



## ORIGINAL ARTICLE

# Cross-cultural adaptation and linguistic validation of age-group-specific haemophilia patient-reported outcome (PRO) instruments for patients and parents

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**Summary.** Currently, haemophilia care aims to provide the best possible quality of life for individuals living with this chronic disease. Many factors are known to influence treatment adherence, including treatment satisfaction. Health-related quality of life (HRQoL) and treatment satisfaction are, therefore, important outcomes in clinical trials and clinical practice. As individuals' perception of their well-being often differs from that of their physician, it is recommended that self-report instruments are used to assess patient-reported outcomes (PROs). The way that the impact of haemophilia is perceived by the patient and their family can be different, so it is important to assess how parents perceive the impact on their children. A series of PRO instruments have been developed, adapted to different age groups and parents of patients with haemophilia. To allow the instruments to be used internationally, culturally adapted and linguistically validated translations

have been developed; some instruments have been translated into 61 languages. Here, we report the process used for cultural adaptation of the Haemo-QoL, Haem-A-QoL and Hemo-Sat into 28 languages. Equivalent concepts for 22 items that were difficult to adapt culturally for particular languages were identified and classed as semantic/conceptual (17 items), cultural (three items), idiomatic (one item), and grammatical (one item) problems. This has resulted in linguistically validated versions of these instruments, which can be used to assess HRQoL and treatment satisfaction in clinical trials and clinical practice. They will provide new insights into areas of haemophilia that remain poorly understood today.

**Keywords:** age-specific instruments, haemophilia, health-related quality of life, linguistic validation, patient-reported outcomes, treatment satisfaction

## Introduction

Haemophilia is a rare inherited disease caused by deficiency of coagulation factor VIII (haemophilia A) or factor IX (haemophilia B) [1]. These factors are necessary in the generation of thrombin and, consequently, in blood clotting. The severity of the disease is defined using the residual plasma activity of the clotting factor: severe: <1%, moderate: between 1% and 5%, and mild: between 5% and 40% [2]. Haemophilia A and B are X-linked genetic disorders and therefore occur almost exclusively in males. Haemophilia A is

the most frequent of the two diseases, with an estimated annual incidence of 1 in 5000 male births and a prevalence of 1 in 12 000, compared with the estimated prevalence of around 1 in 30 000 male births for haemophilia B [3]. People with haemophilia are at risk of various types of bleeding (e.g. mucosal or joint bleeds), but those with severe haemophilia typically suffer from bleeding, both spontaneous and after light trauma, into joints which leads to crippling, painful arthritis due to haemarthrosis [4].

The main treatment available today is the infusion of concentrated plasma-derived or recombinant clotting factor into the vein, either as prophylaxis or as on-demand treatment [5,6]. A recent Cochrane systematic review concluded that there was strong evidence that prophylaxis preserves joint function in children with haemophilia compared with on-demand treatment [7]. A major difficulty is that adherence to current prophylactic treatment regimens is low in all

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age groups and this can limit treatment effectiveness [8,9]. Many factors are known to influence treatment adherence, such as knowledge about the disease and treatment, disease severity, treatment satisfaction [10–12] and frequency of administration [13].

Currently, the overriding aim of haemophilia care is to ensure the best possible quality of life for the individuals living with the disease. For this reason capturing quality of life data has become a relevant outcome measurement in clinical trials for new medical products in this disease area as for other chronic diseases [14,15]. In many areas the patients' perception of their well-being differs from that of their physician, and for health-related quality of life (HRQoL) and other outcome dimensions reported by patient-reported outcome (PRO) instruments, the patients' perception is most important [16]. Thus, it is recommended to use self-report instruments to assess PROs, except when this is not possible, i.e. children too young to understand the questions [17,18].

In the case of haemophilia, the perception of the impact of the disease is different for children and their parents, so this aspect should also be evaluated. PRO instruments can be generic (i.e. used across diseases) or disease-specific. These latter instruments are more sensitive to changes and can provide a more detailed assessment of the symptoms and difficulties associated with the specific diseases. In children self-report instruments need to be adapted to their age and development status [19]. In addition, when the instruments are used in multinational clinical trials they need to be translated and culturally adapted [18]. As treatment satisfaction can play an important role in treatment adherence, which in turn can impact treatment effectiveness, it is important to measure this as well [10,11].

The most widely used instruments for assessing HRQoL in haemophilia patients have been generic instruments such as the MOS 36-item Short-Form Health Survey (SF-36), EuroQol 5-Dimensions (EQ-5D) and the Child Health Questionnaire [20–22]. In particular, much of the research in paediatric haemophilia has, until recently, been based on ad hoc questions rather than standardized or psychometrically tested instruments [23]. Recent research has sought to address the lack of disease-specific instruments to assess HRQoL in individuals with haemophilia and a number of haemophilia-specific instruments that measure HRQoL and other dimensions, such as treatment satisfaction have been developed [21–25]. These instruments include the following:

