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CLINICAL RESEARCH

The potential impact of gene therapy on health-related quality of life (HRQoL) domains in haemophilia

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Introduction: Haemophilia is an inherited bleeding disorder characterised by spontaneous bleeding, often leading to impaired health-related quality of life (HRQoL). Commonly used treatments include episodic and prophylactic treatment regimens. Gene therapies could soon become available, potentially creating a paradigm shift in patient management. **Aim:** This paper proposes hypotheses about the potential impact of gene therapy on HRQoL domains in haemophilia, and how these impacts might differ compared with existing treatments. **Methods:** An expert working group with 10 individuals experienced in haemophilia and HRQoL research was established to discuss potential impacts of gene therapy on HRQoL in general and for specific domains in haemophilia. As part of a one-day workshop, domains of three widely used patient-reported outcome (PRO)

As gene therapy becomes available as a treatment option for people with haemophilia, it will be important to ensure that validated haemophilia-specific instruments used to assess HRQoL are able to capture both favourable and less favourable outcomes, including potential long-term effects.

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instruments were explored: the Haemo-QoL-A, the Patient Reported Outcomes, Burden and Experiences (PROBE), and the Haemophilia Activities List (HAL).

Results: **The group expected a greater improvement in HRQoL from gene therapy compared with existing treatments for the following domains: physical/role functioning, worry, and consequences of bleeding (Haemo-QoL-A); haemophilia-related health and EQ-5D-5L (part of the PROBE); leg and arm function, and leisure activities (HAL). In contrast, the experts suggested that no change or potential deterioration might be observed for the emotional impact (HAL) and treatment concerns (Haemo-QoL-A) domains.**

Conclusions: **Current PRO instruments in haemophilia have limitations when applied in the context of gene therapy, and no single instrument fully captures the relevant HRQoL domains. However, the PROBE and Haemo-QoL-A were considered as the most suitable existing instruments. As haemophilia treatments evolve, further research should examine the potential effectiveness of existing PRO instruments as compared to the development of novel PRO measures.**

Keywords: *Haemophilia, gene therapy, patient-reported outcomes, health-related quality of life*

Haemophilia is an inherited bleeding disorder characterised by recurrent bleeds, most commonly musculoskeletal, caused by blood clotting factor deficiencies. The two most common types of haemophilia are types A and B, characterised by factor VIII (FVIII) and factor IX (FIX) deficiency, respectively. Severe haemophilia (both A and B) is clinically characterised by plasma levels of FVIII or FIX activity below 1% [1], whereby spontaneous bleeds occur. When these comprise joint bleeds, arthropathy can develop over time [2]. People with haemophilia (PWH) commonly report physical limitations, chronic pain, and problems undertaking activities of daily living (ADLs), due to recurrent bleeds [3,4]. Impaired physical function has been reported to negatively impact ADLs and productivity, through absenteeism from work and school [5,6].

Observational studies consistently demonstrate that PWH experience impairments in health-related quality of life (HRQoL) and psychosocial functioning [7-10]. In addition, a large proportion of PWH disclose having low self-esteem, negative self-image, chronic stress, anxiety, depression, severe pain, arthropathy, and episodic bleeds [7,11-15]. Assessing the impact of haemophilia on individuals' HRQoL is important to understand the burden of illness, the efficacy of novel treatments and quality of care against the expectations of PWH [16].

Commonly used treatments for haemophilia include episodic treatment, prophylactic treatment with clotting factor concentrates (CFCs), or prophylactic treatment with non-replacement therapies. Episodic treatment (also known as on-demand therapy) is administered in the event of an acute bleed (spontaneous or traumatic), while prophylactic treatment regimens with clotting factor or non-replacement therapies are administered via regular infusions, which aim to reduce the frequency of bleeding events [17,18]. Prophylactic treatment regimens have been found to markedly decrease the number of annual bleeding episodes and pain in comparison to episodic therapy [18]. While evidence suggests that these commonly used haemophilia therapies can be effective at reducing the risk of bleeds, challenges remain regarding the costliness of treatment and lack of efficacy regarding long-term prevention of joint disease [1,20]. Emicizumab-kxwh (Hemlibra®), a long-acting, extended half-life, non-factor therapy, is another common treatment used for haemophilia [1], which can be injected with lower frequency [20]. One study found that almost all participants reported a preference for Emicizumab-kxwh prophylaxis compared with their regimen prior to study enrolment (episodic or another type of prophylactic treatment) [20].

The current haemophilia treatment landscape is expected to undergo a paradigm shift with the anticipated availability of novel haemophilia therapies for patients, in particular the availability of gene therapy. Gene therapy using viral vectors enables viruses to target specific cells and tissues to deliver genetic material [21]. Early gene therapy trials in haemophilia A used retroviral and adenoviral factors which were well-tolerated with minimal side effects but did not lead to sustainable FVIII expression [22]. However, adeno-associated viruses (AAV) have now demonstrated long-term benefits, including increased factor levels and decreased bleeding rates, in phase 1/2 studies for both haemophilia A and B [22-24]. Phase 3 AAV gene therapy trials are still underway and there are not yet any approved gene therapies for haemophilia A or B on the market.

