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LETTER TO THE EDITOR

Harmonizing patient-reported outcome measurements in inherited bleeding disorders with PROMIS

In recent years, advances regarding novel therapeutic approaches in inherited bleeding disorders and other rare disease entities underline the need for systematic outcome measurement in healthcare and research.[1] Traditionally, haemophilia treatment centres have focused on clinical outcomes such as bleeding frequency, functional status and joint damage as well as health-related quality of life (HRQoL). Assessment of HRQoL or the person's perception of their own health and functioning is essential to fully understand the impact of a chronic, potentially debilitating, disease on the individual and to evaluate the implications of varying treatment strategies.[2] In order to gain insight into these perspectives, patient-reported outcomes (PROs) should be measured. Combining these PROs with clinical outcomes, corrected for case-mix variables, ensures adequate analysis of treatment choice and personalization when possible.

Selecting a set of outcomes that are important for patients with an inherited bleeding disorder is mandatory before application in healthcare and research can be accomplished. Recently, several initiatives have led to core outcomes sets for haemophilia in collaboration with patients and patient advocates.[1,3] Both Dover et al. and van Balen et al. used a nominal consensus process with an international group of haemophilia experts to select a core set of health outcomes for persons with haemophilia.[1,3] Another core outcome set, the Core-HEM, was specifically developed by Iorio et al. for the evaluation of gene therapy in persons with haemophilia.[4] An initiative by the World Federation of Hemophilia (WFH) resulted in the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire, which combines questions related to demographics, general health problems, haemophilia-related health problems and HRQoL.[5] The PROBE questionnaire can be applied in both persons with haemophilia and persons without a bleeding disorder, enabling the assessment and comparison of the impact of disease and possible treatment interventions with other disease fields using one measurement tool[5] (Table 1).

Similarities exist between the various outcome sets for haemophilia and the PROBE questionnaire. Even though they were designed for a different purpose, they almost all include the PROs pain, ability to engage in daily or usual activities and mental health. Unfortunately, barriers exist for the implementation of these outcome sets in healthcare and research. Barriers include: choices and harmonization of outcome sets e.g., selected PROs and recommended measurement tools also called Patient Reported Outcome Measures (PROMs) and general incomprehension of terminology and interpretation of results. Other commonly mentioned barriers in implementation studies are the high number of recommended PROMs for different patient groups, especially when patients have multi- or comorbidity, the high number of questions per PROM, as well as varying psychometric properties and scoring methods of PROMs measuring the same domains.[6] To overcome these issues, the Patient-Reported Outcomes Measurement Information System (PROMIS ®) project was initiated by a cooperative group of scientists from several U.S.-based academic institutions and the National Institute of Health.[7] The PROMIS project collected, combined and transformed existing PROMs into a new, state-of-the-art assessment system for measuring patient-reported health and well-being of adults and children. PROMIS has created a set of item banks to evaluate and monitor different general domains e.g., physical, mental and social health in both children and adults.

PROMIS has several advantages compared to more traditional PROMs, that are based on Classical Test Theory. Firstly, PROMIS is based on Item Response Theory (IRT) which makes it possible to scale items and persons on a single metric, improving the interpretability of the acquired scores. In addition, IRT enables the application of Computer Adaptive Testing (CAT), where the next item presented to the patient depends, based on an algorithm, on the responses to earlier items.[7] If, for example, a patient answers that he or she has difficulty walking, the PROMIS CAT will not offer an item about running. CAT therefore lowers the burden of outcome assessment by administrating a limited number of more relevant questions with a higher reliability.[7] A second advantage is that PROMIS item banks are generic and can therefore be applied across medical conditions. Important as many patients have comorbidities, especially older patients with inherited bleeding disorders. In addition PROMIS can be used for benchmarking purposes. Moreover, PROMIS is especially suitable for patients with rare diseases, or without diagnoses, who often visit multiple healthcare professionals, as they are generic and reliable, and answers can be used by all involved treatment teams.[6]

In 2009, the Dutch-Flemish PROMIS group was founded to translate the PROMIS item banks into Netherlands and Flemish (Belgium), to establish reference values for the Dutch and Flemish populations, and to validate and ultimately implement the defined measures. Since then, many generic Dutch PROMIS item banks have been validated across a wide range of medical conditions. Within the field of inherited bleeding disorders, forces were united to start a Dutch research group for PROMIS implementation in inherited bleeding disorders, which consists of a multidisciplinary team of representatives from multiple haemophilia treatment centres in the Netherlands.

