discussion



This thesis aimed to define, measure and quantify relevant health outcomes for persons with the congenital bleeding disorder hemophilia. Standardization of health outcomes measurement will help optimize treatment, facilitate individual decision-making and allow for comparison of outcomes across settings and over time, thus contributing to the best health outcomes. This chapter summarizes the main findings and discusses strengths and limitations, methodological considerations, and future directions.

Summary of main findings

In **Chapter 2** we explored patients' perspectives on a program that aimed to further engage persons with hemophilia in their care and to stimulate them in making their own treatment decisions. As part of this program, persons with hemophilia were encouraged to tailor their prophylaxis regimens according to their needs, and to discuss their needs and corresponding changes to their schedules with the hemophilia clinic team. The team, in turn, attempted to support them in these decisions by providing information about pharmacokinetics in visual formats in order to increase patient independence. We conducted an interview study with 18 adults with mild, moderate or severe hemophilia to understand their experiences with this program and whether they thought it affected the number of bleeds and other outcomes. The interviews were analyzed using descriptive content analysis. Most participants were satisfied with the amount of information they received and felt confident in making decisions about their treatment schedules. Some participants had changed their prophylaxis schedules based on the information provided by the clinic team and experienced fewer bleeds. These findings show that patient engagement strategies may increase patient independence and understanding of the effects of hemophilia treatment.

In **Chapter 3** we performed a qualitative interview study among Dutch persons with hemophilia to explore the factors that may play a role in patients' decisions about whether or not to switch to a new treatment product. When the interviews were conducted, new treatment products such as extended half-life products were emerging, but gene therapy and non-factor products were not yet on the market. Twelve men with hemophilia and two mothers were interviewed. Participants were generally satisfied with their current treatment and did not experience problems with their current treatment. Facilitators for switching to a new treatment product were ease of administration and bleed protection that was at least as effective as their current product. Barriers were fear of the unknown (e.g., potential transmission of viral pathogens, development of inhibitors, long-term safety of gene therapy) and not wanting to be a 'guinea pig' for new products, even after market approval. Most participants were aware of the high costs of current hemophilia medication and said they used their products responsibly. As an additional finding, some wondered whether participation in high-risk activities was

justified, because this leads to increased usage and because the availability of treatment depended on society's willingness-to-pay for these products.

Chapter 4 describes value-based health care for hemophilia. Value-based health care aims to improve value for patients. Defining a standard set of outcomes and measuring them in an appropriate way will allow for comparison over time and across settings. Eventually, this will lead to improved value for patients and potentially reduced costs of care because services that do not improve value will be eliminated. Even for hemophilia care, where 99 percent of the costs can be attributed to coagulation factor replacement therapy, optimizing health outcomes while maintaining the same costs will contribute to value-based health care.

As a first step toward value-based health care, **Chapter 5** describes the development of a standard set of outcomes. Over 3000 possible health outcomes were identified from a systematic literature search. Subsequent voting rounds by hemophilia professionals and patient representatives from six continents led to the selection of the following ten health outcomes in three hierarchically ordered tiers: 1) cure; 2) impact of disease on life expectancy; 3) ability to engage in normal daily activities; 4) severe bleeding episodes; 5) number of days lost from school or work; 6) chronic pain; 7) disease and treatment complications; 8) sustainability of physical functioning; 9) social functioning; and 10) mental health. The group of hemophilia experts identified the following eleven demographic factors, baseline clinical factors and treatment factors as risk-adjustment variables: age; gender; individual socio-economic status; availability of and access to treatment; co-morbidities; severity of hemophilia; degree of joint damage; psychological well-being; inhibitor status; health literacy and which hemophilia care professionals are involved in the management of hemophilia. Finally, recommended hemophilia-specific instruments to measure the ten most important health outcomes were: (ped)HAL (except leisure activities and sports); FISH; HJHS; PROBE Chronic pain; Haemo-QoL-A Role functioning; Haemo-QoL-A Emotional impact; and CHO-KLAT. Recommended adult PROMIS item banks were Self-efficacy for managing chronic conditions - managing daily activities; Pain intensity; Pain interference; Physical Function; Physical Function for samples with mobility aid users; Ability to participate in social roles and activities; Self-efficacy for managing social interactions; Anxiety; Depression; General life satisfaction; and Positive affect. Recommended pediatric PROMIS item banks were: Upper extremity; Mobility; Pain intensity; Pain interference; Physical Activity; Strength impact; Family relationships; Peer relationships; Anxiety; Depressive symptoms; Life satisfaction; and Positive affect. The standard set of outcomes is ready for implementation in clinical practice.

Chapter 6 describes the validation of the Dutch-Flemish version of the PROMIS Profile-29, which consists of seven short forms that are considered important by many patient groups: Physical function; Anxiety; Depression; Fatigue; Sleep disturbance; Ability to Participate in Social Roles and Activities; and Pain (interference and intensity). Some of these domains included health outcomes identified in the standard set of outcomes.

Using data from the sixth Hemophilia in the Netherlands study (HiN-6), we evaluated structural validity, internal consistency and construct validity of each of the PROMIS-29 subscales. We found evidence of structural validity, internal consistency and construct validity for Physical Function, Depression and Sleep Disturbance. Construct validity was also sufficient for Anxiety, Fatigue and Pain Intensity. Some pre-defined hypotheses for structural and construct validity were not confirmed; however, small changes in the methods for cut-off values affect the number of hypotheses confirmed and the conclusions. These results indicate that PROMIS short forms that measure these domains may be used in clinical and research settings among persons with hemophilia.

Chapter 7 quantifies two of the most important outcomes for persons with hemophilia: social and economic participation. Three types of outcomes were assessed in the Dutch hemophilia population: educational outcomes, labor market participation and the ability to participate in social roles and activities. Participation in education and educational attainment of Dutch persons with hemophilia were similar to or higher than among the general population. Absenteeism from school was also increased. The most important labor market indicators, i.e. the employment-to-population ratio, unemployment and occupational disability, were worse than in the general population, especially for individuals with severe hemophilia. Absenteeism from work and the ability to participate in social roles and activities were similar to or better than in the general population. However, the latter was worse for the oldest age group with severe hemophilia. Most participants did not feel that hemophilia had impacted their career or education.

Strengths and limitations

The findings and implications of the studies described in this thesis should be interpreted in the light of some overall strengths and limitations. Strengths and limitations of each of the studies have been discussed in earlier chapters. This section therefore considers some overall strengths and limitations.

Strengths

A strength of the studies described in this thesis is that health outcomes were considered from the patient perspective. Since the goal of clinical care is to provide value for individuals with hemophilia, the voice of persons with hemophilia is of major importance. In **Chapters 2, 3** and **5**, persons with hemophilia or their representatives (such as mothers of boys with hemophilia) actively participated and expressed their views, ensuring relevance of the presented work.

Another strength is the combination of methods used to explore health outcomes. The qualitative methods (**Chapters 2** and **3**), the consensus-based approach (**Chapter 5**) and the quantitative HiN survey (**Chapters 6** and **7**) supplement each

other and thereby provide a comprehensive assessment of relevant health outcomes for persons with hemophilia. Qualitative research aims to understand the 'what', 'how' or 'why' of a phenomenon from the perspective of patients, and respondents may even be a selective group of patients who can provide insight into a phenomenon. Results from qualitative research may also help improve doctor-patient communication.[1] **Chapters 2** and **3** provided such context on switching decisions and on the information persons with hemophilia use to adjust their treatment schedules. These contexts may help to understand treatment behavior and outcomes. Such contextual information would not have emerged with other methods, such as pre-structured questionnaires. **Chapters 5**, **6** and **7** also supplement each other: the health outcomes identified in **Chapter 5** were quantified in the Dutch hemophilia population as part of the HiN study**,** such as days lost from school or work and socio-economic participation (**Chapter 7**). Quantifications of other recommended outcomes, such as the impact on life expectancy, severe bleeding episodes, and disease and treatment complications were also assessed within the HiN studies.[2, 3] Some of the recommended outcomes may be measured with the PROMIS Profile-29, which was validated in **Chapter 6**.

Finally, the HiN study described in **Chapters 6** and **7**, is among the largest and longest running cohort studies of hemophilia in the world. Data from HiN allow for comprehensive assessment of both clinical and patient-relevant health outcomes in a nationally representative sample of persons with hemophilia. As such, HiN data may be used to evaluate the effects of hemophilia care over time.

