Outcome measures for adult and pediatric hemophilia patients with inhibitors

Cedric Hermans1 | Günter Auerswald2 | Gary Benson3 | Gerry Dolan4 |
Anne Duffy5 | Victor Jiménez-Yuste6 | Rolf Ljung7 | Massimo Morfini8 |
Thierry Lambert9 | Mehdi Osooli10 | Silva Zupančić Šalek11,12,13

1Division of Haematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium
2Klinikum Bremen-Mitte, Professor Hess Children’s Hospital, Bremen, Germany
3Northern Ireland Haemophilia Comprehensive Care Centre, Belfast, Ireland
4Department of Haematology, Queens Medical Centre, Nottingham, UK
5Irish Haemophilia Society, Dublin, Ireland
6Hospital Universitario La Paz, Unidad de Coagulopatías, Servicio de Hematología, Universidad Autonoma de Madrid, Madrid, Spain
7Department of Paediatrics and Malmö Centre for Thrombosis and Haemostasis, Lund University, Skåne University Hospital, Malmö, Sweden
8Past President of Italian Association of Haemophilia Centres (AICE), Florence, Italy
9Hemophilia Care Center, Bicêtre AP-HP Hospital and Faculté de Médecine Paris XI, Paris, France
10Malmö Center for Thrombosis and Haemostasis, Department of Translational Medicine, Skåne University Hospital, Malmö, Sweden
11National Haemophilia and Thrombophilia Centre, Department of Haematology, University Hospital Centre Zagreb, Rebro, Zagreb, Croatia
12School of Medicine, University of Zagreb, Zagreb, Croatia
13School of Medicine, University of Osijek, Osijek, Croatia

Abstract
Recent advancements in almost all aspects of hemophilia treatment have vastly improved patient care and management, and new and emerging treatments hold the promise of further progress. However, there remains a scarcity of data on long-term outcomes in hemophilia, particularly among those patients with inhibitors, for whom no validated outcome assessment tools are currently available. At the 15th Zürich Haemophilia Forum, an expert panel reviewed the most important outcome measures in inhibitor patients and considered the challenges associated with assessing outcomes in this population. A framework for outcome assessment in inhibitor patients incorporates traditional hemophilia outcome measures, such as bleed frequency and mortality, alongside measures of health, functioning, disability, social participation, quality of life, and economic considerations. It is important to remember that inhibitor patients differ in their clinical needs, perspectives, and priorities according to age, inhibitor status, degree of joint disease, and activity levels; as a result, the relative importance of different outcome measures will change throughout an inhibitor patient’s life. Challenges inherent in measuring long-term outcomes in inhibitor patients include the small number of known patients, the subjective nature of many outcome assessment tools, and the risk of overburdening patients with repeated requests to complete questionnaires or participate in studies. Therefore, there is an urgent need to reach
consensus on the most important and appropriate assessment tools for measuring outcomes in this population. These tools should ideally be standardized, easily applied, and internationally applicable in order to collect and generate quality outcome data.

**KEYWORDS**

adults, children, hemophilia, inhibitors, outcome assessment, treatment outcome

---

1 | INTRODUCTION

The last 20 years have seen major improvements in almost all aspects of hemophilia treatment and have therefore been described as a new “golden era” in the management of this rare congenital bleeding disorder. Improved standards of care have paralleled the rapid evolution of high-quality, recombinant coagulation factor VIII (FVIII) and factor IX (FIX) concentrates, which are administered on demand or prophylactically to replace the deficient clotting factor in hemophilia A and B, respectively. Together, these treatment advances have greatly improved bleed control and prevention, increased quality of life (QoL), and reduced the burden of disease.

Developments for patients who are refractory to standard replacement therapy due to the development of alloantibodies (inhibitors) against infused FVIII or FIX have followed more slowly. For many years, the only specific therapy for treating acute bleeds in these inhibitor patients was plasma-derived activated prothrombin complex concentrate (pd-aPCC [FVIII inhibitor bypassing activity]). However, within the last four decades, this otherwise limited therapeutic armamentarium for inhibitor patients has also been expanded: first, by the introduction of immune tolerance induction (ITI), which offers the possibility of inhibitor eradication, and then by the development of recombinant activated factor VII (rFVIIa, B, respectively). Together, these treatment advances have greatly improved bleed control and prevention, increased quality of life (QoL), and reduced the burden of disease.