To assess how a gene therapy product could potentially impact the HRQoL of PWH, an international, multidisciplinary working group (WG) was established, and a workshop was convened to critically review the measurement of HRQoL in haemophilia, now that novel mechanisms such as gene therapy are currently undergoing assessment in clinical trials. The main aim of this workshop was to form hypotheses of the potential impact of gene therapy on distinct HRQoL domains to support the identification of patient-reported outcome (PRO) instruments most capable of capturing potential changes in the HRQoL of PWH as a result of undergoing gene therapy.

The aim of this article is to summarise the WG's conclusions regarding the perceived impact of gene therapy on the HRQoL of PWH.

METHODS

Working group members

An international, multidisciplinary WG was formed to discuss potential impacts of gene therapy on HRQoL domains. The WG members represented four countries: US, UK, Ireland and Germany. The group experts were purposively selected to include individuals with a wide range of expertise who had published research in the fields of haemophilia and the development and validation of HRQoL PROs, or who were key members of patient advocacy groups in haemophilia. A list of 17 potential members was compiled. Of these, 10 individuals agreed to take part, consisting of clinicians (n=3), patient advocates from the World Federation of Hemophilia, the Haemophilia Society, and the Irish Haemophilia Society (n=3), HRQoL expert (n=1), and industry representatives from a pharmaceutical company and a contract research organisation (CRO) (n=3). Two of the WG members were haemophilia A patients, although neither had undergone gene therapy to date. As gene therapy trials are still ongoing with a small sample of patients, it was not feasible to include gene therapy patients within the WG.

Literature review and selection of PRO instruments

A targeted literature review was conducted in Embase and MEDLINE to identify publications in the past 20 years (search included publications from 1999–2019 that included key themes relating to the impact of haemophilia on HRQoL. The findings from the literature were used to inform the WG objectives and goals. The WG reviewed widely used haemophilia-specific PRO instruments for their suitability to assess the impact of investigational gene therapies for haemophilia according to their methodological quality and dissemination in clinical research. Three PRO instruments were selected, namely the Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A), the Patient Reported Outcomes, Burden and Experiences (PROBE) questionnaire, and the Haemophilia Activities List (HAL). All three instruments are widely accepted and used to assess HRQoL and ADLs for PWH, and the PROBE in particular was developed to capture patient experience. To date, these instruments have been included in more than 30 clinical trials combined [27]. Since these specific instruments are currently being utilised in the phase 3, open label, single arm clinical trial of gene therapy in haemophilia A (Clinicaltrials.gov identifier: NCT03370913) [28], an empirical test of their performance according to the hypotheses formulated by the WG is possible upon completion of the study.

PRO instruments

The Haemo-QoL-A, developed in 2008, is a self-administered 41-item instrument with a four-week recall period, and validated for use in haemophilia A and B populations [29]. It consists of six domains: physical functioning, role functioning, worry, consequences of bleeding, emotional impact, and treatment concerns. Higher domain scores are associated with higher HRQoL and lower impairment [29].

The PROBE is a self-administered 29-item instrument, which was developed and validated in 2018 for haemophilia A and B patients [30-32]. It consists of four sections, which for the purposes of the workshop were referred to as domains: demographic data, PRO-general health problems, haemophilia-related health, and the 5-level EQ-5D version (EQ-5D-5L) and EQ visual analogue scale (EQ VAS). With the exception of the EQ-5D-5L and EQ VAS, the recall period is tailored by question from current state, in the past 12 months or ever experienced a specified event. Higher scores on the PROBE relate to better HRQoL [33,34].

The HAL is a self-administered 42-item instrument with a four-week recall period, developed in 2004 and validated in 2006, for haemophilia A and B patients [35,36]. The HAL has seven domains: lying down/sitting/kneeling/standing, functions of the legs, functions of the arms, use of transportation, self-care, household tasks, and leisure activities. Higher domain scores relate to fewer functional limitations and better HRQoL [35].