- HRQoL
    - Canadian Haemophilia Outcomes Kids' Life Assessment Tool (CHO-KLAT) [26–28];
    - Haemo-QoL [23,29,30];
    - Haem-A-QoL [31,32];
    - Hemofilia-QoL [33,34];
    - Hemolatin-QoL [35,36];
    - MedTap (Haemo-QoL-A) [28,37]
  - Physical Functioning
    - Haemophilia Activity List [38,39];
    - HEP-Test-Q [40]
  - Treatment Satisfaction
    - Hemo-Sat [32,41]
- The advantage of the disease-specific instruments is that they are able to assess specific issues that are relevant to haemophilia. As such, these questionnaires are expected to be more sensitive to clinically significant changes [42]. In this study we focus on three haemophilia-specific PRO instruments, namely the Haemo-QoL, Haem-A-QoL and Hemo-Sat as follows:
- Haemo-QoL long form
    - CI: for children aged 4–7 years – contains 21 items in eight domains
    - CII: for children aged 8–12 years – contains 64 items in 10 domains
    - CIII: for children aged 13–16 years – contains 77 items in 12 domains
    - and corresponding parent-proxy forms (PI, PII and PIII)
  - Haemo-QoL short form
    - CI-SF: for children aged 4–7 years – contains 16 items
    - CII-III-SF: for children aged 8–16 years – contains 35 items
    - and corresponding parent-proxy forms (PI-SF, PII-III-SF)
  - Haemo-QoL-Index
    - for children aged 4–16 years with a self-report and parent-proxy version – contains eight items
  - Haem-A-QoL for adults >17 years – contains 46 items in 10 domains
  - Hemo-SAT: a patient satisfaction scale for parents (Hemo-Sat<sub>p</sub>) and adults (Hemo-Sat<sub>A</sub>) – contains 35 and 34 items, respectively, in six domains

The paediatric Haemo-QoL questionnaire was originally validated in 339 haemophilic children and their parents in German, Italian, French, Spanish, Dutch and English [23]; the psychometric characteristics were found to be satisfactory. Cronbach's alpha for the total Haemo-QoL score ranged from  $\alpha = 0.85$  for age groups I and II to  $\alpha = 0.91$  for age group III. The adult Haem-A-QoL was originally validated in 233 adult haemophilia patients in Italian [32] with good values for reliability. Cronbach's alpha for the Haem-A-QoL total score was  $\alpha = 0.96$ . The Hemo-SAT questionnaire, developed originally in 233 adult

haemophilia patients in Italian, is for assessing treatment satisfaction in parents of children with haemophilia (Hemo-Sat<sub>p</sub>) and in adults (Hemo-Sat<sub>A</sub>). The psychometric evaluation of the adult questionnaire gave satisfactory results, Cronbach's alpha for the Hemo-Sat<sub>A</sub> total score was  $\alpha = 0.90$  [32].

Given that haemophilia is a rare disease, clinical trials need to be multicentre to enable sufficient numbers of patients to be enrolled in trials, and this often requires international trials to be organized. As HRQoL is an important clinical outcome, it is essential to have validated questionnaires in diverse languages. Different cultures view the world in different ways and these differences are often reflected in the languages. These differences involve all aspects of life, including how people view their health and its effect on their physical well-being. Hence, translation of questionnaires cannot be simply word for word. The translation must capture the complex ideas represented by various concepts in different cultures and therefore a rigorous methodology for achieving this is needed [43–46].

The objectives of this study are to describe the process used for the translation of the Haemo-QoL, Haem-A-QoL and Hemo-Sat instruments and the types of difficulties encountered and the solutions that were found.

## Methods

Linguistic validation involves producing an appropriately translated version of the original instrument, which is usually done by specialized institutes using appropriate linguistic validation procedures. This is the first step in the cultural adaptation of an instrument; the second step is the psychometric testing which will be described in a future publication.

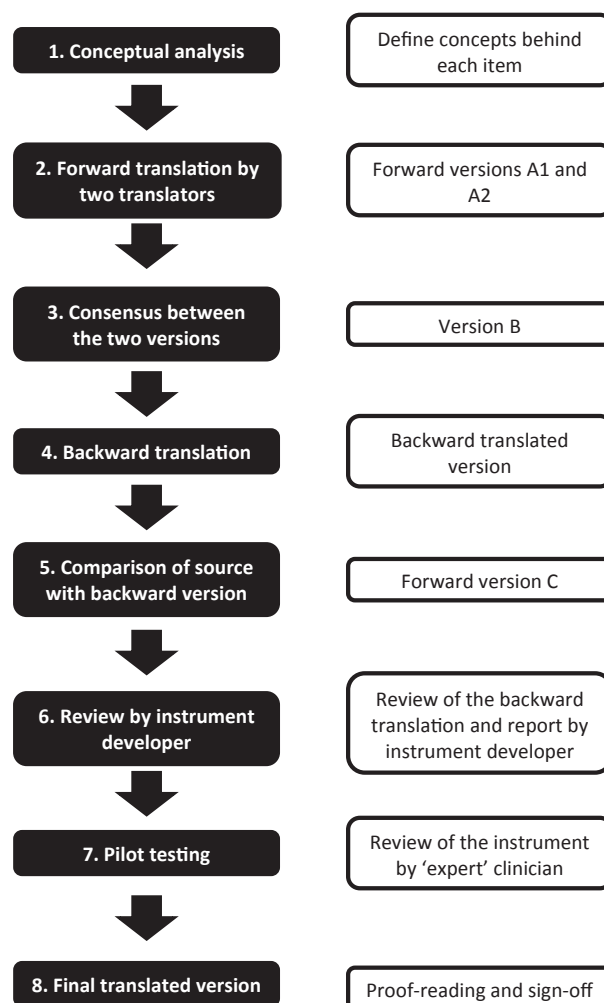
The original languages for the different instruments validated in this project were:

- Haemo-QoL – British English
- Haem-A-QoL – Italian
- Hemo-SAT – Italian

The instruments were translated into languages that can be grouped into six 'language families' (Indo-European, Ural-Altaic, Afro-Asiatic, Japonic, Sino-Tibetan and Austronesian) based on their origins (Table 1). The different language versions were developed using a standard linguistic validation process or a variation of this (Fig. 1 and Table 2). This process involved two independent forward translations by native speakers of the target language, a reconciliation step and one backward translation step by a native speaker of the original language (or adaptation step or quality check on existing version for some languages), review of the backward translation and backward translation report by the developer, and a review of

**Table 1.** The six language families for the 28 languages into which the haemophilia-specific PRO instruments were translated.

|               |                   |         |   |
|---------------|-------------------|---------|---|
| Indo-European | Germanic          | West    | Afrikaans, English (Canada, South Africa, USA), German (Switzerland)  |
|               | Italic            | North   | Danish, Icelandic, Norwegian, Swedish   |
|               |                   | Romance | French (Canada, France, Switzerland), Italian (Italy, Switzerland), Portuguese (Brazil), Romanian, Spanish (Spain, USA) |
| Ural-Altaic   | Balto-Slavic      | Slavic  | Croatian, Polish, Serbian   |
|               | Uralic            | Ugric   | Hungarian   |
| Afro-asiatic  | Semitic           | Finnic  | Finnish   |
|               |                   | Turkic  | Turkish   |
| Japonic       | Sinitic           |         | Hebrew (Israel)   |
| Sino-Tibetan  |                   |         | Japanese  |
| Austronesian  | Malayo-Polynesian |         | Mandarin Chinese (Taiwan)   |
|               |                   |         | Malay (Malaysia)  |



**Fig. 1.** Description of the linguistic validation process used.

**Table 2.** Methodology used for the translation of the Haemo-QoL long form (all six children and parent versions), Haem-A-QoL and Hemo-Sat instruments. The dark grey cells correspond to no translation to the language indicated for that instrument.

| Countries     | Languages  | Haemo-QoL<br>(parent and<br>children long<br>versions)   | Haem-A-QoL     | Hemo-Sat                             |                                      |
|---------------|--|--|----------------|--------------------------------------|--------------------------------------|
|               |  |  |                | Parent                               | Adult                                |
| Brazil        | Portuguese   | B on an existing translation, DR, CR                     |                | B on an existing translation, DR, CR |                                      |
| Canada        | French   | 2F, 1B, CR   |                | 2F, 1B, DR, CR                       |                                      |
| Canada        | English<br>(based on original<br>UK English version)                   | A, CR  |                | A, DR, CR                            |                                      |
| Croatia       | Croatian   | B on an existing translation, DR, CR                     |                | 2F, 1B, DR, CR                       |                                      |
| Denmark       | Danish   | B on an existing translation, DR, CR                     |                | B on an existing translation, DR, CR |                                      |
| Finland       | Finnish  | B on an existing translation, DR, CR                     |                |                                      |                                      |
| France        | French   | B on an existing translation, DR, CR                     |                |                                      | B on an existing translation, DR, CR |
| Hungary       | Hungarian  | B on an existing translation, DR, CR                     |                | B on an existing translation, DR, CR |                                      |
| Iceland       | Icelandic  | 2F, 1B, CR   |                |                                      |                                      |
| Israel        | Hebrew   | B on an existing translation, DR, CR                     | 2F, 1B, DR, CR |                                      | 2F, 1B, DR, CR                       |
| Italy         | Italian  | B on an existing translation, DR                         |                |                                      | B on an existing translation, DR     |
| Japan         | Japanese   | 2F, 1B, CR   |                | 2F, 1B, DR, CR                       |                                      |
| Malaysia      | Malay  | 2F, 1B, CR   |                | 2F, 1B, CR                           |                                      |
| Norwegian     | Norwegian  | 2F, 1B, CR   |                |                                      |                                      |
| Poland        | Polish   | B on an existing translation, DR, CR                     | 2F, 1B, DR, CR | B on an existing translation, DR, CR |                                      |
| Romania       | Romanian   | F (on the injection scale and open questions), B, DR, CR |                |                                      |                                      |
| Serbia        | Serbian  | 2F, 1B, CR   |                | 2F, 1B, CR                           |                                      |
| South Africa  | Afrikaans  | 2F, 1B, CR   |                |                                      |                                      |
| South Africa  | English (based on original UK English version)                         | A, CR  |                |                                      |                                      |
| Spanish       | Spain  | B on an existing translation, DR, CR                     |                | 2F, 1B, DR, CR                       |                                      |
| Sweden        | Swedish  | B on an existing translation, DR, CR                     |                |                                      |                                      |
| Switzerland   | French (based on French version for France)                            | A, DR, CR  |                |                                      | A, DR, CR                            |
| Switzerland   | German (based on German version for Germany produced by the developer) | A, DR, CR  |                |                                      | A, DR, CR                            |
| Switzerland   | Italian (based on Italian version for Italy)                           | A, DR, CR  |                |                                      | A, DR, CR                            |
| Taiwan        | Mandarin Chinese   | 2F, 1B, CR   |                | 2F, 1B, CR                           |                                      |
| Turkey        | Turkish  | F (on the injection scale and open questions), B, DR, CR |                | B on an existing translation, DR, CR |                                      |
| United States | English (based on original UK English version)                         | A, CR  |                | A, CR                                |                                      |
| United States | Spanish*   | 2F, 1B, CR   |                | 2F, 1B, CR                           |                                      |

F – Forward Translation Step: 2 translations by qualified translators => reconciliation.