Despite recent advances in hemophilia management, however, and despite the promises of further improvements offered by new or emerging products, limitations in hemophilia treatment still exist. One such limitation is the global scarcity of data on long-term outcomes in hemophilia. At its most foundational level, outcome assessment aims to measure how the patient feels, functions, and survives following health care interventions and is therefore essential in evaluating the effect of an intervention and ensuring effective healthcare delivery. While validated tools are available for those with hemophilia, the same is not well defined for patients with inhibitors. The best way to evaluate hemophilia treatment is not well defined, and even less information and guidance is available on measuring treatment outcomes in patients who develop inhibitors. For instance, although there is growing interest in outcome measures for hemophilia patients, with several recent publications addressing this topic, little is known about the applicability of these “classical” outcome scores to hemophilia patients with inhibitors.

Members of the Zürich Haemophilia Forum convened for their 15th meeting in May 2015 to discuss which outcome measures should be monitored in patients with severe hemophilia and current or persistent inhibitors. The panel reviewed current knowledge on outcomes in hemophilia care before considering the specific challenges and limitations associated with identifying and implementing optimal outcome measures in inhibitor patients. This article summarizes the panel’s discussions and recommendations.

2 | WHY ARE OUTCOME MEASURES NEEDED IN HEMOPHILIA?

In an age of evidence-based medicine, the practice of documenting specific outcomes—and using appropriate instruments and tools to assess them—needs to be established as part of the regular evaluation of hemophilia patients. The assessment of clearly defined outcome measures is important for several key reasons. First, validated and standardized outcome assessment tools are required for research, including clinical trials, and for enabling long-term patient follow-up. The follow-up and clinical care of individual patients, together with resource allocation, would also benefit from standardized outcome measurement, particularly in light of growing evidence that treatment for each patient should be individualized.

Outcome measurement is also important from an economic viewpoint. The high cost of hemophilia care, coupled with a global economic recession and limited resources in even high-income countries, inevitably means that some restrictions in hemophilia care will be requested by payers over the next few years in terms of products and treatment regimens used. In this climate, it is crucial to collect outcome data to demonstrate treatment value and to justify costs.

While this is important for the hemophilia population as a whole, it may also be important for supporting and justifying requests for more intensive treatment in individual patients.

3 | OUTCOME MEASUREMENT IN INHIBITOR PATIENTS

Joint bleeds are the hallmark of hemophilia, with recurrent joint bleeds eventually producing a crippling and irreversible arthropathy. Clearly, the first goal of hemophilia care is to manage bleeding. For inhibitor patients, however, bleeds are often more difficult to control than in those patients without inhibitors. This increases the risk of orthopedic complications and significant disability, with subsequent impact on QoL, physical activity, and daily living. In addition to bleed management, key treatment goals for inhibitor patients are avoidance...
TABLE 1  Suggested framework for key outcome assessments and tools in hemophilia