Limitations

Some limitations need to be considered as well. One limitation is that there have been important developments in hemophilia treatment that could not fully be taken into account in our studies: new treatment products for hemophilia have entered the market in recent years, and effective treatment for hepatitis C (hcv) became available.[4] When this interview study was conducted between March and December 2017, use of extended half-life coagulation factor products (EHL) and the non-factor-based emicizumab was still limited among for Dutch persons with hemophilia. For example, in 2019, 7 percent of persons with hemophilia A and 29 percent of persons with hemophilia B who received prophylaxis used extended half-life products, and 1 percent used emicizumab.[3] The wider availability of new treatment products in recent years may have changed the perceived barriers and facilitators presented in **Chapter 3**. Still, the identified barriers and facilitators increase our understanding of factors that play a role in switching to a new treatment product. Our finding that most participants were aware of the high costs of current treatment products (and potentially future products) may still be relevant, regardless of the exact features of new products. It cannot be ruled out, however, that additional barriers and facilitators may play a role in switching decisions now that new extended half-life (EHL) products and emicizumab are available and patients are aware

of the specific features of these products, such as a lower injection frequency. As new products continue to be developed, including next-generation FVIII mimetic bispecific antibodies and products with an even longer half-life,[5, 6] further research into barriers and facilitators in switching decisions may be necessary.

The availability of effective treatment for hcv may have affected some of the results presented in **Chapters 6** and **7**. Most Dutch persons with hemophilia were treated successfully for their hcv infection by the end of 2018, when data collection for HiN-6 was ongoing. We attempted to capture this change in treatment by updating data on hcv status collected from electronic medical records. Despite this, there may have been a small overestimation of the number of persons with an active hcv infection, but this only affected the descriptive characteristics of **Chapters 6** and **7**.

Another limitation is that the PROMs proposed in **Chapter 5** still need to be validated. This may delay the implementation of PROMs in hemophilia care. Validation of such instruments requires large patient numbers, especially for structural validity.[7] The HiN-6 study would have been ideal for this purpose. However, data collection for HiN-6 was performed in parallel to development of the standard set of outcomes. The most relevant health outcomes and which PROMs to use to measure these outcomes could not be fully anticipated. Therefore, we decided to validate the PROMIS Profile-29 in HiN-6, expecting that this instrument would cover the most relevant health outcomes. Indeed, the PROMIS Profile-29 partially covered the four health outcomes pain, sustainability of physical functioning, social functioning and mental health. Additional PROMs may be validated to cover all relevant PROs in full. It should be noted, however, that it may not have been feasible to validate more instruments in the HiN survey, as this would have increased the length of the questionnaire, posing a disproportionally large burden on participants.

As an overall limitation, most studies described in this thesis, except for **Chapter 5**, apply only to men with hemophilia, as the HiN study only included men. Female carriers may also be considered persons with hemophilia, based on a combination of personal bleeding history and baseline plasma FVIII or IX concentrations.[8] Though the health outcomes identified in **Chapter 5** are relevant to them as well, we did not assess or quantify health outcomes for this patient group in HiN-6. Conclusions of the studies presented in this thesis may therefore not apply to women with hemophilia.

Methodological considerations

In addition to strengths and limitations in our efforts to define and measure relevant health outcomes for hemophilia, methodological quality of the studies should also be considered. The validity of the results presented in this thesis are discussed separately for the qualitative studies and for the quantitative studies.

Validity of qualitative research

Three of the studies presented in this thesis were qualitative studies (**Chapters 2**, **3** and **5**). In qualitative research, respondents are not sampled randomly and the sample is not intended to be representative of the population from which it originates. Validity of qualitative research is established by methods that include saturation, 'testing' emerging theory with subsequent respondents, simple counts to provide some perspective on how common participants' views are, and by respondent validation, i.e. reporting findings back to participants. This may help ensure the researchers interpreted participants' views correctly.[1] Evaluation of saturation was used in **Chapters 2, 3** and **5**. In **Chapter 5,** in which a standard set of health outcomes was identified, saturation was reached by consensus and frequency counts were used extensively: possible health outcomes were listed, voted on and their rankings discussed until consensus was reached in a delphi-like procedure. Simple counts were also used in **Chapters 2** and **3,** and respondent validation was used in **Chapter 3**.

However, it should be noted that the perspectives of persons with severe hemophilia presented in **Chapters 2** and **3** may not be generalizable to persons with non-severe hemophilia, as only persons with severe hemophilia are likely to self-infuse with coagulation factor VIII or IX and make treatment decisions.

Validity of HiN-6 data

Chapters 6 and **7** used data from the observational HiN study. Validity of observational studies may be limited by confounding, selection and information bias, and missing data.

Confounding

Confounding occurs when the effect of the exposure is mixed with the effect of another variable: a confounding factor has associations with both the exposure and the outcome. Also, a confounder must not be an effect of the exposure; i.e. a factor that is an intermediate step in the causal pathway from exposure to disease.[9]

The results presented in **Chapter 6** and **7** may be confounded by age. Participants with severe hemophilia were younger than participants with mild hemophilia. Younger individuals generally also have better outcomes than older individuals. As shown in **Chapter 6**, the differences in outcomes measured by PROMIS-29 subscales between individuals with and without hiv and between those with and without joint disease became smaller when adjusted for age and severity, suggesting confounding by age. In **Chapter 7**, labor market indicators were lower for persons with severe hemophilia. This may be caused by joint disease and disability, which are the result of recurrent joint bleeding. Frequent bleeding and joint disease may affect one's ability to complete education and to participate in the labor market. However, the relationship between hemophilia severity, as a proxy for joint disease, and participation may also be confounded by age, as older individuals are more likely to have joint disease and are also

more likely to be unemployed or have an occupational disability, even in the general population.[10] Therefore, we stratified some of our analyses by age group. Despite this, residual confounding is still possible due to misclassification of hemophilia severity or confounding within broad age strata. On the other hand, stratification into narrower age groups would lead to imprecise results because of low numbers in each stratum. [9] Misclassification of hemophilia severity, further discussed below, is likely to be low, but cannot be ruled out completely.

Bias

Selection bias and information bias may have affected the validity of the results described in **Chapters 6** and **7** of this thesis. Selection bias includes non-response bias and ascertainment bias. Information bias includes misclassification bias.

Non-response bias occurs if certain individuals are less likely to respond to an invitation to participate in research, and if the response is different for exposed and non-exposed persons.[11] As discussed in **Chapters 6** and **7**, selective non-response may have occurred if higher educated individuals or those with many health problems were more likely to respond to the invitation to participate in HiN-6. In HiN-6, participants were representative of the full Dutch hemophilia population in terms of disease severity (37 percent, 13 percent and 48 percent had severe, moderate and mild disease in HiN-6, respectively, compared to 33 percent, 13 percent and 54 percent in the population). Also, large ceiling effects were observed on PROMIS Profile-29 domains. This means that many respondents achieved the highest, or best score possible. Therefore, persons with few health problems appeared to be as likely to have responded as persons with more health problems. It is unlikely that selective non-response affected our findings to a large extent.

Another potential source of selection bias is ascertainment bias. Ascertainment bias arises when certain individuals are more likely to be part of the research population than others.[12] Persons with severe hemophilia are more likely to be registered at one of the Dutch treatment centers, and at a younger age, because of their disease severity. Persons with mild hemophilia are more likely to be diagnosed later in life;[13] the median age at diagnosis was 5.8 months for severe hemophilia, 9.0 months for moderate hemophilia and 28.6 months for mild hemophilia in a French cohort, with the 75th percentile ranging up to 7 years old in mild hemophilia.[14] Persons with mild hemophilia may not be aware that they have hemophilia until they experience co-morbidities for which they need a medical intervention.[15] For these reasons, persons with mild hemophilia are less likely to be registered at a treatment center.[13] Persons with severe hemophilia are therefore also more likely to have been included in HiN-6. Participants with severe hemophilia had a median age of 33 years while participants with mild hemophilia had a median age of 48 years. This may be the result of a lower life expectancy of persons with severe hemophilia,[2] but it may also indicate ascertainment bias. If ascertainment bias occurred, it likely limits our understanding of the variability in outcomes of persons

with hemophilia. Ascertainment bias may have led to underestimation of the differences in outcomes between mild and severe hemophilia: only diagnosed individuals were included, who may also have more hemophilia symptoms and associated worse outcomes than the undiagnosed population.

The magnitude of ascertainment bias is unknown. However, recent estimates of hemophilia prevalence may provide some insight into this type of selection bias. Based on recent estimates of prevalence from registry studies from other countries,[16] the number of persons with hemophilia in the Netherlands is expected to be 2524 (95% confidence interval: 2132 - 2916), based on a Dutch male population of 8.527 million in 2018.[17] In HiN-6, 2192 of them were identified (87 percent), of whom 1312 (52 percent of total) participated in either the questionnaire or provided informed consent for extraction of data from electronic medical records. This means that 13 percent, or 332 - 724 persons with hemophilia were not registered at one of the hemophilia treatment centers and may remain undiagnosed. Of the total population, 62.9 percent is expected to have non-severe-hemophilia;[16] in HiN-6, the proportion of persons with non-severe hemophilia was 67 percent. Ascertainment bias may therefore be limited.