B – Backward Translation Step: 1 translation by a qualified translator.

DR – Developer’s review of the backward translation and reports.

A – Adaptation Step: review and adaptation of the mother language version to the context of the target country.

CR – Clinician’s Review Step: review by a clinician appointed by the sponsor/developer.

\*Important remarks for US Spanish: to encompass the multiethnic dimension of US Spanish, the *forward* translations were produced by one Mexican and one South American translator, respectively, and reconciled during a meeting held by the consultant with the forward translators and three other translators of Caribbean, Mexican and Central American origins.

the forward translation by a clinician, native speaker of the target language. We extracted data from the reports of the linguistic validation process for each translation on the types of difficulties encountered and

solutions found. The types of difficulties encountered were grouped into four groups:

- Idiomatic (I)

Table 3. Most problematic items classified by type of difficulty: I = idiomatic; S = semantic; G = grammatical.

| Questionnaire and items  | Type    | Comments   | Examples   |
|--|---------|--|--|
| Haemo-QoL  |         |  |  |
| I felt on top of the world   | I       | A very idiomatic English expression for which various alternatives were used in the translated languages to be as close as possible to the original meaning  | 'I have felt super well' (French Canadian, US Spanish), 'I felt very happy' (Malay, Mandarin)  |
| I felt pleased with myself   | S       | In some languages, a direct equivalent would not have conveyed the original concept or would have been inappropriate. Other expressions were used  | 'I felt satisfied with myself' (Hebrew, Mandarin, Norwegian, US Spanish)   |
| I felt restricted by my parents  | S and G | In some languages, a literal translation would have sounded vague. Additional words had to be inserted to clarify the meaning. Some languages use the active form instead  | For example, 'I felt my parents were limiting me' (Afrikaans), 'I have felt that my parents have restricted me' (Norwegian)                            |
| I was a 'success' with my friends                                      | S       | This item was problematic in some languages: often misinterpreted as 'I was successful'. Other expressions were used   | 'I was popular' (Afrikaans, US English), 'I was popular among my friends' (Hebrew, Serbian)  |
| I avoided others to notice my illness                                  | S       | The meaning of original wording was not clear to all translators at the beginning. It is difficult, in the phrasing of the English, to ascertain whether the question asks about the respondent avoiding other people or avoiding others' attention. This generated a lot of discussion and the initial translations were then changed to reflect the original meaning | 'I did not want others to notice my illness' (SA and US English), 'I kept others unaware of my illness' (Japanese)                                     |
| Did you have to stay quiet (e.g. lie in bed) when you had bleeds?      | S       | The expression 'stay quiet' is ambiguous and can be confused with 'keep quiet', i.e. not talking. It was very often translated as 'stay calm' to avoid this confusion  | 'to stay still' (Afrikaans, Icelandic), 'to stay calm' (Mandarin, Polish, Turkish)   |
| My swellings hurt  | S       | Different alternatives were used for 'swellings' in various languages  | 'bruises' (CA and SA English), 'swollen areas' (Turkish), 'swollen parts' (Mandarin)   |
| ..I was unable to do as much with my friends because of my haemophilia | S       | The expression 'do as much' was not easy to translate in some languages and was often misinterpreted and clarification had to be brought as to the original meaning  | 'I could not do as many things' (Afrikaans, Mandarin, US Spanish), 'I was unable to do as many things' (Japanese)                                      |
| and then about haemophilia and your PERCEIVED SUPPORT                  | S       | 'Perceived support' very often translated using a paraphrase as a literal translation does not exist in most languages   | 'Support you felt you were receiving' (French for Canada and France), 'Support you get from others' (Hungarian), 'Support as you see it' (Japanese)    |
| I was able to participate at school in spite of my haemophilia         | S       | The intended meaning of the original 'participate at school' is 'go to school' according to the developer. However, in most languages a literal translation would not have conveyed this concept and other alternatives had to be found  | 'attend school' (Japanese, Malay, Polish, Turkish), 'got to school' (Icelandic, Hebrew, Hungarian, Mandarin)   |
| I was in control of my complaints due to haemophilia                   | S       | The expression 'was in control of' proved problematic to translate in several languages as a direct equivalent was inappropriate. Other more idiomatic alternatives were used  | 'I felt that my hemophilia symptoms were under control' (US English), 'I had control over my complaints' (German for Switzerland)                      |
| What about RELATIONSHIPS?  | S       | In some languages, additional wording was required to reflect the original meaning implied in 'relationships'  | 'relationships with girls' (Italian, French Canadian, Japanese), 'personal relationships' (Malay, Polish), or 'love relationships' (Croatian, Serbian) |
| ... I had to refrain from sports like rollerblading or soccer          | C       | The examples of sports were culturally adapted   | 'rugby or soccer' (SA English), 'ice-skating or sports like soccer' (Mandarin), 'soccer, skating or roller' (Romanian)                                 |
| Haemo-QoL CI (Young Child 4–7 version)                                 |         |  |  |
| I coped well with the assignments set in nursery school/kindergarten   | S       | 'Coped well' and 'assignments' not translated literally in some languages. Had to be adapted to common vocabulary used by young children   | 'I did well' (Mandarin, Serbian, US Spanish), 'tasks' (Afrikaans, Hungarian, Icelandic, Malay)   |
| Now, we would like to know about nursery school/kindergarten           | C       | Cultural adaptation of 'nursery school/kindergarten'. For example, 'Daycare/preschool' (Turkish), 'reception class or at preschool' (Polish)   |  |