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body function</strong></td>
<td>Physical scores&lt;br&gt; WFH Physical Examination Score (Gilbert score)(^{25})&lt;br&gt; HJHS(^{26})&lt;br&gt; Gait analysis(^{27})</td>
</tr>
<tr>
<td><strong>Body structure</strong></td>
<td>Imaging technique scores&lt;br&gt; Conventional radiography (X-ray)&lt;br&gt; Arnold-Hilgartner scoring system(^{18})&lt;br&gt; Pettersson score(^{29})&lt;br&gt; MRI&lt;br&gt; Denver score(^{20})&lt;br&gt; European MRI score(^{31})&lt;br&gt; “Compatible” score (combined Denver + European scores)(^{26})&lt;br&gt; IPSG score(^{33})&lt;br&gt; Ultrasoundography(^{34-36})</td>
</tr>
<tr>
<td><strong>Participation and activity</strong></td>
<td>Functional scores&lt;br&gt; FISH(^{37})&lt;br&gt; HAL(^{38})&lt;br&gt; PedHAL(^{39})</td>
</tr>
<tr>
<td><strong>Health-related QoL</strong></td>
<td>Non-specific for hemophilia&lt;br&gt; SF-36(^{40})&lt;br&gt; SF-12(^{41})&lt;br&gt; Specific for hemophilia(^{a})&lt;br&gt; Haemo-QoL (adults(^{42}) and children(^{43,44})&lt;br&gt; CHO-KLAT (children)(^{39})</td>
</tr>
<tr>
<td><strong>Mortality(^{b})</strong></td>
<td>Incidence of deaths(^{11})&lt;br&gt; Life expectancy/survival</td>
</tr>
<tr>
<td><strong>Bleeding frequency/severity</strong></td>
<td>Number of bleeds (ABR)(^{11})&lt;br&gt; Severity of bleeds&lt;br&gt; Joint ABR&lt;br&gt; Bleeding in target joints</td>
</tr>
<tr>
<td><strong>Bone mineral density</strong></td>
<td>Imaging techniques&lt;br&gt; Dual-energy X-ray absorptiometry(^{45,47})&lt;br&gt; Quantitative ultrasonography(^{48})</td>
</tr>
<tr>
<td><strong>Health economics</strong></td>
<td>EQ-5D(^{49})&lt;br&gt; Clinical outcomes(^{11})&lt;br&gt; Direct medical costs(^{11})&lt;br&gt; Clotting factor consumption(^{11})&lt;br&gt; QALYs/DALYs&lt;br&gt; Orthopedic surgery costs(^{11})&lt;br&gt; Work/school days lost (for patient or parent/guardian/partner) due to bleeds&lt;br&gt; Hemophilia-related hospitalizations</td>
</tr>
</tbody>
</table>

\(^{a}\) Hemophilia-specific QoL questionnaires should be adapted for each country or culture.\(^{11}\)

\(^{b}\) Mortality may be more useful as an outcome measure in less developed (rather than developed) countries.

A suggested framework for outcome assessments that is relevant for today’s landscape of hemophilia management, including specific tools for measuring each outcome, is summarized in Table 1. This framework incorporates traditional hemophilia outcome measures, such as mortality and bleeding frequency, together with categories from the International Classification of Functioning, Disability and Health (ICF). The ICF, which integrates both medical and social models, is used by the World Health Organization (WHO) to measure health and disability. It extends beyond just the disease to model functioning and disability according to three broad categories: body function, body structure, and activity and participation.\(^{23,24}\) “Body function” refers to anatomy, “body structure” to physiology, and “activity and participation” to activities of daily living, social participation, and participation in life events.\(^{23}\) As all of these outcomes may be strongly affected by the presence of inhibitors, it is now necessary to consider how this framework can be applied to outcome assessment in the inhibitor patient population.

It is important to note that the majority of assessment tools are relevant to hemophilia patients with or without inhibitors, although their relative importance and frequency of application may differ. The existence of a common set of assessment tools suitable for both patient populations highlights the emerging disparity that exists between the two groups in terms of measuring treatment outcomes, and may help to provide leverage within healthcare systems to improve care for inhibitor patients.

4 | WHAT ARE THE CHALLENGES OF OUTCOME MEASUREMENT IN INHIBITOR PATIENTS?

The long-term assessment of outcomes in hemophilia patients with inhibitors is hindered by several factors, foremost among which is the small number of known patients. In the UK, for example, there were just 230 patients with inhibitors in 2014 (hemophilia A, \(n=220\); hemophilia B, \(n=10\)).\(^{49}\) and the incidence of new inhibitors across all age groups has been reported as just 10.92 per 1000 patient-years at risk.\(^{50}\) As inhibitor patients are so rare, their geographical spread in a given area or country adds to the challenges inherent in their treatment and assessment. Also, patient responses between the two currently available bypassing agents are variable and not consistent for all bleeds, the data available do not indicate a difference in effectiveness between these two agents,\(^{21,51}\) and patients often undergo changes in their treatment regimens (eg, changes in bypassing agents, changing from on demand to prophylaxis, initiation of ITI). Without careful documentation, it may be difficult to determine which treatment factors may relate to a change in outcome. Furthermore, while the patient’s perspective is vital for the assessment of certain outcomes (eg, QoL, burden of daily treatment, and treatment of arthropathy and improvement of QoL). Together, these goals necessitate consideration of other outcome measures beyond just bleed control, such as the early detection and quantification of joint disease by physical criteria or various imaging techniques, health-related QoL, and, as discussed above, economic considerations.\(^{11}\)
satisfaction), and thus necessitates the use of patient-reported outcomes, there is inherent variability in patients’ individual perceptions.