The amount of ascertainment bias may be smaller than in HiN-5, likely as a result of improved diagnosis.[18] In HiN-5, 1567 persons with hemophilia were identified. Extrapolating the current prevalence to 2001, this is 67 percent of an expected 2341 individuals at the time. Data were collected on 1066 of them, or 45.5 percent of the total population;[19] 6.5 percentage points lower than the 52 percent who participated in HiN-6. Also, the composition of participants was different between HiN-5 and HiN-6: more participants with severe and fewer with mild hemophilia participated in HiN-5 than in HiN-6. These results suggest that the amount of ascertainment bias has changed. Any differences in outcomes between HiN-5 and HiN-6 at the population level may therefore be inflated.

Finally, misclassification bias may have occurred in HiN-6. Misclassification bias occurs when individuals are assigned to a different exposure category than the one they should be in,[20] for example due to self-report. In HiN-6, type and severity of hemophilia, treatment mode (prophylaxis or not), inhibitor status and hiv and hcv status were self-reported. In order to prevent misclassification, we verified these variables with electronic medical records when available. For 280 of 1009 individuals who completed the questionnaire (27.8 percent), electronic medical record data were not available. It is possible that some of these individuals were misclassified. Misclassification in this group may be estimated by determining discrepancies between questionnaire and electronic medical record data for individuals with complete data (n = 729). Eight of 729 individuals (1.1 percent) reported a discrepant type of hemophilia, 30 (4.1 percent) reported a discrepant status for prophylaxis use and three (0.4 percent) reported a discrepant hiv status. Disease severity and hcv status were known for all participants. Assuming a similar misclassification among those with only questionnaire data, misclassification bias is unlikely to have affected the results presented in **Chapters 6** and **7** to a large extent.

Missing data

The HiN-6 questionnaire used for the analyses presented in **Chapters 6** and **7** was long. The burden of completing such an extensive questionnaire may have led to missing values (or items that were completed randomly), and this may have been more likely to occur further on in the questionnaire. Missingness can be classified intro three types of missing data: missing completely at random (MCAR), missing not at random (MNAR) or missing at random (MAR).[21]

When data are missing completely at random (MCAR), missingness does not depend on any other variable.[21] This may be the case for data on absenteeism. Due to a routing error in the electronic version of the questionnaire, the first 403 responders did not receive the question on absenteeism. However, it is possible these 403 responders were different from later responders, for example because they were more eager to participate or because they were more likely to be included first because of the severity of their hemophilia (ascertainment bias). In that case, missing data cannot be assumed to be MCAR, but instead may be missing at random.

If data are missing at random (MAR), missingness depends on observed patient characteristics,[21] such as the severity of hemophilia. Outcome data of PROMIS-29 subscales may be MAR: missing values were more likely to occur for mild than for severe hemophilia (**Chapter 6**). However, there also appeared to be an order effect: the subscales at the end of PROMIS-29 had more missing values than the subscales in the beginning. As discussed in **Chapter 6**, this may have to do with differences in relevance of the subscales. 'Relevance' was a characteristic that was not observed in the HiN questionnaire.

If missingness is due to such unobserved variables, data are missing not at random (MNAR).[21] Missing data on labor market status and educational attainment may be MNAR, as there were no differences in missingness between severities of hemophilia (**Chapter 7**), but missingness may still depend on some unobserved variable. Except for data on absenteeism, the proportion of missings on outcome data was lower than 15 percent, which is considered an acceptable limit for missing data.[22]

Future directions

Future directions for research and clinical practice are described below for the two parts of this thesis: perspectives on information and communication and outcomes assessment.

Perspectives on information and communication

The results of this thesis show that ease of use of a treatment product and its ability to control bleeds are important facilitators in decisions whether or not to switch to a

different treatment product. Barriers are fear of unknown side effects and not wanting to be a research subject for new products (**Chapter 3**). These results emphasize the need for effective communication about new treatment options.

Several efforts have been made by others. For example, a gene therapy lexicon was recently developed to support hemophilia care providers in their communication about gene therapy. Persons with hemophilia were generally well aware of currently available products and do not need explanations of the difference between gene therapy and coagulation factor replacement therapy.[23] Also, there is considerable heterogeneity in thresholds at which persons with hemophilia would prefer gene therapy over prophylactic coagulation factor replacement therapy.[24] In communicating about gene therapy, it is therefore important to manage expectations on who will benefit from gene therapy once it becomes available.[23] This includes information about whether the benefits may outweigh the side effects (e.g. liver toxicity), the fact that gene therapy will not be a cure for hemophilia and that up to 23 percent of the population already has neutralizing antibodies against the adeno-associated viral vectors that are used for gene therapy. This means that gene therapy may be ineffective for these individuals.[25] Personalized communication strategies may need to be developed further as new knowledge about safety and efficacy of gene therapy trials becomes available.

Not all persons with hemophilia may want to undergo gene therapy when it becomes available. Some of the reasons participants in a recent qualitative study mentioned were similar to the ones we identified in **Chapter 3**, such as concerns about long-term efficacy, safety, and a lack of treatment burden of current treatment. Interestingly, another reason for not undergoing gene therapy was that it would mean a loss of identity as a person with hemophilia.[26] Health care providers may need to be aware that such a negative impact may also occur post-gene therapy. Any such concerns may be addressed by education and counselling.[26]

Since gene therapy is not a suitable treatment option for most persons with severe hemophilia in the near future, communication may also be directed at everyday treatment decisions such as the dosing schedule. As was shown in **Chapter 2**, a clinic approach focused on patient engagement resulted in participation in treatment decisions, increased understanding and improved clinician-patient communication. Further, a mobile app with personalized bleed and infusion data and a clinic session during which pharmacokinetic profiles were shown was likely to have improved self-management skills. Although the effects of the engagement strategy on bleeding outcomes was not evaluated, self-management may improve adherence.[27, 28] Self-management is an important element of health, which may be defined as 'the ability of people to adapt and to self-manage, in the face of social, physical and emotional challenges'.[29] Self-management and empowerment are also part of one of the principles of care according to the World Federation of Hemophilia's Treatment Guidelines.[18]

Visual treatment data facilitate conversations between persons with hemophilia and their clinicians. In 2018, a mobile app ('Vaste Prik') was developed as part of the Dutch Hemophilia Registry HemoNED. The registry aims to include all persons with hemophilia in the Netherlands, starting with those with severe hemophilia. In the app, persons with hemophilia can track their coagulation factor infusions, bleeds, and their stock of treatment products with expiration dates. The app also has an alert function for administering prophylaxis according to the agreed treatment schedule. The data from the app are stored in a secured database which can be accessed by the hemophilia treatment center.[30] The bleeds and infusion data from this database may help to inform treatment decisions,[30] such as switching to a new treatment product or changing a treatment schedule, and evaluate their effects on bleeding outcomes over time. Visualized data from the app, such as graphs, may also help to engage patients in their care.

Many treatment products of different types are available for hemophilia care, and new products continue to be developed.[5, 6] This increases the choice in treatment options even further. Decision aids may need to be developed for this purpose. Such decision aids support persons with hemophilia in their treatment decisions by providing guidance and decision coaching, for example by providing information on the harms and benefits of each treatment option in a systematic way.[31]

Outcomes assessment

In an effort to facilitate value-based health care, a standard set of the most relevant hemophilia outcomes was developed in **Chapter 5**, along with recommendations to measure these outcomes. Five PROMIS short forms that measure four of the recommended health outcomes were validated in **Chapter 6** and some of the participation outcomes were measured in **Chapter 7**.

The standard set of health outcomes included instruments to measure clinical outcomes as well as PROMs. Some of the recommended PROMs were recently improved or validated in the Dutch hemophilia population. For example, the length of the Pediatric Hemophilia Activities List (PedHAL) and the adult Hemophilia Activities List (HAL) was reduced,[32, 33] and a first step towards shortening was taken by identifying less relevant items in the Hemophilia Joint Health Score (HJHS).[34] Also, the four PROMIS computerized adaptive tests (CATs) Physical functioning, Fatigue, Pain interference and Satisfaction with social roles and activities were recently shown to be feasible and relevant and to have sufficient measurement properties in Dutch adults with hemophilia. The domain Ability to participate in social roles and activities was shown to discriminate well between different ages and hemophilia severities. The CATs for depression and anxiety were shown to have limited convergent validity, and the CAT for depression also had large ceiling effects.[35] Future research may be aimed at achieving optimal measurement properties for these CATs. The PROMIS pediatric item banks recommended in **Chapter 5** also still need validation in the Dutch pediatric hemophilia population.