(continued)

Table 3. (Continued).

| Questionnaire and items   | Type | Comments   | Examples   |
|---|------|--|--|
| Parent versions   |      |  |  |
| We really appreciate you taking the time to complete this questionnaire about your son's well-being and health-related quality of life. This questionnaire is similar to the version for your child. We would like to know your assessment of your child's well-being. Please complete the questionnaire yourself according to the instructions, i.e. without asking your child | S    | The term 'well-being' could not be translated literally in some languages. Other alternatives had to be found to render this concept | 'how your child feels' (Polish), 'health and happiness' (Serbian)  |
| Haem-A-QoL  |      |  |  |
| I didn't have the freedom to travel where I wanted  | S    | A direct translation was not felt to be acceptable in some languages. More idiomatic expressions were used                           | 'I was not free to travel where I wanted' (Afrikaans, Hebrew, Mandarin), 'I have not been able to travel freely where I wanted' (Finnish)                                      |
| My everyday work/school activities were endangered by my haemophilia  | S    | The word 'endangered' could not be translated literally in some languages. Other expressions as well as the active form were used    | 'jeopardized' (CA and US English, Japanese, Turkish), 'threatened' (Danish, Polish, Serbian), 'affected' (French Canadian, Malay, Mandarin)                                    |
| I was dependent on the factor concentrate because of my haemophilia   | S    | Different expressions were used for 'factor concentrate' in the translations   | 'factor product' (Danish), 'blood products' (Japanese), 'clotting factor' (Malay)  |
| What about PARTNERSHIP AND SEXUALITY?   | C    | 'Partnership' translated with different alternatives in some languages   | 'love relationships and sexuality' (Serbian), 'relationships and sexuality' (CA English, French Canadian, Norwegian, Romanian), 'personal relationships and sexuality' (Malay) |
| Hemo-SAT  |      |  |  |
| Ease and convenience  | S    | Direct translation was not appropriate in some languages. Other expressions were used  | 'simplicity and convenience' (Croatian), 'ease and comfort' (Hebrew, Turkish)  |
| I am satisfied with the availability of the person on duty at the centre/hospital   | S    | 'Availability' was not easy to translate literally in some languages   | 'with how I can get hold of staff' (Danish), 'with the fact that the staff is always available' (Japanese)   |

- Cultural (C)
- Grammatical (G)
- Semantic/conceptual (S)

The items that caused problems in several languages were identified and the solutions found were listed.

## Results

The questionnaires have been linguistically validated in up to 28 target languages: Haemo-QoL ( $n = 28$ ), Haem-A-QoL ( $n = 11$ ), Hemo-Sat ( $n = 21$ ) (Table 2). The items that presented the most difficulties are summarized in Table 3. We have listed 22 items for which problems were found, mainly concerning semantic/conceptual (17 items), cultural (three items), idiomatic (one item), and grammatical (one item) problems.

Only one idiomatic problem was identified – in the original Haemo-QoL CIII questionnaire: the wording was 'I felt on top of the world' (Table 4). In the English languages (Canada, South Africa, USA) the expression was kept and in Hebrew, a similar expression to the original was used: 'I felt like I was on top of the world'. In most of the other languages this item was translated using words such as 'happy' or 'good'.

Three items were classified as being cultural problems. The first on the Haemo-QoL CIII questionnaire: 'I had to refrain from sports like rollerblading or soccer' was addressed by adapting the sports to those played in the different countries (Table 5). The second on the Haemo-QoL CI version involved nursery school/kindergarten, which, due to the different educational systems, do not always exist or apply to the same age group, so this was adapted to the education systems in the different countries. The third was encountered in the translation of the Haem-A-QoL questionnaire and involved 'partnership and sexuality' – the term partnership had to be clarified using alternative terms in some languages (Table 3).

One item on the Haemo-QoL CIII questionnaire was found to present semantic and grammatical problems: 'I felt restricted by my parents' this needed more words to clarify the meaning and some languages chose to use an active form. The other 17 items were found to present semantic problems (Table 3). For example, on the Haemo-QoL CIII questionnaire, the question: 'What about relationships?' in which it was implicit that this was about relationships with girls, needed to be clarified in some languages such as Italian, by adding the word 'with girls' (Table 6). In other languages, such as

**Table 4.** Example of how the expression: 'I felt on top of the world' was culturally adapted in different language families.