As with all hemophilia patients, one of the biggest challenges in measuring outcomes in the inhibitor population is the changing clinical and social needs of patients at different stages of life. Also, the same patients are approached repeatedly for multiple studies, which means there is a danger that inhibitor patients could become disengaged and unwilling to cooperate if they receive numerous requests to participate in studies or complete questionnaires and assessments without an obvious benefit to them. Therefore, there is a need to reach consensus on which outcomes should be prioritized in inhibitor patients, and at which stages of life, so that outcome measurement can be optimized and patients do not become overloaded by burdensome assessment requests and invitations for study participation.

5 | MEASURING OUTCOMES: NOT ALL INHIBITOR PATIENTS ARE THE SAME

While the outcome measures necessary for treatment evaluation in inhibitor patients coincide with those suggested for the hemophilia population as a whole (Table 1), it is important to recognize that not all inhibitor patients are the same: Patients differ in their clinical needs, perspectives, outlook, and priorities according to age, inhibitor status, degree of joint disease, and level of activity. For example, as patients grow older, arthropathy increases but the bleeding rate decreases, such that simply monitoring bleeding rate in an elderly inhibitor patient is unlikely to provide helpful information on the patient’s overall well-being or treatment outcome. It is crucial for clinicians to be aware of the inhibitor patient’s changing profile as they age and move through different stages of life.

We propose four main categories of inhibitor patients: (i) new inhibitor patients; (ii) patients aged 5-15 years with long-standing, persistent inhibitors; (iii) patients aged 16-50 years with long-standing, persistent inhibitors; and (iv) patients aged >50 years with long-standing, persistent inhibitors. Each of these categories is briefly summarized below.

5.1 | New inhibitor patients

At this age, patients have little involvement in social activities. These patients are usually very young at the time of inhibitor development (median age, 15 months), with good joint health and a strong possibility that ITI may successfully eradicate the inhibitor. As such, these children are candidates for ITI (or other) studies. However, they still face a risk of bleeding before successful ITI is accomplished and bleeding may be persistent if ITI fails. In common with patients in the categories below, the characteristics and outcomes of individuals who have not yet been treated with ITI may differ from those for whom ITI is unsuccessful, but the management approaches show some similarities. Inhibitors can also develop later in life, including—although they are not the subject of this review—in some patients with mild-to-moderate hemophilia.

5.2 | Patients aged 5-15 years with long-standing, persistent inhibitors

These patients are treated with bypassing agents, but may already have one or more impaired joints. The risk of serious bleeds is high in this group, as the children are still growing and are usually very physically active. These children may be suitable candidates for new or further ITI attempts.

5.3 | Patients aged 16-50 years with long-standing, persistent inhibitors

This patient group is sometimes poorly treated for bleeds and arthropathy is often evident in one or more joints. Work and social activities may be affected and orthopedic surgery may be needed. While these patients have not yet undergone ITI, they may eventually be considered for such treatment.

5.4 | Patients aged >50 years with long-standing, persistent inhibitors

These older patients often have a history of minimal or no treatment during their younger years. They often have multiple orthopedic and age-related comorbidities and may have already undergone several orthopedic surgeries. If an older patient with a low inhibitor titer requires further orthopedic procedures, ITI could be considered to eliminate the inhibitor prior to surgery.

In light of these four categories of inhibitor patients, the challenge is to choose outcome assessment tools that are applicable to changing clinical scenarios and patient needs, so that the most meaningful data for the patient’s clinical care and longer-term follow-up can be obtained. This means that the relative utility of the different types of outcome measures available (Table 1) will differ between the four inhibitor patient groups listed above.

6 | WHICH ARE THE MOST APPROPRIATE OUTCOME MEASURES TO ASSESS FOR INHIBITOR PATIENTS, AND WHEN?