Workshop

A workshop was held in New York, US, on 23 March 2019, and attended in person by all 10 WG members. The workshop consisted of four sessions: 1) discussion around the general disease impact on the HRQoL of PWH, 2) assessment of commonly used existing haemophilia therapies and their impact on HRQoL, 3) assessment of the strengths and weaknesses of the three pre-selected haemophilia-specific PRO instruments, and 4) breakout sessions to form hypotheses about the potential impacts of gene therapy on HRQoL in comparison to the current standard of care. The workshop approach was designed to discuss these topics and build consensus of opinion. During the breakout sessions, three sub-groups were formed, with each group assigned to a haemophilia-specific PRO instrument (Haemo-QoL-A, PROBE or HAL). The groups discussed the potential impacts of gene therapy on each of the PRO instrument domains relative to the most common treatments (episodic treatment, prophylactic treatment with CFCs, prophylactic treatment with non-replacement therapies) on the market. Each group developed charts to illustrate domains that they anticipated would change, in terms of direction of change (no change, improvement, deterioration) and its magnitude (weak, moderate, strong). Each group then presented their results and developed consensus with the wider WG on the potential impact of gene therapy on the HRQoL domains.

Follow-up teleconferences and email correspondence for final consensus building

Following the in-person workshop, the WG took part in two follow-up teleconferences to further discuss and review workshop breakout session results. These calls were used to ensure consensus among group members on the hypothesised impacts of gene therapy on HRQoL domains in haemophilia. Members unable to attend the virtual meetings were asked to provide feedback via email.

RESULTS

HRQoL concepts most relevant to PWH

WG members discussed a range of HRQoL-related concepts they perceived to be of high importance for PWH, independent of treatment. These included fatigue, pain intensity/interference, lifestyle adaptations, and emotional and behavioural domains (i.e., worry and strategy to avoid bleeds). The WG also discussed the potential impact of key clinical outcomes on HRQoL such as factor activity level, annualised bleeding rate (ABR) including intensity, frequency, and duration of bleeds; frequency of treatment dosing; and the concept of target joints. Of note, WG members discussed the full range of outcomes, acknowledging that key clinical outcomes such as ABR, although highly regarded by some regulatory agencies as the optimal primary outcome to measure treatment efficacy, will not fully capture the anticipated impact of change when comparing PWH pre- and post-gene therapy, without consideration of additional outcomes. In the context of gene therapy, the WG noted that hospitalisation outcomes (i.e., number of visits or admittance rates) were potentially relevant when investigating treatment efficacy. For the PRO instruments assessed by the WG, domains that measured these concepts, particularly those that captured physical impact on HRQoL such as pain and fatigue, were regarded as most important and relevant to PWH. Emotional wellbeing, including freedom from anxiety and worry, were also identified as important.

Assessment of PRO instruments

The WG members discussed the strengths and weaknesses of each haemophilia-specific PRO instrument assessed in the workshop. The PROBE was found to be the most inclusive and conceptually relevant PRO instrument of the three under review, as the instrument is considered to cover a wide range of concepts to holistically assess the health of PWH. This finding is likely due to the systematic inclusion of PWH in all aspects of concept development, testing and validation of the PROBE, which helped to ensure items are patient-centric and relevant [37]. Limitations of the PROBE discussed and proposed by the WG included potential ceiling effects and the extended recall period of 12 months [33]. If ceiling effects exist, the instrument may not be able to detect improvements in scores; therefore, patients with higher scores before their treatment would have no room for an increase (improvement) in scores following treatment. Additionally, patients may have difficulty accurately remembering and responding to questions regarding their health status when the recall period is as long as 12 months.

The WG agreed that the Haemo-QoL-A consists of relevant items that would be important to patients, such as difficulties of travelling, concerns about having children, or having a career. The group also discussed the usefulness of the 'worry' domain specifically in the assessment of novel therapies, as items such as 'I am hopeful about the future' and 'I enjoy life' could potentially articulate some of the unique benefits of advanced therapies. However, a potential effect on the emotional doman was discussed, whereby advanced novel therapies may be perceived to have a more positive effect on HRQoL compared with patients' experience with existing therapies.

Finally, for the HAL, the group noted a lack of evidence regarding its psychometric properties for use as a PRO tool. Additionally, some of the domains contained items considered outdated due to the instrument being developed when the standard of care in haemophilia and the expectations of treatment outcomes were different to that of the present day.

Impact of gene therapy on the HRQoL domains

The results from the breakout sessions on the hypothesised potential impact of gene therapy on the HRQoL domains across the three instruments were as follows:

1. Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A)