|  |                       |                                      |                                      | CIII-HAEMO-QOL (adolescents 13–16 years old) |   |
|--|-----------------------|--------------------------------------|--------------------------------------|--|---|
|  |                       |                                      |                                      | I felt on top of the world                   |   |
| Languages by linguistic families and subfamilies |                       |                                      |                                      | Final version                                | Backtranslation of final version              |
| Indo-European                                    | Germanic              | West                                 | Afrikaans                            | het ek hoogs in my skik gevoel               | <i>I felt very happy</i>                      |
|  |                       |                                      | English (Canada)                     | I felt on top of the world.                  | NA  |
|  |                       |                                      | English (South Africa)               | I felt on top of the world.                  | NA  |
|  |                       |                                      | English (USA)                        | I felt on top of the world                   | NA  |
|  |                       |                                      | German (Switzerland)                 | fühlte ich mich wohl in meiner Haut          | <i>I felt good in my skin</i>                 |
|  |                       | North                                | Danish                               | har jeg følt mig på toppen                   | <i>I have felt on top</i>                     |
|  |                       |                                      | Icelandic                            | leið mér ákaflega vel                        | <i>I felt extremely good</i>                  |
|  |                       |                                      | Norwegian                            | har jeg følt meg helt på top                 | <i>I have felt totally on top</i>             |
|  |                       |                                      | Swedish                              | har jag mått toppen                          | <i>I have reached the top</i>                 |
|  |                       |                                      | Italianic                            | Romance                                      | French (Canada)                               |
|  | French (France)       | Je me suis senti vraiment bien       | <i>I have felt really well</i>       |  |   |
|  | French (Switzerland)  | Je me suis senti vraiment bien       | <i>I have felt really well</i>       |  |   |
|  | Italian (Italy)       | mi sentivo veramente al massimo      | <i>I felt really at maximum</i>      |  |   |
|  | Italian (Switzerland) | mi sono sentito veramente al massimo | <i>I have felt really at maximum</i> |  |   |
|  | Portuguese (Brazil)   | eu me senti ótimo                    | <i>I felt optimum</i>                |  |   |
|  | Romanian              | m-am simțit foarte bine              | <i>I felt very well</i>              |  |   |
|  | Spanish (Spain)       | me he sentido súper bien             | <i>I have felt super well</i>        |  |   |
|  | Spanish (USA)         | me senti super bien                  | <i>I felt super well</i>             |  |   |
|  | Balto-Slavic          | Slavic                               | Croatian                             | osjećao sam se stvarno dobro                 | <i>I felt really good</i>                     |
|  |                       |                                      | Polish                               | czułem się naprawdę dobrze                   | <i>I really felt good</i>                     |
| Serbian  |                       |                                      | osećao sam se sjajno                 | <i>I felt great</i>                          |   |
| Hungarian  |                       |                                      | fantasztikusan éreztem magam         | <i>I felt fantastic</i>                      |   |
| Finnish  |                       |                                      | minusta on tuntunut oikein hyvältä   | <i>I have felt really good</i>               |   |
| Ural-Altaic                                      | Altaic                | Turkic                               | Turkish                              | sevîncen uçuyordum                           | <i>I was so happy that I felt like flying</i> |
|  |                       |                                      | Hebrew                               | הרגשתי כאילו אני על פסגת העולם               | <i>I felt like I was on top of the world</i>  |
| Japonic  |                       |                                      | Japanese                             | 最高の気分だった。                                    | <i>I was feeling great</i>                    |
| Sino-Tibetan                                     | Sinitic               |                                      | Mandarin Chinese (Taiwan)            | 我覺得非常高興                                      | <i>I felt very happy</i>                      |
| Austronesian                                     | Malayo-Polynesian     |                                      | Malay for Malaysia                   | saya rasa sungguh gembira                    | <i>I felt very happy</i>                      |

Finnish, this was rephrased to ask about 'dating girls' and in Serbian the question asked about 'love relationships' (Table 6).

## Discussion

A rigorous method, i.e. a linguistic validation, has been used to translate the Haemo-QoL, Haem-A-QoL and Hemo-Sat instruments in up to 28 languages. Although some concepts were found to be difficult to adapt and translate into certain languages, these concepts were sufficiently well described so that equivalent concepts were found in various languages.

The methodology for the cultural and linguistic validation of these instruments usually requires pilot-testing in the population targeted; this is known as the cognitive interview. In this setting due to the population targeted, the instruments were validated only by clinicians who treat these patients. Although this methodology, called clinician's review, has been validated in some settings involving other rare populations, it has been suggested that a pragmatic approach is valid [47].

The cultural and linguistic adaptation of instruments such as this series of PRO instruments, which are destined to be used to evaluate HRQoL and treatment sat-

isfaction in patients with haemophilia in both clinical trials and clinical practice, is a pivotal step for increasing their usefulness and relevance. In many situations, clinical trials in haemophilia need to be multicentre to be able to recruit sufficient numbers of patients, and this often means that trials are international. If the data for the PROs are to be reliably collected and analysed, it is essential that the instruments in different target languages cover the same concepts, even if the wording has to be modified to reflect the equivalent concepts in the target languages [45]. Not all the instruments are available in all languages; however, further linguistic validations have been performed so that currently the Long Form of the Haemo-QoL is available for each age-group version in 34 languages for children and parents (additional 21 languages are available only for children aged 13–17 years). For the Short Form of the Haemo-QoL, 45 languages are available for children aged 8–17 years. Hemo-Sat is available both for adults and parents in 28 languages [29 languages for the adult version (Hemo-Sat<sub>A</sub>) and 37 languages for the parent version (Hemo-Sat<sub>P</sub>)], and Haem-A-QoL is available in 61 languages (a detailed list of languages can be provided by the corresponding author).

It is an added advantage that the Haemo-QoL questionnaires are available in parent-proxy versions; in

Table 5. Example of how the expression: 'I had to refrain from sports like rollerblading or soccer' was culturally adapted in different language families.

