On outcomes for hemophilia

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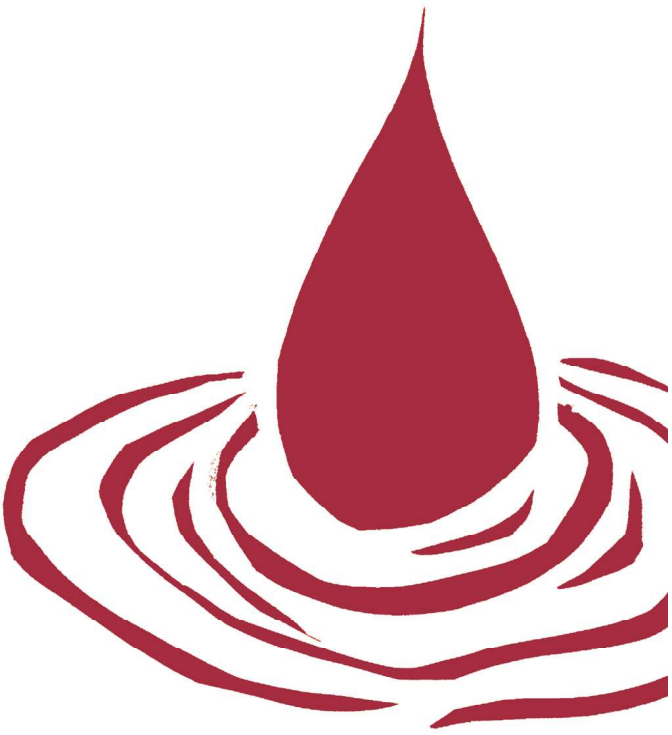
PART III

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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