The sub-group assigned to the Haemo-QoL-A hypothesised the 'worry' and 'emotional impact' domains would potentially be most important to PWH, due to the mental and emotional concepts measured within these domains. As shown in Table 1, the group speculated that the 'physical functioning' domain score would show a weak increase (i.e., better HRQoL) for gene therapy in comparison with existing therapies. For the 'worry' domain, the group hypothesised a moderate to strong increase, indicating improved HRQoL to varying degrees (Table 1). However, it was noted that worries could be ingrained and long-lasting for PWH, thus changes in this domain may not occur in the short term following gene therapy administration. It was considered that the 'emotional impact' domain could increase or decrease in potential recipients of gene therapy compared to a baseline use of existing regimens, which would largely depend upon individual psychological and emotional responses to the new therapy paradigm. The group discussed the potential for PWH to feel a new sense of freedom after receiving gene therapy, or on the contrary, a feeling of loss of identity, and therefore the hypothesised directionality of change should encompass both potential scenarios. It was expected that there would be fewer 'consequences of bleeding' as therapies advance, and therefore scores on this domain would likely strongly increase (i.e., better HRQoL) in gene therapy relative to commonly used existing therapies. No expected change was predicted in the 'treatment concerns' domain score for gene therapy relative to existing therapies, as some of the items within the domain are not applicable in the context of gene therapy. For instance, treatment concern items on the Haemo-QoL, such as 'I worry about being treated by health care providers who do not know how to treat haemophilia' may lack relevance in the context of gene therapy, as gene therapy would only be administered by highly trained specialists. However, due to the novelty of the therapy, some patients may be apprehensive of their health care provider not having sufficient experience. The Haemo-QoL-A item 'I worry about the availability of haemophilia products' would most likely not be applicable to a PWH receiving gene therapy, as it is expected to be a one-time treatment only.

2. Patient Reported Outcomes, Burden and Experiences (PROBE)

The sub-group assigned to the PROBE considered that the PRO-general health problems section would potentially be the most important to PWH, particularly the items regarding acute and chronic pain, and the impact on HRQoL. The items regarding ADLs were also considered important to PWH and likely to be associated with scores on the pain items. For example, the more severe pain or discomfort, the lower the ability to perform ADLs, as pain would likely affect the ability of individual PWH to conduct daily activities. As shown in Table 2, it was hypothesised that gene therapy would strongly increase (i.e., better health status) the 'demographic data' (which includes clinical characteristics) domain score. Although demographic data is not commonly considered an outcome, within the context of gene therapy, certain demographics and clinical characteristics may be affected positively by gene therapy; for example, patient weight, as effective therapy could enable some PWH to partake in more physical activity and enable them to maintain healthier body weight or composition. In addition, the group speculated that PWH who receive gene therapy might be able to stay in educational systems longer or with reduced absenteeism due to haemophilia-related health problems. It was suggested that if an approved gene therapy product were only available to adult PWH, these effects might not be as pronounced as they might be in younger patients, such as students, for whom the positive effects of better school attendance would be most impactful. Relationship status was also suggested to change due to reduced disease burden and stress. For example, some patients may experience difficulty in forming and maintaining a long-term relationship due to the limitations of haemophilia and disease-related health problems. Similarly, the group speculated that the 'PRO-general health problems' domain would see a strong and positive (i.e., better health status) effect for gene therapy relative to commonly used existing therapies, as it is hypothesised that gene therapy would improve factor activity levels helping to reduce bleed risk. This could potentially lead to decreased chronic and acute pain, increased ability to partake in ADLs, ability to uphold school and work responsibilities, and a reduction of anxiety and depression. Furthermore, increased factor levels could result in the cessation of prophylactic treatment. The 'haemophilia-related health' domain would be expected to strongly increase (i.e., better health status) for gene therapy relative to commonly used existing treatments, given its potential long-term outcomes.

3. Haemophilia Activities List (HAL)

The sub-group assigned to the HAL considered the 'leisure activities' domain to be potentially the most important domain to patients, as the ability to partake in activities may have a strong and positive impact on a patient's emotional wellbeing. As shown in Table 3, they hypothesised an expectation that gene therapy would strongly increase (i.e., less impairment/better functionality) the 'leisure activities' domain score relative to commonly used existing therapies, as increased factor activity levels might increase a person's confidence to partake in activities. In contrast, the group speculated there would be no change in the 'lying down/sitting/kneeling/standing' domain, as this is more likely to be impacted by rehabilitative therapy than any form of medical treatment. Further, there was an expectation of a greater increase in scores (i.e., less impairment/better functionality) for the 'functions of the legs' and 'functions of the arms' domain scores for gene therapy compared with commonly used existing therapies over a 12-month period from baseline. However, the group considered these changes may occur slowly following gene therapy administration, and thus the HAL recall period of one month may be too short to detect any potential effects. The listed activities within the 'self-care' and 'household tasks' domains were considered to be "outdated" and no longer relevant in the present day. Therefore, the group concluded that if unexpected results or an absence of change were observed on these domains, these would most likely be due to the lack of relevant items within respective domain.

Directionality and magnitude of change, and group rationale of domain changes

Each breakout session sub-group discussed the anticipated domain changes for PWH treated with gene therapy compared with commonly used existing therapies. Within the results tables (Tables 1–3), hypothesised directionality of change is represented in four ways: 1) an upward arrow signifying an 'improvement' in domain score/HRQoL, 2) a sideways arrow signifying 'no change' in domain score/stable HRQoL, 3) a downward arrow signifying a 'worsening' in domain score/HRQoL, and 4) a combination of arrows if expected changes may vary. The hypothesised magnitude of change is demonstrated by four categories: 1) 'weak' for a change of minimal strength/effect, 2) 'moderate' for a change of noticeable strength/effect, 3) 'strong' for a change of great strength/effect, and 4) 'variable' for a change that may be of any strength. The rationale includes comments made by one or more members of the WG, which provides reasoning and insight for the hypothesised domain changes.