Ideally, one CAT for each patient-reported health outcome from the standard set is validated or improved. In order to implement the full set of health outcomes, the PROMIS adult item banks Pain intensity, Physical function for samples with mobility aid users, Self-efficacy for managing social interactions, General life satisfaction, and Positive affect still need to be validated for use in the Dutch hemophilia population.

The standard set is largely ready for implementation in Dutch hemophilia care. Some of the clinical health outcomes are currently measured in Dutch clinical practice, such as the occurrence of major bleeds from the mobile app. Complications such as inhibitor status and infections are already recorded in electronic medical records. Other relevant health outcomes from the standard set, such as social functioning and participation, pain and days lost from work of school, are usually addressed during outpatient clinic appointments, but they are not always routinely measured and recorded. The Vaste Prik mobile app or the HemoNED registry may be expanded to include measurement of these outcomes in clinical practice. Such a web-based program (KLIK) that collects electronic PROs is already in use in pediatric hemophilia care. Children or their parents complete online questionnaires prior to their clinic visit; clinicians may then address any concerns that emerge from the questionnaires.[36] Children and parents are generally satisfied with the KLIK portal, but areas for improvement include the layout and content of the portal.[37] Recently, PROMIS CATs were implemented in KLIK and efforts are underway to fully integrate the KLIK portal with the electronic health record.[37]

Once instruments including PROMIS CATs or short forms are implemented in clinical care, they provide an additional advantage: when administered electronically, whether through the mobile app or a patient portal, results can be fed back to patients. Feeding back individual scores on relevant outcome domains may enhance patient-clinician communication, help identify areas for improvement and enhance patient engagement.[38, 39] In pediatric care, for example, traffic light colors were preferred for communicating personal scores on individual items of PROMIS CATs, while line graphs including reference lines and a background in traffic light colors were preferred to show changes over time on domain scores.[40] Also, the directionality of scores should be made clear, with patients and clinicians preferring 'higher is better'.[38, 40] For PROMIS domains higher scores currently indicate a higher degree of the construct being measured,[41] which means that for domains such as anxiety or depression scores may need to be converted to a score in which a higher score is a better score on that domain. Whether such visual communication tools are suitable for use in hemophilia populations, and which outcomes are most suitable to be communicated in visual formats needs to be investigated further.

As a next step towards value-based health care, outcomes sets and instruments for different conditions, including hemophilia, may need to be standardized further. Many outcomes sets and instruments are currently available for a wide range of conditions, but outcomes may overlap between conditions. Recently, 307 patient-reported

outcomes and 114 instruments were identified among 39 standard sets developed by the International Consortium for Health Outcomes Measurement (ICHOM). There was considerable overlap between the PROs: only 22 of 307 were unique PRO concepts, with the ability to participate in social roles, physical functioning, health-related quality of life, pain intensity, depression, general mental health, anxiety, fatigue and overall quality of life as common outcomes recommended across many outcomes sets.[42] Most of these health outcomes are also part of the standard set in **Chapter 5,** suggesting they are not unique to hemophilia. In the Netherlands, the use of generic PROMs is already advocated. Such standardization may contribute to a more value-based health care system because it reduces overlap and enables comparisons across diseases and with the general population.[43]

A focus on value-based health care also implies that services that do not contribute to value should be de-implemented. Three forces have been described that drive de-implementation: evidence, eminence and economics.[44] If there is sufficient evidence that a current practice provides little value, it should be de-adopted. Next, broad consensus is needed about what constitutes low-value care. Finally, removing financial incentives is necessary to de-implement such low-vale services.[44] The standard set of health outcomes for hemophilia, but also those developed for other conditions, forms the basis for high-value care. Such standard sets also imply that any outcomes currently monitored in clinical care but not included in the standard sets may need to be de-implemented.

This thesis addressed only one of the six elements Michael Porter considers necessary for value-based health care: measuring outcomes.[45] As described in **Chapter 4**, another necessary element of value-based health care is an enabling information technology platform that facilitates recording and sharing of data between care providers. The Vaste Prik mobile app and the HemoNED registry may help to achieve this goal. In order to implement value-based health care for hemophilia, the feasibility of implementation of the other elements of Porter's framework needs to be evaluated by experts in health economics and organization of care. These elements include integrated practice units, bundled payments for care cycles, integrated care delivery across separate facilities and expanding services across geography.

The future of HiN studies

The HiN studies started with a short survey in 1972. Over time, the survey became longer and each time more outcomes were assessed with partially overlapping questionnaires, resulting in a wealth of data, but with an increased participant burden. For future HiN studies, a balance needs to be found between limiting participant burden as much as possible and gathering high-quality data. The results from this thesis and subsequent developments provide an opportunity to improve future HiN studies.

The introduction of the Vaste Prik app and the HemoNED registry will allow for almost real-time monitoring of bleeds and treatment data. Currently, bleeds and treatment data are primarily collected for clinical purposes, but they may be extracted periodically for health care evaluations and research purposes. These data will be much more reliable than bleeds data collected in previous HiN surveys, which were collected in six to 15 year-intervals, and only asked participants about bleeds in the last 12 months. More reliable bleeds and treatment data may be used to evaluate the effects of interventions and treatment decisions on bleeding rates. More reliable data may also help to understand the variability in bleeding phenotype. Any other outcomes that will have been incorporated into the Vaste Prik app and the HemoNED registry may also be extracted on a regular basis for research purposes. The feasibility of such clinical data extraction for research, and at which frequency, will need to be assessed, taking into account the General Data Protection Regulation (AVG in Dutch), which was implemented in 2018. Persons with mild hemophilia may not yet have been included in the registry. For this reason, and also depending on future research questions, data extraction may still need to be supplemented with a questionnaire.

Conclusions

The high standard of Dutch hemophilia care and the availability of prophylaxis provide an opportunity to focus on health outcomes beyond mortality. Using both qualitative and quantitative methods, this thesis defined, measured and quantified relevant health outcomes for persons with hemophilia. In the first part of this thesis we showed that communication and information provision about treatment options and prophylaxis regimes may support persons with hemophilia in their decisions about current and future treatment products. This will likely result in improved bleeding outcomes. In the second part, we took the first steps towards value-based health care for hemophilia by defining a standard set of ten relevant health outcomes, including instruments to measure these outcomes. Routine measurement of the standard set may be implemented in clinical practice in order to further improve hemophilia care that adds value for patients. Already, the high standard of care has resulted in near-normal socio-economic participation of Dutch persons with hemophilia. Development of more sophisticated data collection tools will help to monitor relevant health outcomes over time.

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APPENDICES

Nederlandse samenvatting

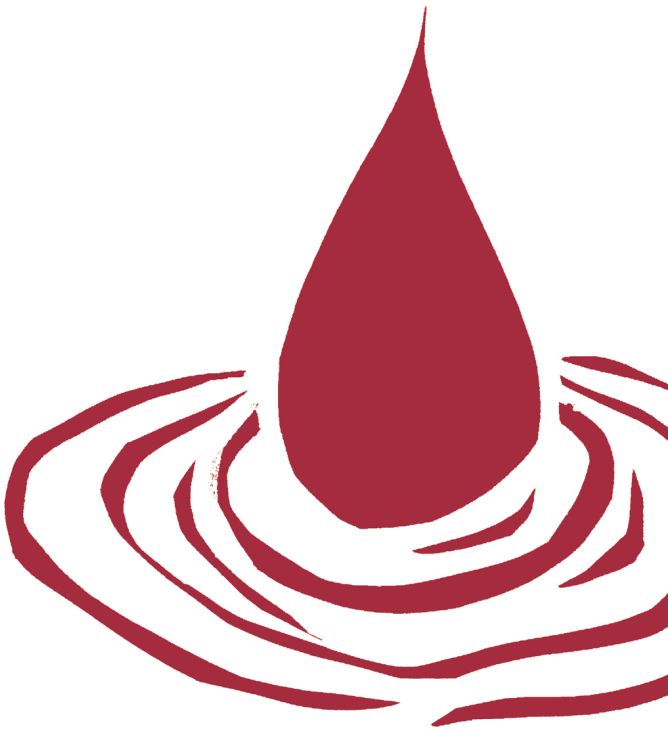
Factsheet Hemofilie in Nederland 6

Portfolio

List of publications

Dankwoord

Curriculum Vitae



Het belangrijkste doel van de zorg is waarde te leveren voor patiënten. Die 'waarde' bestaat uit optimale gezondheidsuitkomsten. Wat die gezondheidsuitkomsten zijn voor de erfelijke bloedstollingsstoornis hemofilie, hoe je die meet en hoe het gesteld is met de gezondheid van de Nederlandse hemofiliepopulatie is onderwerp van dit proefschrift. Uniforme meetmethoden van dezelfde uitkomsten zullen bijdragen aan het optimaliseren van zorg. Bovendien maken uniforme uitkomstmetingen het mogelijk gezondheidsuitkomsten van mensen met hemofilie onderling en over de tijd te vergelijken. Ook komt aan de orde hoe mensen met hemofilie beslissingen nemen over hun behandeling, bijvoorbeeld hoe en wanneer ze zichzelf behandelen, maar ook hoe ze besluiten al dan niet over te stappen op een nieuw behandelproduct.