The panel’s recommendations for the relative importance of different outcome measures at various stages of an inhibitor patient’s life are summarized in Table 2 and outlined below.

6.1 | New inhibitor patients

For very young patients who often have pristine joints and who develop inhibitors, body function (physical scores), body structure
Hermans Het Mal imaging technique scores), and bleeding frequency are likely to be the most important outcome measures, as they allow joint health to be monitored and, hopefully, controlled. As indicated in Table 2, participation and activity (functional scores) may not be so important for this group, as they have little involvement in daily or social activities at such an early age. Although QoL is probably the least important outcome measure at this stage, the panel agreed that inhibitor development does decrease QoL for these young children.

6.2 | Patients aged 5-15 years with long-standing, persistent inhibitors

Body function (physical scores), body structure (imaging technique scores), and bleeding frequency remain important in this group. Additionally, participation and activity (functional scores) gain greater relevance for these patients than when they were younger, as physical activity and social participation have become more important. At this stage in their lives, inhibitor patients do not want to feel different from their peers.

6.3 | Patients aged 16-50 years with long-standing, persistent inhibitors

For many young adult patients, inhibitors have a strong impact on social activities and work. Therefore, QoL and participation may take priority over the other outcome measures at this stage of life. The utility of bleeding frequency as an outcome measure is also likely to be declining.

6.4 | Patients aged >50 years with long-standing, persistent inhibitors

Older inhibitor patients often have multiple comorbidities, which can have a major psychological impact and subsequent effect on QoL. Therefore, the panel agreed that QoL is the most important outcome to measure in these older patients. Body function, participation and activity, and bleeding frequency are less important than in earlier stages of life; body structure may not be relevant at all, although bone mineral density measurements may be helpful in determining which patients may be at risk of spontaneous fracture.

7 | Are currently available outcome measures applicable to patients with inhibitors?

Given the scarcity of data available on outcome assessment in haemophilia patients with inhibitors, it is important to consider whether the outcome measures and tools currently used to evaluate outcomes in non-inhibitor patients are directly applicable to inhibitor patients. The panel’s recommendations are summarized below, along with appropriate caveats where necessary.

In terms of physical scores used to assess body function (Table 1), the panel agreed that the Hemophilia Joint Health Score (HJHS) appears to be a useful, validated scoring method in patients aged 4-18 years. The HJHS has also been used in adults and in patients with and without inhibitors. While it may be more useful as an epidemiological tool than as a tool to monitor individual inhibitor patients, the collection of HJHS data over time could be used, for example, to develop a predictive model for the development of joint arthropathy.

For body structure outcomes, there was agreement that imaging scores are equally valid for inhibitor and non-inhibitor patients alike (Table 1). It is important to bear in mind, however, that imaging techniques are complementary and clinicians should not rely on the results of a single test. Also, patients with inhibitors (especially young patients) may require more frequent monitoring, starting at an earlier age, as they are more likely to experience both clinical and subclinical bleeds. As the ankle is the first joint to be affected by joint disease, it may serve as an indicator of early arthropathy in outcome assessment. However, the panel recognized some difficulties in using imaging techniques to assess outcomes in very young children (<5 years). It is

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>New inhibitor patients</th>
<th>Patients with long-standing inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5-15 y</td>
</tr>
<tr>
<td>Body function (physical scores)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Body structure (imaging technique scores)</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Participation and activity (functional scores)</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>QoL</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bleeding frequency</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Health economics</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Relative importance of the different outcome measures is indicated by the number of “+” symbols, where “+” is least important and “++++” is most important.

NA, not applicable; QoL, quality of life.
aEvaluation of bone mineral density may be appropriate in some patients.
often very difficult to know which structure is being looked at in these developing joints and ultrasound techniques, in particular, require further investigation and validation in this patient group. Ultrasound may, however, be helpful as a tool to guide advice on the most suitable physical activity for inhibitor patients to undertake.