DISCUSSION

An expert WG was formed to critically review the measurement of HRQoL in haemophilia using PRO instruments, in the potential advent of a paradigm shift from existing treatment regimens to gene therapies. Instrument domains were reviewed to discuss how HRQoL might differ between potential gene therapy recipients and those on existing therapies.

Key HRQoL domains perceived to be of most relevance to PWH were identified: fatigue, pain intensity and pain interference, lifestyle adaptations, and emotional and behavioural domains. In the context of gene therapy, WG members suggested – drawing from direct experience as PWH or clinicians treating PWH – that unexpected changes may be observed in some domains. For example, domains related to emotional wellbeing would generally be expected to show improvements in the long term. However, deterioration may also be observed if a patient has success with gene therapy as a one-time treatment, due to a potential loss of identity associated with being a member of the haemophilia community. Moreover, an alleviated burden of disease could present opportunities previously unavailable to individuals in active treatment, such as travelling, new physical activities, or different careers. While this should trigger positive reactions, it may also trigger a sense of being overwhelmed or feeling regretful that gene therapy was not available earlier. A 'reverse disability paradox' could manifest in PWH undergoing gene therapy. This concept builds on the 'disability paradox' whereby patients with disabilities report good HRQoL despite having a disability, due to adapting to their way of life [38]. A reverse disability paradox in PWH receiving gene therapy could therefore result in lower HRQoL scores than expected. As gene therapy trials are ongoing in haemophilia A, the durability of the effect of gene therapy on FVIII expression and the impact on patients' treatment experience are still to be established.

The WG's critical review of currently used haemophilia-specific PRO instruments (Haemo-QoL-A, PROBE, HAL) concluded that none of them were likely to fully capture change in HRQoL in PWH treated with gene therapy as they were developed in a pre-gene therapy landscape. While some domains are predicted to capture change in HRQoL well, others may be less relevant in PWH treated with a gene therapy. Looking at HRQoL data on both a domain level and a total score level may be more insightful, but the suitability of these PRO instruments to appropriately assess HRQoL in the context of gene therapy must be considered cautiously. However, if comparing novel therapies (such as gene therapy) to classical ones, it is important that favourable and less favourable potential outcomes are compared across all treatments involved. Expanding existing instruments to assess gene therapy outcomes or creating novel comprehensive instruments could be relevant options.

Haemo-QoL-A was considered to include items that measure concepts of importance to PWH. In addition, it was noted that the 'worry' domain might be useful specifically in the context of novel therapies, as some items within the domain (e.g. "I am hopeful about the future") may articulate some of the benefits of more advanced novel therapies. However, the WG acknowledged that either an increase or decrease in emotional domain scores could be feasible. An increase in score could be attributed to placebo-type effects due to expectations around an advanced product, while a decrease could be linked to a sense of regret or lost opportunities pre-gene therapy. Items within the treatment domain may not be suitable to assess treatment concerns in the context of gene therapy. For example, one item assesses concern on being treated by health care providers who do not know how to treat haemophilia, which is unlikely to be applicable to a clinician administering gene therapy.

The PROBE was discussed as useful in the context of gene therapy, as it captures patient demographics such as educational status, relationship status and body weight, as well as HRQoL data. It was deemed the most 'inclusive' of the three PRO instruments under review due to the comprehensiveness of its items and domains. The WG expressed concerns regarding potential ceiling effects which could affect the PROBE's ability to detect improvement in HRQoL. There were concerns that the 12-month recall period may be too long, although the WG also considered that a longer recall period might provide a more holistic view of treatment impact on HRQoL for therapies where some effects of treatment take a longer time to manifest, such as rehabilitative or gene therapy. It was also noted that the 12-month recall period is tailored by question from current state and not applicable to all items within the instrument, such as those on recent bleeds and ADLs.

Some domains in the HAL measure dated concepts, e.g. within the self-care and household tasks domains, and do not include common ADLs such as keyboard and smartphone use. The lack of psychometric and cross-cultural validation of the HAL was discussed, and additional limitations around potential ceiling effects for men older than 40 years of age were noted. As such, the HAL may be a more suitable PRO instrument in the assessment of efficacy for existing regimens as opposed to investigational treatments such as gene therapy.