Hemofilie

Hemofilie is een zeldzame erfelijke bloedstollingsstoornis die voorkomt bij 2500-2600 mannen in Nederland. Zij hebben te weinig van het stollingseiwit factor VIII (hemofilie A) of factor IX (hemofilie B), veroorzaakt door een mutatie. Bij ernstige hemofilie is de concentratie stollingsfactor <0.01 IU/mL (<1 procent), bij matig-ernstige hemofilie is die 0.01-0.05 IU/mL (1-5 procent) en bij lichte hemofilie is die 0.05-0.4 IU/mL. Zij hebben daardoor een verhoogde bloedingsneiging die zich bij ernstige hemofilie uit in gewrichtsbloedingen (voornamelijk in enkels, knieën en ellebogen) en spierbloedingen. Gewrichtsbloedingen veroorzaken synovitis en oxidatieve stress die het kraakbeen aantasten. Bloedingen in vitale organen kunnen levensbedreigend zijn. Mensen met lichte hemofilie bloeden vooral door trauma of medische ingrepen. Van oudsher is de term 'hemofilie' gereserveerd voor mannen, maar ook van draagsters wordt steeds vaker erkend dat zij hemofilie hebben. Bij hen uit hemofilie zich vooral in hevige menstruaties.

De behandeling van hemofilie bestaat uit intraveneuze toediening van de ontbrekende stollingsfactor, ofwel profylactisch om bloedingen te voorkomen bij ernstige of matig-ernstige hemofilie, ofwel om een bloeding te behandelen bij lichte hemofilie. In het verleden werd stollingsfactor voornamelijk bereid uit plasma van bloeddonoren. Een deel van de Nederlandse hemofiliepopulatie raakte tussen 1982-1985 besmet met het humaan immunodeficiëntievirus (hiv) afkomstig van besmet bloed en veel van hen overleden aan de gevolgen van verworven immunodeficiëntiesyndroom (aids). Daarnaast liep twee derde hepatitis C (hcv) op.

Een andere mogelijke complicatie van behandeling met stollingsfactoren is remmervorming: een immuunreactie tegen de toegediende stollingsfactor VIII, waardoor die niet meer werkzaam is en bloedingen moeilijker te voorkomen en te behandelen zijn. Naar schatting een derde van de mensen met ernstige hemofilie A ontwikkelt in zijn leven een remmer.

Hoewel de levensverwachting van mensen met hemofilie inmiddels vrijwel gelijk is aan die van de Nederlandse bevolking, kampen veel mensen nog met de gevolgen van besmettingen met hiv en hcv, gewrichtsschade door eerdere bloedingen of remmers. Door deze multiproblematiek zijn er grote verschillen in gezondheid binnen de hemofiliepopulatie. De aard en omvang van die verschillen is niet volledig duidelijk voor de Nederlandse hemofiliepopulatie. Daarnaast is een breed scala aan stollingsfactorproducten beschikbaar. Ook deze behandelkeuzes beïnvloeden bloedingsuitkomsten en dus de algemene gezondheid van mensen met hemofilie.

Samenvatting van resultaten

In dit proefschrift maakten we deels gebruik van gegevens die we verzamelden voor de zesde Hemofilie in Nederlandstudie (HiN-6); een van de oudste en langstlopende dynamische cohortstudies naar hemofilie ter wereld.

Deel I van dit proefschrift gaat over behandelkeuzes. In **hoofdstuk 2** onderzochten we de ervaringen met een programma dat erop gericht was mensen met hemofilie zelfstandiger behandelbeslissingen te laten nemen. Veel van hen gaven aan dat ze voldoende zelfvertrouwen hadden om zelf hun beslissingen te nemen, en dat inzicht in hun eigen bloedings- en behandelgeschiedenis daarbij hielp.

In **hoofdstuk 3** interviewden we 12 mannen met hemofilie en 2 moeders van kinderen met hemofilie over de redenen om al dan niet over te stappen op een nieuw behandelproduct, zoals producten met een langere halfwaardetijd, producten met een ander werkingsmechanisme dan stollingsfactor, of gentherapie. Over het algemeen waren de geïnterviewden tevreden met hun huidige behandelproduct. Redenen om over te stappen waren gemakkelijker toediening en minstens even goede bescherming tegen bloedingen als hun huidige product. Redenen om niet over te stappen waren angst voor het onbekende, zoals besmetting met nog onbekende ziekteverwekkers, remmervorming of de langetermijneffecten van gentherapie. Daarnaast wilde een aantal geïnterviewden liever wachten met overstappen totdat producten een tijdje op de markt waren en veilig bevonden waren. Ten slotte waren alle deelnemers zich bewust van de hoge kosten van huidige behandeling en vroegen sommigen zich af of hoog-risicoactiviteiten wel verantwoord waren als dat leidde tot meer verbruik van stollingsfactorproducten, omdat de maatschappij opdraait voor de kosten daarvan.

Deel II van dit proefschrift gaat over het definiëren, meten en kwantificeren van belangrijke gezondheidsuitkomsten voor mensen met hemofilie. Het doel van de gezondheidszorg is het bereiken van de beste uitkomsten voor de patiënt, afgezet tegen de kosten om die uitkomsten te bereiken. Dit concept heet waardegedreven zorg (*value-based health care*). **Hoofdstuk 4** beschrijft de zes onderdelen van waardegedreven zorg. Voor hemofilie is het startpunt voor daarvoor een verzameling van kernuitkomsten

vast te stellen die regelmatig gemeten zouden moeten worden bij mensen met hemofilie, om op die manier verbetering op die uitkomsten te kunnen volgen.

De belangrijkste uitkomsten voor mannen en vrouwen met hemofilie zijn genezing; invloed op levensverwachting; kunnen deelnemen aan het dagelijks leven; het aantal ernstige bloedingen; het aantal dagen school- of werkverzuim; chronische pijn; complicaties van hemofilie of de behandeling (remmervorming, virusbesmetting, prikproblemen); lichamelijk functioneren op lange termijn; sociaal functioneren; en geestelijke gezondheid. Deze verzameling van uitkomsten stelden we vast met een internationaal team van hemofiliebehandelaren en onderzoekers. De ontwikkeling hiervan staat beschreven in **hoofdstuk 5**. Ook selecteerden we de meest geschikte vragenlijsten om deze uitkomsten te kunnen meten. Dit waren zowel hemofiliespecifieke als generieke vragenlijsten.

Niet alle vragenlijsten om die uitkomsten te meten zijn gevalideerd bij mensen met hemofilie. We maakten daarom gebruik van gegevens uit HiN-6 om de Nederlandstalige versie van PROMIS-29 te valideren (**hoofdstuk 6**). PROMIS-29 is een generieke vragenlijst die zeven domeinen van kwaliteit van leven meet: lichamelijk functioneren, angst, depressie, vermoeidheid, slaapstoornissen, het vermogen om een aandeel te hebben in sociale rollen en activiteiten, belemmeringen door pijn, en pijnintensiteit. Begripsvaliditeit was voldoende voor vijf van deze domeinen en voor pijnintensiteit. Structurele validiteit en interne consistentie bleken voldoende voor drie domeinen. Een aantal van de in hoofdstuk 5 gedefinieerde uitkomsten voor hemofilie kunnen dus gemeten worden met domeinen van de PROMIS-29.