When considering bleeding frequency as an outcome measure, it was thought that the accurate recording of bleeding episodes is particularly important for patients with inhibitors. However, as bleeding frequency decreases in older patients with more severe arthropathy, bleeding frequency should not be considered alone, but should instead be used in conjunction with other treatment outcome measures. The panel also agreed that, while bleeding rate is an important outcome measure, the collection of such data is complicated by it being a patient-reported outcome. For example, subclinical bleeds may escape detection by patients and parents, even though they may cause joint damage in susceptible patients; bleed symptoms may also be attributed to another condition or it may be thought that a bleed has occurred when there is no actual bleeding. All of these scenarios can lead to a disparity between patient-reported bleeding frequency and the development of joint disease. In addition, to improve the accuracy of patient-reported annualized bleeding rates, the panel recommended that patients use the data recorded in their diaries over many months of the year, rather than just multiplying the number of bleeds experienced in the last month by 12. Furthermore, when assessing bleeding frequency as an outcome, it is important to have realistic treatment goals in mind: A goal of zero bleeds, for instance, may not be achievable for inhibitor patients. Although the treatment goal should ideally be the same for all patients, regardless of inhibitor status, a decision should be made regarding how many bleeds is acceptable (eg, five or 10 bleeds per year) and how treatment should be modified when bleeding exceeds this level.

Mortality was not considered to be an appropriate outcome measure for inhibitor patients in developed countries with good access to treatment. However, for less developed countries without good treatment access, mortality rate may still be a useful outcome measure. While it has been suggested that inhibitor development may be less frequent in these countries, it is possible that the higher mortality rates among hemophilia patients in less developed countries may mask the real rate of inhibitor development.

Quality of life is a vital outcome to measure not only for inhibitor patients, but also for their carers and families, as acute bleeds have been shown to interfere with the daily activities of all these groups. A recent pilot test of the HEMophilia associated CAREgiver Burden scale (HEMOCAB™) also suggests that the overall burden imposed by hemophilia is greater for carers of inhibitor patients than for carers of non-inhibitor patients. However, it is difficult to gain an accurate overall picture of QoL: Questionnaires used to assess this outcome are complex, and the results obtained are greatly influenced by the time of recording, with patients reporting worse QoL on days when bleeds occur vs non-bleed days. The day-to-day variability in pain and disability suggests that new methods are needed to assess the impact of bleeding on QoL in inhibitor patients. New QoL assessment tools that are more applicable for younger inhibitor patients may also be needed, as their concerns and priorities usually differ from those of older patients. As inhibitor patients have more erratic bleeding patterns than those without inhibitors, it is important to identify and prioritize optimal QoL assessments that can be performed regularly throughout the year in order to obtain meaningful data. Finally, while existing QoL scores may be applicable for monitoring individual patients over time, they are unlikely to be helpful when comparing QoL between different populations of inhibitor patients (eg, between patients from Europe and Africa). Generic QoL tools may be useful, however, in comparing QoL between inhibitor patients and patients with other disorders, such as diabetes.

Finally, the panel also agreed that treatment adherence would be a useful additional outcome measure to consider, as poor adherence may negatively impact treatment success and joint health.

### 8 | FURTHER CONSIDERATIONS AND FUTURE DIRECTIONS

It is hoped that the panel’s recommendations for outcome assessment in inhibitor patients, as summarized in this article, will serve as both foundation and catalyst for further discussion, as well as a critical assessment of how best to measure long-term outcomes in the heterogeneous population of hemophilia patients with inhibitors. The current lack of consistency in outcome measurement, coupled with the rarity of outcome assessment outside clinical trials, highlights the urgent need to reach consensus on routine outcome measures that are appropriate for inhibitor patients and that can be performed routinely for regular, long-term follow-up. It is clear that there is no “one-size-fits-all” approach to outcome assessment throughout the entire course of an inhibitor patient’s life: The most appropriate assessment tools will differ according to the patient’s stage of life, perceptions, and priorities. Defining the most appropriate outcome measures to use at any point in their life and disease course may increase patients’ willingness to cooperate with assessments and questionnaires, as there will be fewer for them to do. Similarly, it is important to prioritize patient enrollment in studies that may provide real treatment benefits and improved QoL.