Limitations of this paper must be considered. While the WG members were carefully selected based on their experience in the haemophilia and PRO fields, spaces were limited to ensure a productive working atmosphere at the workshop. Thus, not all experts in this field were able to contribute their perspectives and expertise to the discussions of HRQoL in PWH who receive gene therapy. However, the heterogeneity of the expert sample is likely to be sufficiently representative of the many perspectives within the large and highly engaged haemophilia community. It should also be considered that the WG discussions were opinion-based according to each of the member's knowledge and experiences of haemophilia. Furthermore, the remit of the WG was to assess three PRO instruments commonly used in haemophilia, although there are approximately nine haemophilia-specific PRO instruments available, none of which are currently validated in gene therapy [39].

Despite these limitations, the WG is hopeful that this initiative instigates ongoing discussions and further research around assessing and interpreting HRQoL in potential therapeutic advancements. Gene therapy represents the possibility of a major paradigm shift in the natural history and treatment of haemophilia, and it is imperative to ensure that its impacts are well understood. Considering that the impact of gene therapy on patient-reported outcomes should be understood *a priori* from the patient perspective. While a review of available and well-introduced instruments is important in this respect, the development and testing of new measures may also be needed. The coreHEM [40], which was developed to determine a set of outcome measures to assess the efficacy, safety and effectiveness of gene therapy for haemophilia, could be a useful guide for reviewing or developing a new instrument. Guidelines for the development of such an instrument should first and foremost use qualitative data collected from PWH, followed by psychometric testing and examination of its application within and across patient groups, research designs and cultural contexts.

CONCLUSION

The limitations related to HRQoL assessment highlighted by the expert WG indicate the importance of the context of use when measuring HRQoL to ensure PRO instruments have good content validity and are sensitive to change on all relevant domains. It is important that the tools used to assess HRQoL are developed with a patient-centric approach to ensure that the concepts and outcomes of most importance from the patient perspective are appropriately captured and measured [41]. Currently, multiple instruments exist which measure HRQoL in haemophilia. Although it may not be possible to identify a single PRO instrument that comprehensively assesses all aspects of HRQoL in PWH treated with investigational gene therapies, using multiple haemophilia-specific instruments to assess HRQoL may help address the limitations of a single instrument. However, patient fatigue is an important consideration when multiple instruments are administered. The overall opinion of this WG concluded that the most appropriate tools currently available for measuring HRQoL in haemophilia (in the advent of a potential gene therapy) appear to be the PROBE, despite being novel, and the Haemo-QoL-A.

Further research is warranted, through patient interviews and additional expert input, to better understand HRQoL in PWH who are currently participating in gene therapy clinical trials or, if gene therapy receives approval, who may receive an approved gene therapy product in the future. Examining potential long-term effects on HRQoL in the context of gene therapy will help in understanding whether effects are sustained over time. Further research will also be important to understand the appropriateness of currently validated haemophilia-specific PRO instruments in assessing HRQoL in PWH who receive gene therapy, including ensuring these validated instruments enable both favourable and less favourable outcomes to be captured for the purposes of comparing novel therapies to traditional treatments [40]. Existing instruments could be expanded to more comprehensively assess gene therapy outcomes, but future work should include haemophilia-specific instruments developed *de novo* to be suitable for application in the context of novel treatment regimens such as gene therapy. Understanding how different study designs might impact HRQoL assessment (e.g. study duration and schedule of assessments) should be considered. Collectively, this evidence could be used to provide wider context to better understand potential paradigm shifts in the treatment landscape for haemophilia.