Ten slotte maakten we in **hoofdstuk 7** wederom gebruik van gegevens uit HiN-6 om één van de belangrijkste uitkomsten voor de Nederlandse hemofiliepopulatie te kwantificeren, namelijk deelname aan onderwijs, de arbeidsmarkt en de maatschappij. De deelname aan onderwijs en het hoogst behaalde opleidingsniveau waren gelijk aan of hoger dan onder de Nederlandse bevolking. De netto arbeidsmarktparticipatie was lager dan die van Nederlandse mannen, vooral voor mannen met ernstige hemofilie. Dat komt waarschijnlijk mede door een relatief hoog aantal gepensioneerden en arbeidsongeschikten, die niet onder de beroepsbevolking vallen. Ook voor het vermogen om een aandeel te hebben in sociale rollen en activiteiten scoorden vooral de oudere mannen met ernstige hemofilie lager dan de Nederlandse bevolking. Verder was het schoolverzuim hoger dan onder Nederlandse tieners. Van de werkenden hadden mannen met hemofilie juist minder vaak verzuim dan Nederlandse mannen. Ten slotte vonden de meeste mensen dat hemofilie hun keuze voor opleiding of beroep niet of nauwelijks beïnvloed had.

Beperkingen van het onderzoek

Voor dit proefschrift gebruikten we zowel kwalitatieve als epidemiologische methoden, die ieder hun beperkingen kennen.

In kwalitatief onderzoek hoeft de onderzochte populatie niet representatief te zijn voor de gehele populatie. Dit type onderzoek is immers vooral gericht op het beantwoorden van de waarom-vraag: juist van een klein aantal mensen wilden we weten wat hun behandeloverwegingen waren. Zowel in hoofdstuk 2 als in hoofdstuk 3 bestudeerden we voornamelijk mensen met matig-ernstige of ernstige hemofilie die profylaxe gebruikten. Dat betekent echter ook dat de resultaten uit deze hoofdstukken mogelijk niet generaliseerbaar zijn naar, maar waarschijnlijk ook niet eens van toepassing zijn op mensen met lichte hemofilie of naar vrouwen met hemofilie, aangezien zij heel andere behandelbeslissingen nemen.

Ook de gegevens uit HiN-6 kunnen onderhevig zijn aan onzuiverheden (*bias*) en vertekening (*confounding*). Zo is het mogelijk dat sommige mensen de vragenlijst niet invulden omdat zij bijvoorbeeld onvoldoende Nederlands konden lezen, laagopgeleid waren en daardoor de vragen niet begrepen, of omdat zij weinig last hadden van hun hemofilie en daarom het nut niet inzagen van het invullen van een lange vragenlijst. Mensen die wel veel last hebben van hemofilie vulden daarentegen de vragenlijst mogelijk juist vaker in, omdat ze het belangrijk vonden dat artsen en onderzoekers aandacht besteedden aan hun aandoening. Deze selectieve deelname heeft als mogelijk gevolg dat wij de gerapporteerde uitkomsten, zoals een lagere arbeidsparticipatie, ongunstiger inschatten dan daadwerkelijk het geval is.

Verder is het bekend dat sommige mensen met hemofilie pas later in hun leven de diagnose krijgen omdat ze nauwelijks bloedingen hebben. Hun verhoogde bloedingsneiging wordt dan pas opgemerkt als ze een operatie ondergaan. Het is daardoor mogelijk dat er mensen zijn die wel hemofilie hebben, maar die niet als zodanig bekend zijn bij één van de zes Nederlandse hemofiliebehandelcentra. Zij zitten daardoor ook niet in het onderzoek. Ook dit kan betekenen dat onze resultaten de werkelijke situatie overschatten.

Doordat mensen met lichte hemofilie mogelijk pas later in hun leven de diagnose krijgen, zijn zij ook pas op latere leeftijd bekend bij een hemofiliebehandelcentrum, zeker vergeleken met mensen met ernstige hemofilie, die al van jongsaf aan ingeschreven staan bij een behandelcentrum. Dat betekent dat mensen met lichte hemofilie ouder zijn dan mensen met ernstige hemofilie; dit zien we inderdaad terug in de resultaten. Dit heeft tot gevolg dat bijvoorbeeld arbeidsmarktparticipatie minder goed te vergelijken is tussen mensen met lichte of ernstige hemofilie.

Toekomst

De medische ontwikkelingen gaan snel. De meeste mensen met hepatitis C zijn inmiddels succesvol behandeld. Inmiddels zijn nieuwe behandelproducten op de markt waardoor mensen met hemofilie niet of nauwelijks nog bloedingen krijgen. Binnen enkele jaren wordt gentherapie mogelijk goedgekeurd als behandeloptie. Daarmee lijken de grootste problemen voor mensen met hemofilie opgelost. Toch zijn er zeker nog mogelijkheden voor verdere verbetering van de hemofiliezorg.

Ten eerste maakt de nog grotere keus aan behandelopties communicatie over die vele mogelijkheden nog belangrijker. Niet iedereen blijkt bijvoorbeeld behoefte te hebben aan gentherapie of daarvoor in aanmerking te komen. Het is daarom belangrijk de verwachtingen en mogelijkheden van de verschillende opties duidelijk te bespreken met mensen met hemofilie. Keuzehulpen met daarin informatie over de voor- en nadelen in begrijpelijke taal kunnen daarbij ondersteunen. Ook gegevens over bloedingen en behandeling afkomstig uit hemofiliebehandelapps kunnen daarbij een rol spelen.

Ten tweede is er verbetering mogelijk aan bestaande vragenlijsten. Sommige vragenlijsten die de kernuitkomsten meten moeten nog gevalideerd worden voor hemofilie, andere kunnen worden ingekort. In de nabije toekomst kunnen de belangrijkste uitkomsten gemeten worden met computerized adaptive tests (CAT), waarbij de computer de volgende vraag selecteert op basis van het antwoord op een vraag. Kan iemand bijvoorbeeld niet een half uur wandelen, dan hoeft die persoon ook niet de vraag te beantwoorden of hij een half uur kan hardlopen. Met efficiëntere vragenlijsten kunnen kernuitkomsten betrouwbaar gemeten worden zonder daarmee de patiënt onnodig te belasten. Mogelijk kunnen CATs worden ingebouwd in de bestaande Nederlandse app Vaste Prik, waarin mensen met ernstige hemofilie hun bloedings- en behandelgegevens bijhouden.

Tot nu toe maakten de HiN-onderzoeken gebruik van een eenmalige vragenlijst. De app en het in 2018 opgerichte hemofilieregister bieden mogelijkheden voor toekomstige HiN-onderzoeken. Het voordeel daarvan zou zijn dat onderzoekers bijna real-time toegang zouden hebben tot bloedings- en behandelgegevens, en dat daardoor ook de effecten van behandelkeuzes of interventies nog betrouwbaarder te meten zijn. Wel is de laatste jaren de privacywetgeving aangescherpt, waardoor gebruik van voor zorgdoeleinden verzamelde gegevens beperkt mogelijk is. De haalbaarheid van het gebruik van dergelijke gegevens zal onderzocht moeten worden. Ook zullen nog niet alle mensen met hemofilie zijn opgenomen in het hemofilieregister, waardoor vragenlijsten mogelijk nog steeds nodig zullen zijn.

Conclusies

In dit proefschrift lieten we zien dat informatie en communicatie over behandelmogelijkheden behandelbeslissingen kan ondersteunen. Een betere zelfredzaamheid hierin zal waarschijnlijk ook invloed hebben op het aantal bloedingen.

Verder zetten we de eerste stap richting waardegedreven zorg voor hemofilie. Als de vastgestelde kernuitkomsten routinematig gemeten worden in de zorg, zal dat waarde toevoegen voor mensen met hemofilie.

Het gaat steeds beter met de Nederlandse hemofiliepopulatie. Vermoedelijk komt dat door de hoge kwaliteit van de Nederlandse zorg en de beschikbaarheid van stollingsfactor.

Wat is hemofilie?