Outcome measures should also be applicable at both the micro (individual patient) and macro (population) level. Therefore, both of these scenarios should be included when considering outcome assessment in hemophilia patients (with or without inhibitors). Measuring outcomes at the population level, when large collaborative research cohorts are necessary, is associated with significant challenges. This was highlighted recently by an international observational study that sought to determine whether the HJHS could be used to compare outcomes of three different prophylaxis regimens in pediatric hemophilia patients without inhibitors from centers in the UK, Sweden, and the Netherlands. It was reported that comparison of the different prophylactic regimens using the HJHS was hindered by differences in assessment between different physiotherapists, both within and between centers, suggesting that additional interobserver standardization of the
HJHS must be performed when undertaking multicenter research. Furthermore, the timeframe for meaningful standardization in outcome measures typically involves years and decades, rather than months, which presents considerable challenges to investigators and funding bodies when trying to design appropriate studies.

Logistical challenges are also present at the micro (individual patient) level, not least of which are the problems of how to integrate outcome tools into routine care and how to use the resulting data in the clinic. At this individual level, it will also be important to share the results of outcome assessments with patients in a timely manner, as this may help them to understand how treatment has impacted their symptoms, QoL, and joint status, and also why their doctors may recommend treatment changes. This will help to gain patients’ trust and support and may motivate them to participate in future assessments. From a practical point of view, careful planning ahead of each patient visit may enable such outcome assessments to be performed without extending the time needed for each visit.

The outcome measures ultimately selected as most appropriate for use in inhibitor patients should ideally be standardized, easily applied, and internationally applicable in order to collect and generate quality outcome data. While barriers to such standardization exist (such as limited resources, infrastructure, knowledge, and expertise), using a smaller number of standardized tools is preferable to collecting data using multiple, non-standardized tools. The development of a suitable computerized data collection system may facilitate standardized data collection and documentation of the outcomes assessed: in addition, given the rarity of inhibitor patients, collaboration between the various existing patient registries and databases would be very beneficial. As the hemophilia community is geographically scattered, a centralized forum could be established to provide relevant news and other information, such as the availability of registries and treatment developments, as well as clinical trials that are enrolling patients or are already underway. These and other issues all need to be discussed and resolved by the international hemophilia community if the key challenges associated with outcome measurement in inhibitor patients are to be overcome and the best standards of care, assessment, and follow-up achieved.

ACKNOWLEDGEMENTS

Novo Nordisk provided financial support for the 15th Zürich Haemophilia Forum and for medical writing assistance, which was provided by Julie Smith, and Jessica Beishon of PAREXEL, in compliance with international guidelines for good publication practice. This manuscript has been reviewed for medical accuracy by Novo Nordisk Health Care AG.

CONFLICT OF INTEREST

C.H. has acted as a consultant and been a board member for Baxter, Bayer, CAF-DCF, CSL Behring, LFB, Octapharma, Novo Nordisk, Pfizer, and Sobi Biogen, and has received grants from Baxter, Bayer, and Pfizer. G.A. has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or consulting and/or funds for research from Baxter, Bayer, Biotest, CSL Behring, Grifols, Novo Nordisk, and Pfizer. G.B. has no conflict of interests to declare. G.D. has received honoraria from Novo Nordisk for speaking and participating on advisory boards. A.D. will receive honoraria payment from Novo Nordisk for reviewing research project grant applications this year. V.J.-Y. has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or consulting and/or funds for research from Baxter, Bayer, CSL Behring, Grifols, Novo Nordisk, Octapharma, and Pfizer. R.L. has, during the last five years, received speaker or consultancy fees from Novo Nordisk, Bayer, Baxter, Sobi, and Pfizer. M.M. acted as a paid consultant to Bayer, Baxter, Novo Nordisk, and Pfizer advisory boards, received speaker fees from CSL Behring, Biotest, Bayer, Kedrion, Novo Nordisk, and Octapharma, and received research grants from Baxter, Bayer, and Pfizer. T.L. has no conflict of interests to declare. M.O. has received honorarium from Bayer to speak at a Bayer hematology conference (Prague 2015). S.Z.S. has received reimbursement for attending symposia and congresses and honoraria payment for speaking from Baxter, Novo Nordisk, and Octapharma.

AUTHORS’ CONTRIBUTION

All authors contributed to the 15th Zürich Haemophilia Forum, on which the manuscript is based, approved the concept and design of the manuscript, critically reviewed the manuscript, and approved the final version.

REFERENCES