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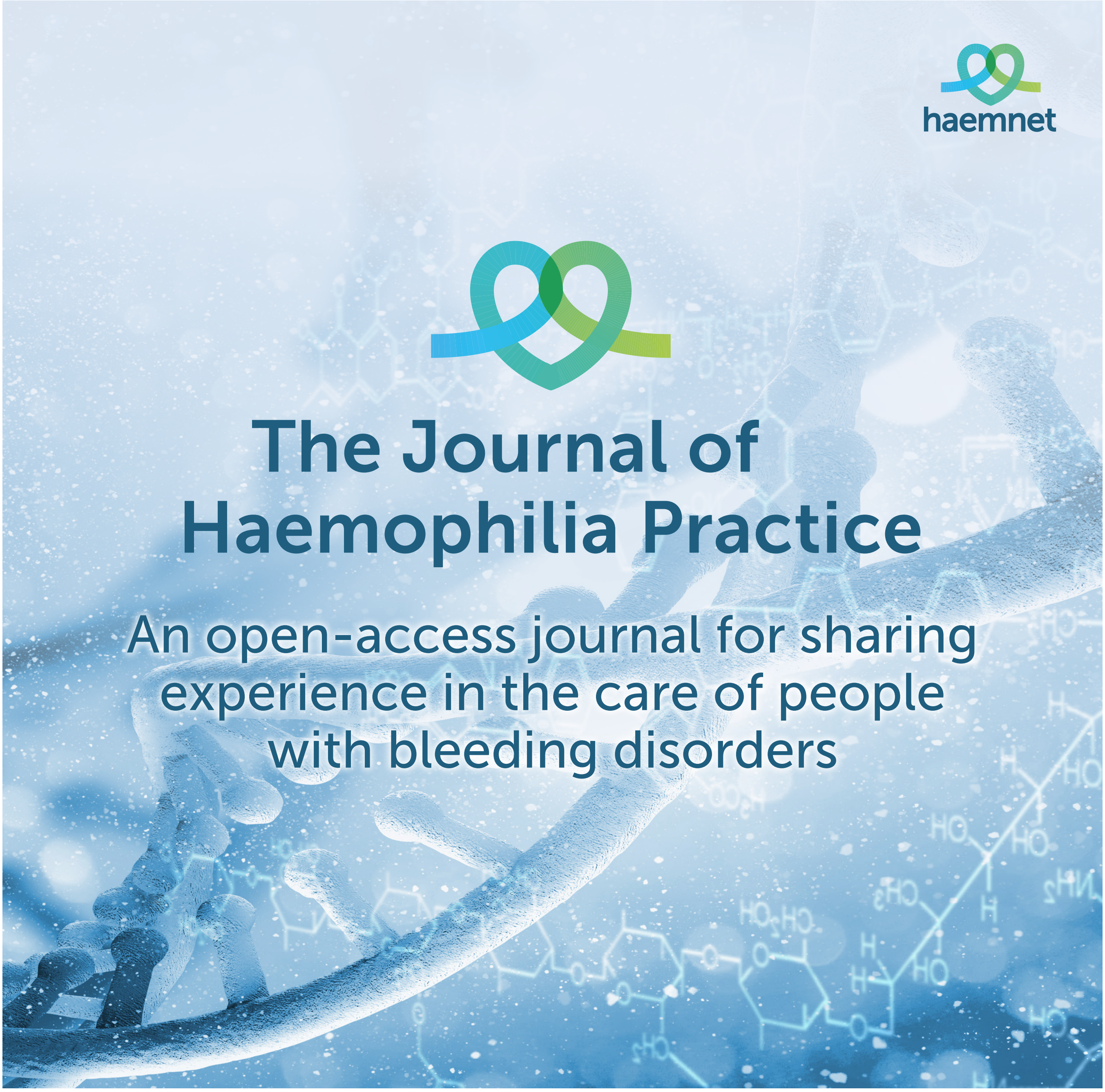

Table 1. Hypothesised effects of potential gene therapy for haemophilia on domains of the Haemophilia-specific Quality of Life Questionnaire for Adults (Haemo-QoL-A)

Haemo-QoL-A domain	PHYSICAL/ROLE FUNCTIONING	WORRY	CONSEQUENCES OF BLEEDING	EMOTIONAL IMPACT	TREATMENT CONCERNS
Hypothesised directionality* and magnitude of domain score	↑ Moderate	↑ Moderate/Strong	↑ Moderate	↑↓ Strong	→ N/A
Score interpretation	Higher/increased scores = Better HRQoL or less impairment Lower/decreased scores = Worse HRQoL or less impairment				
Hypothesis rationale	Physical functioning expected to improve due to stabilised factor levels and fewer joint bleeds Role functioning expected to disappear or become irrelevant in gene therapy due to nature of the therapy	Worries expected to decrease and HRQoL to increase in the long term as factor levels expected to improve with gene therapy	Consequences of bleeding will decrease (and therefore domain score will improve) with treatment advancement as number of bleeds are likely to decrease	The emotional impact of treatment outcomes may either positively impact a patient (e.g., new sense of freedom, ability to partake in rigorous activities) or negatively impact a patient (e.g., loss of identity, reflection of time lost)	Items within domain were considered dated and not fit for purpose in the context of novel treatment regimens, such as gene therapy
Comments from expert working group	Patients will not need to infuse prior to physical activity	Worry may be engrained and long-lasting, therefore perhaps unlikely to change rapidly in the short term Types of worries a PWH may have will be largely impacted by their demographics, such as their age, parental status, type of work or school stage	Although bleeding consequences reduce with treatment advancement, PWH will remain aware/conscious of needing to be compliant with treatment in order to reduce consequences Ability to clot and heal in gene therapy more than any other commonly used existing treatment	There could be a deterioration in emotional wellbeing in the short term on gene therapy, but an improvement in the long term	Advanced or novel treatments can be more costly and are not necessarily covered by insurance or national health service, which could be a potential treatment concern Assumption with gene therapy is patient will only need treatment once Potential selection bias may occur where patients with fewer treatment concerns are more likely to enrol in clinical studies Some uncertainties tend to exist around novel regimens, resulting in potential treatment concerns Known complications or adverse events for commonly used existing therapies may result in treatment concerns