Aangeboren stollingsstoornis bij mannen

Bloedingen in gewrichten of bij operaties

Te voorkomen door injecties met stollingseiwit 2-3 keer per week

Toch hebben velen gewrichtsschade door eerdere bloedingen

In 1972, 1978, 1985, 1992, 2001 en in 2018 werd landelijk onderzoek gedaan onder mensen met hemofilie in Nederland

HIN 6 Hemofilie in Nederland

2192 mannen en jongens werden uitgenodigd

1312 van hen deden mee (respons: 59,9%)

1009 vragen-lijsten

1032 medische dossiers

927 bloed-afnames

27 deelnemers hebben hiv

Mensen met hemofilie zijn onder behandeling bij 1 van de 7 academische ziekenhuizen

Amsterdam UMC University Medical Centers

LUMC Leiden University Medical Center

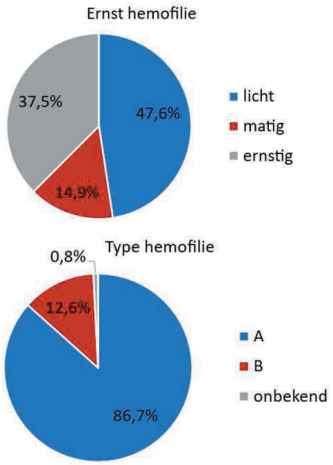
umcg

Radboudumc

Maastricht UMC+

Erasmus MC University Medical Center Rotterdam

UMC Utrecht



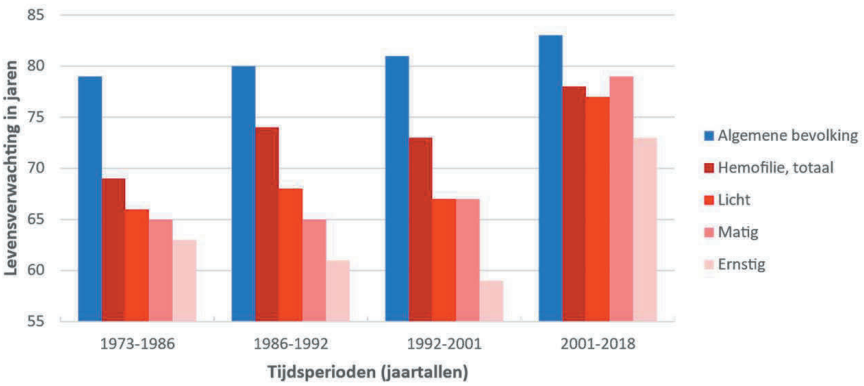
2 Het gemiddeld aantal bloedingen in 2018 voor iemand met ernstige hemofilie

In 1971 waren dat er per jaar 25

Wat mannen met hemofilie het liefste willen:

Genezing	Normale levensverwachting	Meedoen aan de maatschappij	Minder vaak ernstige bloedingen
Minder werk- of schoolverzuim	Minder chronische pijn	Minder complicaties (remmer, virus, prikproblemen)	
Lichamelijk functioneren op langere termijn	Sociaal functioneren	Geestelijke gezondheid	

Mannen met hemofilie worden tegenwoordig bijna net zo oud als andere Nederlandse mannen…



…al worden vooral mannen met ernstige hemofilie wat minder oud door eerdere besmettingen met hiv en/of hepatitis C.

15-24-jarigen volgen net zo vaak onderwijs als hun leeftijdsgenoten zonder hemofilie. Wel verzuimen ze vaker van school.

Mannen met hemofilie nemen net zo goed deel aan sociale activiteiten als mannen zonder hemofilie.

68,2% van de mannen met hemofilie heeft betaald werk

Onder Nederlandse mannen zonder hemofilie is dat **73,2%**

Portfolio

Courses	year	hours
Several journal clubs, Capita Selecta and Friday lessons	2016-2020	56
Weon pre-conference course big data	2016	4
CS50: Introduction to Computer Science – Harvard University (MOOC)	2016	15
Machine learning for data science and analytics – Columbia EdX	2016	35
Epidemiology: An introduction (Rothman) - LUMC	2016	84
BROK (NFU)	2016	42
NVTH PhD course venous thrombosis	2016	28
Introduction to Quality of Life and other PROs – theory, measurement and applications (ISOQOL pre-conference course)	2016	8
Qualitative research in health care - EpidM	2016	56
Focus groups - Evers Research and training, Rotterdam	2016	28
Writing scientific articles – LUMC/Sanquin/VU	2016	84
Data Management Plan crash course	2017	1
Basic methods and reasoning in biostatistics - LUMC	2017	42
NVTH PhD course Bleeding	2017	28
Clinical epidemiology (Schiermonnikoog) - LUMC	2017	56
Statistical aspects of clinical trials - LUMC	2017	28
Clinical epidemiology (Grobbee) - LUMC	2017	84
IRT and CAT using Concerto - University of Cambridge, UK	2018	28
NVTH PhD course arterial thrombosis	2018	28
Regression analysis - LUMC	2018	42
Young investigators workshop EAHAD	2018	4
Causal inference – Erasmus Summer School (Hernan)	2018	84
Survival analysis - LUMC	2018	42
Meta analysis - LUMC	2019	28
Effective communication for PhDs – Leiden University	2019	8
Supervising working groups – LUMC	2019	12
Advanced methods in epidemiology (Poelgeest) - LUMC	2019	56
Clinimetrics - EpidM	2020	84
BROK (registration renewal)	2020	4

Conference attendance and presentations	Year	hours
Weon (annual epidemiology conference), Wageningen, The Netherlands	2016	20
ECTH, The Hague, The Netherlands	2016	20
Poster presentation ISOQOL, Copenhagen, Denmark	2016	28
Nijmegen Multidisciplinary symposium Hemophilia	2017	8

Poster presentation ISTH Conference, Berlin, Germany	2017	28
3-minute pitch and poster presentation, Bayer Hematology conference, Amsterdam, The Netherlands	2017	16
Poster presentation EAHAD, Madrid, Spain	2018	28
Poster presentation WFH, Glasgow, UK	2018	28
Poster presentation ISTH conference, Melbourne, Australia	2019	28
Poster presentation ISOQOL, San Diego, USA	2019	28
Oral presentation PROMIS annual conference, San Diego, USA	2019	12
Poster presentation Weon, Nijmegen, The Netherlands	2022	28

Teaching and supervision	**Year**	**hours**
Academic and Scientific Training Year 1 (AWV1 – medicine)	2016	4
Academic and Scientific Training Year 2 (AWV2 – medicine)	2016	8
Academic and Scientific Training Year 1 (AWV1 – medicine)	2017	12
Academic and Scientific Training Year 2 (AWV2 – medicine)	2017	8
BSc. Student thesis supervision Bridget Baker (health sciences)	2017	24
BSc. Student thesis supervision Marjolein Wesselo (health sciences)	2017	24
Clinical academic research (KWO) – Honours Program medicine	2017	36
SPSS Computer practical Clinical Research in Practice (2x) (CRIP - MSc. biomedical sciences)	2017	8
Health promotion Year 3 (LGB3 - medicine)	2017	12
Academic and Scientific Training Year 1 (AWV1 – medicine)	2018	12
BSc. Student thesis supervision Naweed Shifai (medicine)	2018	6
Questionnaire analysis and design (Capita Selecta presentation)	2018	6
Academic and Scientific Training Year 1 (2x) (AWV1 – medicine)	2019	24
Working group Clinical Research in Practice (CRIP - MSc. biomedical sciences)	2019	4
An introduction to response shift and response shift bias (Capita Selecta presentation)	2019	6

Reviewer activities	**Year**	**hours**
Haemophilia	2018	3
Research and Practice in Thrombosis and Hemostasis	2018	3
Journal of Thrombosis and Haemostasis	2018	3
Dutch journal of medicine (NTvG)	2019	3

Awards	**Year**
Nomination publication prize junior researcher Dutch Society for Epidemiology (VvE)	2022
Nomination Poster Award Dutch Society for Epidemiology (VvE)	2022

LIST OF PUBLICATIONS

This thesis

1. **Erna C van Balen,** Shermarke Hassan, Cees Smit, Mariëtte H Driessens, Erik A M Beckers, Michiel Coppens, Jeroen Eikenboom, Hélène L Hooimeijer, Frank W G Leebeek, Eveline P Mauser-Bunschoten, Lize F D van Vulpen, Saskia E M Schols, Frits R. Rosendaal, Johanna G van der Bom, Samantha C Gouw. Socio-economic participation of persons with hemophilia: results from the sixth Hemophilia in the Netherlands study. Res Pract Thromb Haemost. 2022;6:e12741

2. **Erna C van Balen**, Lotte Haverman, Shermarke Hassan, Elisabeth M Taal, Cees Smit, Mariëtte H Driessens, Erik A M Beckers, Michiel Coppens, Jeroen Eikenboom, Hélène L Hooimeijer, Frank W G Leebeek, Lize F D van Vulpen, Saskia E M Schols, Caroline B Terwee, Frits R Rosendaal, Johanna G van der Bom, Samantha C Gouw. Validation of PROMIS Profile-29 in adults with hemophilia in the Netherlands. J Thromb Haemost. 2021 Nov;19(11):2687-2701. doi: 10.1111/jth.15454.

3. **Erna C van Balen**, Brian O'Mahony, Marjon H Cnossen, Gerard Dolan, Victor S Blanchette, Kathelijn Fischer, Deborah Gue, Jamie O'Hara, Alfonso Iorio, Shannon Jackson, Barbara A Konkle, Diane J Nugent, Donna Coffin, Mark W Skinner, Cees Smit, Alok Srivastava, Fred van Eenennaam, Johanna G van der Bom, Samantha C Gouw. Patient-relevant health outcomes for hemophilia care: Development of an international standard outcomes set. Res Pract Thromb Haemost. 2021 Mar 6;5(4):e12488. doi: 10.1002/rth2.12488.