TABLE 1 Differences across outcome sets for persons with haemophilia

Auteurs	Target population	Purpose	Outcomes	Recommended measure (Disease specific)	Recommended measure (Generic)
Iorio et al. (2018)	Persons with haemophilia	Gene therapy trails	1. Frequency of bleeds 2. Factor activity level 3. Duration of factor VII or factor IX expression **4. Chronic pain** 5. Utilization of healthcare system (direct costs) **6. Mental health**	Not mentioned	Not mentioned
Skinner et al. (2018)	Persons with haemophilia and persons without a bleeding disorder	Research	**1. General health problems** 2. Use of mobility devices 3. Use of pain medication **4. Acute pain** **5. Chronic pain** **6. Difficulties with activities of daily living** 7. Work/school life 8. Surgical history 9. Concurrent medical problems **10. Mobility** **11. Self-care** **12. Usual activities** **13. Pain/discomfort** **14. Anxiety/depression** **15. Global health**	Not mentioned	1-9. PROBE questionnaire 10–14. EQ-5D-5L 15. EQ-VAS

(Continues)

TABLE 1 (Continued)

Auteurs	Target population	Purpose	Outcomes	Recommended measure (Disease specific)	Recommended measure (Generic)
Dover et al. (2020)†	Persons with haemophilia	Research and clinical care	1. Total bleeding events **2. Mobility** **3. Self-care** **4. Usual activities** **5. Pain/discomfort** **6. Anxiety/depression** 7. Treatment adherence 8. Joint health 9. Number and location of bleeds per unit time	8. HJHS	2-6. EQ-5D
van Balen et al. (2021)‡	Persons with haemophilia	Clinical care	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 (work or school) **6. Chronic pain** 7. Complications **8. Sustainability of physical functioning** **9. Social functioning** **10. Mental health**	3. HAL Use of transportation, Self-care, Household tasks 6. PROBE Chronic pain 8. HAL Lying down/ sitting/ kneeling/standing, functions of the legs, function of the arms 8. HJHS 9. Haemo-QoL-A: Role functioning 10. Haemo-QoL-A: Emotional impact	3. PROMIS Self-efficacy for managing chronic conditions – managing daily activities 6. PROMIS Pain intensity, Pain interference 8. PROMIS Physical functioning, Physical functioning for samples with mobility aid users 9. PROMIS Ability to participate in social roles and activities, Self-efficacy for managing social interactions 10. PROMIS Anxiety, Depression, General life satisfaction, Positive affect

The health outcomes in **bold** represent patient-reported outcomes that can only be reported by the patients themselves.

†Dover et al. propose a core outcome set for children and adults with haemophilia. The table only shows the proposed set for adults with haemophilia.

‡van Balen et al. provide recommendations on measurement instruments for both adults and children and for high- and low-income societies. The table only shows the recommended measurement instruments for adults in high income societies.

Abbreviations: EuroQol 5-dimensions 5-level, EQ-VAS; EuroQol 5-dimensions, HAL; EuroQol visual analog scale, HJHS; Haemophilia Activities List, PROMIS; Haemophilia Joint Health Score, EQ-5D; Patient Reported Outcomes, Burdens and Experiences, EQ-5D-5L; Patient-Reported Outcomes Measurement Information System, Haemo-QoL-A: Haemophilia Quality of Life Questionnaire for Adults.; QoL; quality of life, PROBE.