* Upward arrow signifies an 'improvement' in domain score/HRQoL or less impairment; sideways arrow signifies 'no change' in domain score/stable HRQoL; downward arrow signifies a 'worsening' in domain score/HRQoL or more impairment; combination of arrows signifies a variation of change in domain score

Table 2. Hypothesised effects of potential gene therapy for haemophilia on domains of the Patient Reported Outcomes, Burdens and Experiences (PROBE)

PROBE domain	DEMOGRAPHIC DATA	PATIENT-REPORTED OUTCOMES – GENERAL HEALTH PROBLEMS	HAEMOPHILIA-RELATED HEALTH	EQ-5D-5L AND EQ-VAS
Hypothesised directionality* and magnitude of domain score	↑ Strong	↑ Strong	↑ Strong	↑ Moderate/Strong
Score interpretation	Higher/increased scores = Better health status Lower/decreased scores = Worse health status			
Hypothesis rationale	Gene therapy expected to have strong impact on this domain, such as weight change, education level (ability to stay within education) and relationships	Strong impact expected on this domain assuming treatment will result in normal factor levels (40-50%)	Strong impact expected on this domain as ABR, 'target' or damaged joints, range of motion and life-threatening bleeds expected to improve due to higher factor levels	Strong impacts expected on mobility, anxiety and depression, and on EQ-VAS scores Limitations to relevance of items on self-care, usual activities, and type of pain, and therefore difficult to accurately measure
Comments from expert working group	Improved educational status may only be evident at older ages as gene therapy is not available to children	Large impact expected on acute and chronic pain due to decrease in bleeds, anxiety and depression, activities of daily living and school/work Joint surgery outcomes expected to improve due to more protection (normal factor levels), as well as reduced associated surgery costs as less post-surgery complications expected to occur Anxiety and depression are very important concepts within this domain Definition of normal factor levels differs between patients Theoretical increase in risk of heart complications and cancer; however this is not likely to be a major concern for PWH who are more likely to be concerned about efficacy of therapies to increase their ability to partake in activities	Potential for improvement in ABR is dependent upon patient's baseline ABR, which will be different according to geographical location, i.e., PWH in developed countries may report 0-1 ABR (no room for improvement), whereas PWH in developing countries may report 20-30 ABR (room for improvement)	Increased granularity in the detail of the various subdomains is needed Important to consider that PWH have been shown to report much higher utilities than their health status would suggest due to adaptability and coping mechanisms; improvement in scores might only been seen for patients with lower baseline scores

* Upward arrow signifies an 'improvement' in domain score/health status; sideways arrow signifies 'no change' in domain score/no health status improvement; downward arrow signifies a 'worsening' in domain score/health status

Table 3. Hypothesised effects of potential gene therapy for haemophilia on domains of the Haemophilia Activities List (HAL)

HAL domain	LYING-DOWN / SITTING / KNEELING / STANDING	FUNCTION OF THE LEGS	FUNCTION OF THE ARMS	USE OF TRANSPORTATION	SELF-CARE	HOUSEHOLD TASKS	LEISURE ACTIVITIES
Hypothesised directionality* and magnitude of domain scores	→ N/A	↑ Variable	↑ Variable	→ N/A	→ N/A	→ N/A	↑ Variable
Score interpretation	Higher/increased scores = Less functional limitation Lower/decreased scores = More functional limitation						
Hypothesis rationale	Impact of rehabilitative therapy not likely to be seen after 1 month (recall period)	Over time, chance for greater functioning of legs after therapy	Improved function of arms is likely to occur concurrently with improved function of legs	Use of transport is unlikely to change as PWH are not more or less likely to use transport as a result of any treatment regimen	Dated list of self-care activities, thus difficult to accurately measure this HRQoL domain with this instrument	Dated list of household tasks, thus difficult to accurately measure this HRQoL domain with this instrument	Large expected impact of gene therapy after 12 months of therapy
Comments from expert working group	Rehabilitative physiotherapy would have more of an impact on this domain compared with the haemophilia treatment itself	The lower extremities are more commonly affected by this condition, such as the ankles and the knees	The elbows would be the most impacted area in the upper extremities The instrument is not considered to assess function of the upper arms well		Confidence to partake in activities would improve opportunity for self-care Important to consider that PWH adapt well to their condition as they would have been dealing with it their whole life Self-care improves if pain improves	Important to consider that PWH adapt well to their condition as they would have been dealing with it their whole life	Ability to take part in activities is important to emotional wellbeing Domain name considered misleading and should be more reflective of physical activities; 'leisure' is a very broad term In the longer term more intensive sports activities could be started; weight loss is also possible

* Upward arrow signifies an 'improvement' in domain score/less functional limitation; sideway arrow signifies 'no change' in domain score/no change in functional limitation; downward arrow signifies a 'worsening' in domain score/functional limitation