|  |              |         |                        | CIII-HAEMO-QOL (adolescents 13–16 years old)                                     |  |  |
|--|--------------|---------|------------------------|--|--|--|
|  |              |         |                        | ... I had to refrain from sports like rollerblading or soccer                    |  |  |
| Languages by linguistic families and subfamilies |              |         |                        | Final version  | Backward translation of final version  |  |
| Indo-European                                    | Germanic     | West    | Afrikaans              | moes ek my weerhou van sportsoorte soos rolskaats of sokker                      | <i>I had to withhold myself from sports such as roller-skating or soccer</i>                   |  |
|  |              |         | English (Canada)       | I couldn't do sports such as rollerblading or soccer                             |  |  |
|  |              |         | English (South Africa) | I could not do sports like rugby or soccer                                       |  |  |
|  |              |         | English (USA)          | I had to avoid sports like football or skateboarding                             |  |  |
|  |              |         | German (Switzerland)   | musste ich auf Sportarten wie Bladen/Skaten und Fussball verzichten              | <i>I had to give up sports such as blading/skating and football</i>                            |  |
|  |              |         | North                  | Danish   | har jeg været nødt til at lade være med at dyrke sport som f.eks. rulleskøjteløb eller fodbold | <i>I have had to stay away from sports like roller-skating and soccer</i>        |
|  |              |         |                        | Icelandic  | varð ég að sleppa íþróttum eins og línuskautum og fótbolta                                     | <i>I had to skip sports like soccer and roller</i>                               |
|  |              |         |                        | Norwegian  | har jeg måttet holde meg borte fra idretter som å stå på rulleskøyter eller fotball            | <i>I have had to stay away from sports to stand on skates or soccer</i>          |
|  |              |         |                        | Swedish  | har jag fått avstå från idrottsaktiviteter som t.ex. rullskridskoåkning eller fotboll          | <i>I have to refrain from sports activities such as roller-skating or soccer</i> |
|  | Italic       | Romance |                        | French (Canada)  | j'ai dû m'abstenir de faire des sports comme le patin à roues alignées ou le soccer            | <i>I had to abstain to do sports such as inline skating or soccer</i>            |
|  |              |         | French (France)        | j'ai dû renoncer aux sports tels que le patin à roulettes ou le foot             | <i>I had to give up sports such as skating or soccer</i>                                       |  |
|  |              |         | French (Switzerland)   | j'ai dû renoncer aux sports tels que le patin à roulettes ou le foot             | <i>I had to give up sports such as skating or soccer</i>                                       |  |
|  |              |         | Italian (Italy)        | ho dovuto rinunciare a sport come pattinare o giocare a calcio                   | <i>I had to give up sports such as skating or playing soccer</i>                               |  |
|  |              |         | Italian (Switzerland)  | ho dovuto rinunciare a sport come pattinare o giocare a calcio                   | <i>I had to give up sports such as skating or playing soccer</i>                               |  |
|  |              |         | Portuguese (Brazil)    | tive que evitar esportes como patinação/skate e futebol                          | <i>I had to avoid sports like skating and soccer</i>   |  |
|  |              |         | Romanian               | a trebuit să renunț la sporturi precum mersul cu rolele sau fotbalul             | <i>I had to give up sports like soccer, skating or roller</i>                                  |  |
|  |              |         | Spanish (Spain)        | he tenido que dejar de hacer deportes como patinar o jugar a fútbol              | <i>I had to stop doing sports such as skating or playing soccer</i>                            |  |
|  |              |         | Spanish (USA)          | tuve que dejar de hacer deportes como patinar o jugar fútbol                     | <i>I had to stop doing sports such as skating or playing soccer</i>                            |  |
| Ural-Altaic                                      | Balto-Slavic | Slavic  | Croatian               | morao sam se odreći sportova poput vožnje koturaljki ili nogometa                | <i>I had to give up sports such as rollerblading or soccer</i>                                 |  |
|  |              |         | Polish                 | musiałem zrezygnować z takich dyscyplin jak jazda na rolkach i piłka nożna       | <i>I had to resign from such disciplines as roller skating and soccer</i>                      |  |
|  |              |         | Serbian                | morao sam da izbegavam sportove poput vožnje rolera ili fudbala                  | <i>I had to avoid sports like roller-skating or soccer</i>                                     |  |
| Ural-Altaic                                      | Uralic       | Ugric   | Hungarian              | le kellett mondanom olyan sportokról, mint például a görkorcsolya vagy a futball | <i>I had to give up sports like rollerblading or soccer</i>                                    |  |
|  |              |         | Finnic                 | Finnish  | en ole voinut harrastaa esim. rullaluistelua ja jalkapalloa                                    | <i>I have not been able to go rollerblading or play soccer</i>                   |
| Ural-Altaic                                      | Altaic       | Turkic  | Turkish                | patenle kaymak veya futbol gibi sporlardan vazgeçmek zorunda kaldım              | <i>I had to give up sports such as skate, or soccer</i>  |  |
|  |              |         | Afro-asiatic           | Semitic  | Hebrew   | נאלצתי להימנע מפעילויות ספורט כמו החלקה על גלגליות או כדורגל                     |

(continued)



Table 5. (Continued).

| Languages by linguistic families and subfamilies |         |                           | CIII-HAEMO-QOL (adolescents 13–16 years old)   |  |
|--|---------|---------------------------|--|--|
|  |         |                           | Final version  | Backward translation of final version                                  |
| Japonic  |         | Japanese                  | ローラーブレードまたはサッカーなどのスポーツを控えなければならなかった。<br>我必須避免自己進行溜冰或足球之類的運動                                | <i>I had to refrain from sports such as roller blades or soccer</i>    |
| Sino-Tibetan                                     | Sinitic | Mandarin Chinese (Taiwan) | saya terpaksa menahan diri daripada bermain sukan-sukan seperti kasut roda atau bola sepak | <i>I refrained from playing sports such as roller skates or soccer</i> |

Table 6. Example of how the expression: ‘What about relationships?’ was culturally adapted in different language families.