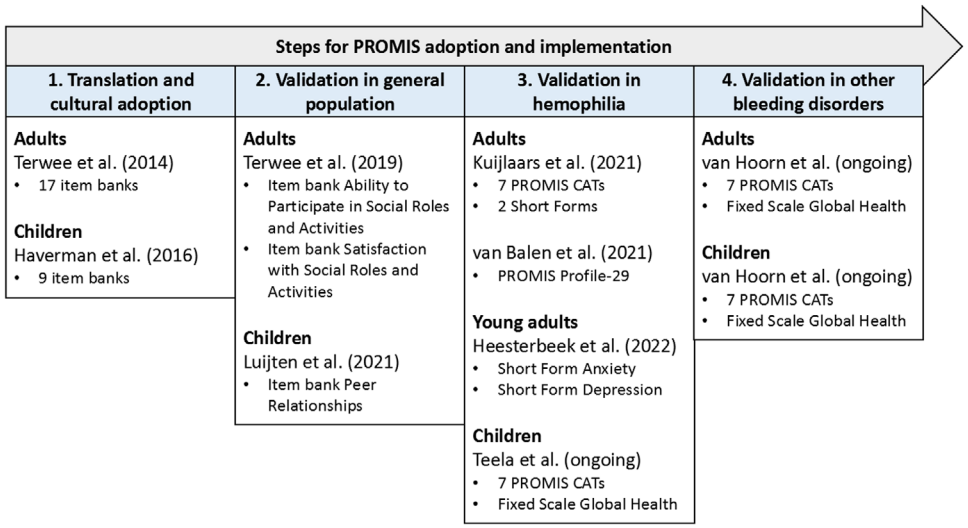

FIGURE 1 Steps for PROMIS adoption and implementation. PROMIS; Patient-Reported Outcomes Measurement Information System, CAT: Computer Adaptive Testing

Various PROMIS measures have been recently validated in (young) adults with haemophilia.[8–10] The validation of PROMIS item banks by adults with haemophilia shows that the PROMIS Profile-29 questionnaire, the 8-item PROMIS anxiety and depression short forms, as well as the PROMIS CATs physical functioning, pain interference, satisfaction with social roles and activities, and fatigue are feasible, reliable and valid alternatives to legacy instruments[9,10] Studies to validate the use of PROMIS CATs in children with haemophilia, in children and adults with other inherited bleeding disorders such as von Willebrand disease, platelet function disorders and the rare bleeding disorders are currently ongoing (Figure 1). These latter studies are currently being performed in collaboration with the SYMPHONY NWO-NWA research consortium. We expect that the ongoing studies will further highlight the advantages of PROMIS. Subsequently, implementation of PROMIS measures may be more feasible within the field of inherited bleeding disorders. These PROMIS sets will need to be enriched with disease specific questions, as these cannot be completely replaced. Disease specific questions, in most cases, will be related to symptoms, and can often be assed with one explicit question about, for example, bleeding frequency, menstrual bleeding, joint damage and other commonly reported disease-related outcomes as included in the PROBE questionnaire[5] and core outcomes sets as developed by Dover et al.,[1] van Balen et al.,[3] and Iorio et al.[4] These questions can then form a supplement to the generic PROMIS item banks, allowing the physicians a complete overview of the patient's health and functioning.

To facilitate the implementation of generic PROMIS item banks in clinical care, the SYMPHONY consortium is involved in the national initiative to harmonize the different IT systems and electronic health records used by the Dutch haemophilia treatment centres. With this initiative, SYMPHONY aims to make the PROMIS item banks available for all patients with inherited bleeding disorders in the Netherlands. The joint commitment to PROMIS by Dutch healthcare professionals involved in inherited bleeding disorders within the haemophilia treatment centres, will not only facilitate the implementation of outcome measurement in overall care for persons with inherited bleeding disorders (inter)nationally, but is also a stepping stone for healthcare innovations in rare diseases at large. To achieve all advantages PROMIS has to offer to the field of inherited bleeding disorders, PROMIS needs to become the national and international standard for generic outcome measurement by persons with inherited bleeding disorders.

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The SYMPHONY consortium, which aims to orchestrate personalized treatment in patients with bleeding disorders, is a unique collaboration between patients, health care professionals and translational and fundamental researchers specialized in inherited bleeding disorders, as well as experts from multiple disciplines. SYMPHONY aims to identify best treatment choice for each individual based on bleeding phenotype. In order to achieve this goal, workpackages have been organized according to three themes e.g. Diagnostics (workpackage 3&4), Treatment (workpackages 5–9) and Fundamental Research (workpackages 10–12). This research received funding from the Netherlands Organization for Scientific Research (NWO) in the framework of the NWA-ORC Call grant agreement NWA.1160.18.038. Principal investigator: Dr M.H. Cnossen. Beneficiaries of the SYMPHONY consortium: Erasmus MC – Sophia Children's Hospital, University Medical Center Rotterdam, project leadership and coordination; Sanquin Diagnostics; Sanquin Research; Amsterdam University Medical Centers; University Medical Center Groningen; University Medical Center Utrecht; Leiden University Medical Center; Radboud University Medical Center; Netherlands Society of Hemophilia Patients (NVHP); Netherlands Society for Thrombosis and Hemostasis (NVTH); Bayer B.V., CSL Behring B.V., Swedish Orphan Biovitrum (Belgium) BVBA/SPRL.

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