4. **Erna C van Balen**, Samantha C Gouw, Jan A Hazelzet, Johanna G van der Bom, Marjon H Cnossen. Defining patient value in haemophilia care. Haemophilia. 2018 Jul;24(4):516-8. doi: 10.1111/hae.13550

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7. **Erna C van Balen.** Als waardegedreven zorg leidt tot lagere kosten, zal implementatie ervan alleen een succes zijn als het niet leidt tot verlies aan inkomsten voor ziekenhuizen. Promotiestelling. Ned Tijdschr Geneeskd. 2022;48

8. Shermarke Hassan, Cees Smit, **Erna C van Balen**, Evelien P Mauser-Bunschoten, Lize F D van Vulpen, Jeroen Eikenboom, Erik A M Beckers, Louise Hooimeijer, Paula F Ypma, Laurens Nieuwenhuizen, Michiel Coppens, Saskia E M Schols, Frank W G Leebeek, Mariëtte H Driessens, Frits R Rosendaal, Johanna G van der Bom, Samantha C Gouw. Gezondheidsuitkomsten van patiënten met hemofilie in Nederland, van 1972 tot 2019. Nederlands Tijdschrift voor Hematologie. 2022;5

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16. **Erna C van Balen**, Rebecca Font, N Cavallé, L Font, M Garcia-Villanueva, Y Benavente, P Brennan, S de Sanjose. Exposure to non-arsenic pesticides is associated with lymphoma among farmers in Spain. Occup Environ Med. 2006 Oct;63(10):663-8. doi: 10.1136/oem.2005.024026.

Dankwoord

Mijn naam staat weliswaar op dit proefschrift, maar dit resultaat was er nooit geweest zonder de medewerking en steun van een heleboel mensen. Die wil ik hier graag bedanken.

Ten eerste ben ik veel dank verschuldigd aan iedereen met hemofilie die de tijd en moeite nam mee te doen aan HiN-6. Degenen die ik daarnaast persoonlijk heb leren kennen tijdens ALV's van de NVHP, het hemofilie-kampeerweekend en poli's hebben mij bovendien een leerzame inkijk gegeven in hun leven met hemofilie, waarvoor ik erg dankbaar ben. Bijzondere dank ook aan Cees Smit, het geweten en collectief geheugen van de HiN-onderzoeken en altijd bereid vragen te beantwoorden.

Daarnaast wil ik alle coördinatoren, researchverpleegkundigen en andere studiemedewerkers van de deelnemende ziekenhuizen hartelijk bedanken voor hun enorme inzet. Zonder jullie hadden we nooit zo'n mooi onderzoek kunnen opzetten.

Veel dank ook aan mijn promotieteam: prof. dr. F.R. Rosendaal, prof. dr. J.G. van der Bom en dr. S.C Gouw. Beste Anske en Frits, bedankt dat ik mocht gaan promoveren op de HiN. Beste Samantha, bedankt voor je gedrevenheid. Je legde de lat hoog, en dat heeft een mooi proefschrift opgeleverd.

Shermarke, mijn partner in crime: *we did it*! Het was niet altijd makkelijk, maar het is ons gelukt! Bovendien heb ik gaandeweg een hoop geleerd over de islam. Dank je wel.

Alle stuurgroepleden van HiN: bedankt dat ik met jullie mee mocht kijken tijdens poli's, voor het waardevolle commentaar op artikelen en voor jullie enthousiasme. Jullie *zijn* HiN-6.

Onderzoek kan niet zonder datamanager. Bedankt Karlijn en Liesbeth, voor de klus die jullie hebben helpen klaren.

Shannon, Deb, Sandra, Linda, Claude, Marian and Rick, thank you for welcoming me to at St Paul's in Vancouver. I had the privilege to meet many of your patients and to observe the delivery of hemophilia care in my favourite city. It was a pleasure to work with you.

Marjan, wat begon met een cursus, mondde uit in twee studentenprojecten met bijbehorende publicatie. Bedankt voor alles wat ik van je heb mogen leren over kwalitatief onderzoek. Bridget en Marjolein, ik had me geen betere studenten kunnen wensen om te begeleiden.

Collega-promovendi van de afdeling klinische epidemiologie en Sanquin: bedankt voor de vele borrels, uitjes naar de Efteling of de Veluwe, Epi-ski, koffiepauzes en pizzalunches; goed voor de soms broodnodige ontspanning en afleiding. Bijzondere dank aan mijn kamergenoten Hugoline, Tim, Deeksha en Inge, die dikwijls de eersten waren om successen en frustraties mee te delen.

Yvonne, Inge en Tamara, als jullie er niet waren, zou er van alles in de soep lopen. Bedankt dat jullie altijd als praktische en gezellige vraagbaak wilden dienen.

Martijn, Anje, Richard, Puck, Edwin en Chelsea, bedankt voor de goede gesprekken aan het kampvuur. Jetteke en de angels, Marjolijn, Cathelijne, Jiska, Annemiek, Eva en Seppe, Roos: dankzij jullie was ik ook regelmatig niet bezig met mijn proefschrift.

Beste oud-collega's van de wetenschapsredactie van de Volkskrant: jullie leerden mij schrijven over wetenschap. Ik weet zeker dat jullie lessen de laatste loodjes van dit proefschrift ten goede zijn gekomen.

(Oud-)collega's van Bureau X en NTvG: fijn dat jullie me de ruimte gaven om in deeltijd te werken, zodat ik daarnaast tijd had om aan dit proefschrift te werken. Bedankt voor jullie interesse.

Jolande, Germen, Joop en Rita, bedankt dat ik af en toe bij jullie in het Drentse land tot rust kon komen. De sauna, gezamenlijke wandelingen in het bos en spelletjes Ticket to Ride hebben mij meer inspiratie, en vooral ook rust, opgeleverd dan jullie vermoeden.

Okki, dank je wel voor het prachtige ontwerp van de cover.

Ben en Marijke, bedankt dat jullie altijd wilden weten hoe het ging met mijn onderzoek.

Suzan, als ik een halve zin zeg, zeg jij de andere helft, en andersom. Wat ben ik blij dat je vandaag naast me staat als paranimf. Vibeke, jouw praktische, maar zeker ook mentale steun in de laatste fase van HiN-6 waren onmisbaar. Bedankt dat je me ook vandaag steunt.

Pap en mam, Lieke en Jean-Paul, Anja, wat fijn dat jullie altijd wilden luisteren naar mijn verhalen, of het nu over p-waarden, stollingsfactoren of onderzoekslogistiek ging. Bedankt voor jullie oprechte nieuwsgierigheid en jullie vragen.

Lieve Tristan, wat beleven wij samen een hoop mooie avonturen. Zonder jou was ik nooit gekomen waar ik nu ben. Niemand inspireert mij meer dan jij. Dank je wel.

Curriculum Vitae

Erna werd geboren in Groningen op 10 oktober 1980. Na het Praedinius Gymnasium studeerde ze milieugezondheidkunde (doctoraal oude stijl) aan de Universiteit Maastricht (2000-2005). Voor haar doctoraalscriptie deed Erna in Barcelona onderzoek naar het risico op lymfomen door blootstelling aan bestrijdingsmiddelen. Daarna volgde ze een masteropleiding Linguistics aan de Universiteit Leiden (2006-2007). Erna werkte achtereenvolgens drie jaar bij het RIVM en drie jaar in Vancouver (Canada) in beleids- en onderzoeksfuncties op het gebied van volksgezondheid en gezonde leefomgeving. Na terugkeer naar Nederland werkte ze ruim een jaar als medisch milieukundig adviseur bij de GGD Rotterdam-Rijnmond. Eind 2015 begon ze met haar promotieonderzoek op de afdeling klinische epidemiologie van het LUMC, waar ze onder leiding van Frits Rosendaal, Anske van der Bom en Samantha Gouw en samen met collega-promovendus Shermarke Hassan de zesde editie van het Hemofilie in Nederland-onderzoek opzette. Ook verbleef Erna opnieuw 3 maanden in Vancouver voor één van de kwalitatieve studies in dit proefschrift. Erna volgde het opleidingstraject tot epidemioloog B en presenteerde haar werk op internationale congressen. Na het vierjarige promotietraject bij het LUMC liep Erna stage bij de wetenschapsredactie van de Volkskrant. Ook werkte ze in deeltijd als onderzoeker bij de GGD Flevoland. Momenteel is Erna nieuwsredacteur bij het Nederlands Tijdschrift voor Geneeskunde.