| Languages by linguistic families and subfamilies |                       |                                       |                                       | CIII-HAEMO-QOL (adolescents 13–16 years old)       |   |
|--|-----------------------|---------------------------------------|---------------------------------------|--|---|
|  |                       |                                       |                                       | Final version                                      | Backward translation of final version           |
| Indo-European                                    | Germanic              | West                                  | Afrikaans                             | Wat van VERHOUDINGS?                               | <i>What about relationships?</i>                |
|  |                       |                                       | English (Canada)                      | What about RELATIONSHIPS...                        |   |
|  |                       |                                       | English (South Africa)                | What about RELATIONSHIPS?                          |   |
|  |                       |                                       | English (USA)                         | What about RELATIONSHIPS?                          |   |
|  |                       |                                       | German (Switzerland)                  | Wie sieht es aus mit BEZIEHUNGEN?                  |   |
|  |                       | North                                 | Danish                                | Hvad med FORHOLD?                                  | <i>What about relationships?</i>                |
|  |                       |                                       | Icelandic                             | Hvað um SAMBÖND?                                   | <i>What about relationships?</i>                |
|  |                       |                                       | Norwegian                             | Hva med FORHOLD?                                   | <i>What about relationships?</i>                |
|  |                       |                                       | Swedish                               | Hur är det med FÖRHÅLLANDEN?                       | <i>What about relationships?</i>                |
|  |                       |                                       | Italic                                | Romance  | French (Canada)                                 |
|  | French (France)       | Que penses-tu de tes RELATIONS ?      |                                       |  | <i>What do you think of your relationships?</i> |
|  | French (Switzerland)  | Que penses-tu de tes RELATIONS ?      |                                       |  | <i>What do you think of your relationships?</i> |
|  | Italian (Italy)       | Come vanno i RAPPORTI CON LE RAGAZZE? |                                       |  | <i>How are the relations with the girls?</i>    |
|  | Italian (Switzerland) | Come vanno i RAPPORTI CON LE RAGAZZE? |                                       |  | <i>How are the relations with the girls?</i>    |
|  |                       |                                       | Portuguese (Brazil)                   | E no que diz respeito a RELACIONAMENTOS?           | <i>And what about relationships?</i>            |
| Romanian   |                       |                                       | Ce se întâmplă cu RELAȚIILE?          | <i>What happens to relationships?</i>              |   |
| Spanish (Spain)                                  |                       |                                       | Qué piensas de tus RELACIONES?        | <i>What do you think of your relationships?</i>    |   |
| Spanish (USA)                                    |                       |                                       | Qué piensas acerca de tus RELACIONES? | <i>What do you think about your relationships?</i> |   |
| Balto-Slavic                                     |                       |                                       | Slavic                                | Croatian   | Kakvo je stanje u LJUBAVNIM VEZAMA?             |
|  | Polish                | Jak układają się ZWIĄZKI PARTNERSKIE? |                                       | <i>How are personal relationships?</i>             |   |
|  | Serbian               | A šta o tvojim LJUBAVNIM VEZAMA?      |                                       | <i>And what about your love relationship?</i>      |   |
| Ural-Altai                                       | Uralic                | Ugric                                 | Hungarian                             | Mi a helyzet a KAPCSOLATAIDDAL?                    | <i>What about relationships?</i>                |
|  |                       |                                       | Finnic                                | Finnish  | Mitä ajattelset SEURUSTELUSTA TYTTÖJEN KANSSA?  |
| Afro-asiatic                                     | Semitic               | Turkic                                | Turkish                               | İLİŞKİLERİN nasıl?                                 | <i>How are relationships?</i>                   |
|  |                       |                                       | Hebrew                                | מה בנוגע למערכות יחסים?                            | <i>What about relationships?</i>                |
| Japonic  |                       | Japanese                              | 女の子たちとの関係についてはどうですか？                  | <i>How about relationships with girls?</i>         |   |
| Sino-Tibetan                                     | Sinitic               | Mandarin Chinese (Taiwan)             | 對於感情的看法？                              | <i>Views about relationships?</i>                  |   |
| Austronesian                                     | Malayo-Polynesian     | Malay for Malaysia                    | Bagaimana dengan HUBUNGAN PERIBADI?   | <i>What about personal relationships?</i>          |   |

haemophilia, as in other chronic conditions, the child's perception of their disease status can be different from that of their parents' perception. Results from a systematic review suggest that parents are able to assess more accurately their child's physical functioning and symptoms than less visible domains, such as social or emotional functioning [19]. The obvious differences between the perspectives of sick children and their healthy parents are a source of increased knowledge and understanding of their HRQoL [19].

To ensure that the conceptual equivalence between the original and translated versions is maintained it is essential to follow internationally validated processes supervised by experts in the field [48,49]. The cultural and linguistic adaptation is an important first step to ensure the validation of these instruments in other languages. The next step is the psychometric validation of each of the new language versions [43,45].

## Conclusions

After the rigorous validation process a large number of different language versions of these instruments that are conceptually and linguistically equivalent to the originals were obtained. The instruments can be used in clinical trials and clinical practice for haemophilia facilitating international comparison and pooling of

data and will provide new insights into areas of haemophilia that remain poorly understood today.

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All authors substantially contributed to research design, or the acquisition, analysis or interpretation of data, drafted the manuscript or revised it critically, and approved the submitted, final version.

## Author contribution

In addition, the authors' specific contributions to the work described in this manuscript were as follows: SvM performed the research and interpreted the data. IGC analysed and interpreted the data. CA analysed and interpreted the data. MSL performed the research and interpreted the data.

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