VALIDATION STUDIES

The Estonian version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR)

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Abstract
The Juvenile Arthritis Multidimensional Assessment Report (JAMAR) is a new parent/patient-reported outcome measure that enables a thorough assessment of the disease status in children with juvenile idiopathic arthritis (JIA). We report the results of the cross-cultural adaptation and validation of the parent and patient versions of the JAMAR in the Estonian language. The reading comprehension of the questionnaire was tested in 10 JIA parents and patients. Each participating centre was asked to collect demographic, clinical data and the JAMAR in 100 consecutive JIA patients or all consecutive patients seen in a 6-month period and to administer the JAMAR to 100 healthy children and their parents. The statistical validation phase explored descriptive statistics and the psychometric issues of the JAMAR: the three Likert assumptions, floor/ceiling effects, internal consistency, Cronbach’s alpha, interscale correlations, test–retest reliability, and construct validity (convergent and discriminant validity). A total of 110 JIA patients (71.8% oligoarticular, 18.2% RF-negative polyarthritis, 10% other categories) and 98 healthy children were enrolled in one paediatric rheumatology centre. Notably, none of the enrolled JIA patients is affected with systemic JIA. The JAMAR components discriminated healthy subjects from JIA patients, except for the Paediatric Rheumatology Quality of Life (HRQoL) Psychosocial Health (PsH) subscales and for the satisfaction with current health status. All JAMAR components revealed good psychometric performances. In conclusion, the Estonian version of the JAMAR is a valid tool for the assessment of children with JIA and is suitable for use both in routine clinical practice and clinical research.

Keywords Juvenile idiopathic arthritis · Disease status · Functional ability · Health-related quality of life · JAMAR

Introduction
The aim of the present study was to cross-culturally adapt and validate the Estonian parent, child/adult version of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) [1] in patients with juvenile idiopathic arthritis

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The JAMAR assesses the most relevant parent/patient-reported outcomes in JIA, including overall well-being, functional status, health-related quality of life (HRQoL), pain, morning stiffness, disease activity/status/course, articular and extra-articular involvement, drug-related side effects/compliance and satisfaction with illness outcome.

This project was part of a larger multinational study conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO) [2] aimed to evaluate the Epidemiology, Outcome and Treatment of Childhood Arthritis (EPOCA) in different geographic areas [3].

We report herein the results of the cross-cultural adaptation and validation of the parent and patient versions of the JAMAR in the Estonian language.

**Materials and methods**

The methodology employed has been described in detail in the introductory paper of the supplement [4]. In brief, it was a cross-sectional study of JIA children, classified according to the ILAR criteria [5, 6] and enrolled from October 2011 to July 2013. Children were recruited after Ethics Committee approval and consent from at least one parent.

**The JAMAR**

The JAMAR [1] includes the following 15 sections:

1. **Assessment of physical function (PF)** using 15 items in which the ability of the child to perform each task is scored as follows: 0 = without difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do and not applicable if it was not possible to answer the question or the patient was unable to perform the task due to their young age or to reasons other than JIA. The total PF score ranges from 0 to 45 and has three components: PF-lower limbs (PF-LL); PF-hand and wrist (PF-HW) and PF-upper segment (PF-US) each scoring from 0 to 15 [7]. Higher scores indicating higher degree of disability [8–10].

2. **Rating of the intensity of the patient’s pain** on a 21-numbered circle visual analogue scale (VAS) [11].

3. **Assessment of the presence of joint pain or swelling** (present/absent for each joint).

4. **Assessment of morning stiffness** (present/absent).

5. **Assessment of extra-articular symptoms** (fever and rash) (present/absent).

6. **Rating of the level of disease activity** on a 21-circle VAS.

7. **Rating of disease status at the time of the visit** (categorical scale).

8. **Rating of disease course from previous visit** (categorical scale).

9. **Checklist of the medications the patient is taking** (list of choices).

10. **Checklist of side effects of medications**.

11. **Report of difficulties with medication administration** (list of items).

12. **Report of school/university/work problems caused by the disease** (list of items).

13. **Assessment of HRQoL**, through the Physical Health (PhH), and Psychosocial Health (PsH) subscales (five items each) and a total score. The four-point Likert response, referring to the prior month, are ‘never’ (score = 0), ‘sometimes’ (score = 1), ‘most of the time’ (score = 2) and ‘all the time’ (score = 3). A ‘not assessable’ column was included in the parent version of the questionnaire to designate questions that cannot be answered because of developmental immaturity. The total HRQoL score ranges from 0 to 30, with higher scores indicating worse HRQoL. A separate score for PhH and PsH (range 0–15) can be calculated [12–14].

14. **Rating of the patient’s overall well-being** on a 21-numbered circle VAS.

15. **A question about satisfaction with the outcome of the illness** (Yes/No) [15].

The JAMAR is available in three versions, one for parent proxy-report (child’s age 2–18), one for child self-report, with the suggested age range of 7–18 years, and one for adults.

**Cross-cultural adaptation and validation**

The process of cross-cultural adaptation was conducted according to the international guidelines with 2–3 forward and backward translations. In those countries for which the translation of JAMAR had been already cross-cultural adapted in a similar language (i.e. Spanish in South American countries), only the probe technique was performed. Reading comprehension and understanding of the translated questionnaires were tested in a probe sample of 10 JIA parents and 10 patients.

Each participating centre was asked to collect demographic, clinical data and the JAMAR in 100 consecutive JIA patients or all consecutive patients seen in a 6-month period and to administer the JAMAR to 100 healthy children and their parents.

The statistical validation phase explored the descriptive statistics and the psychometric issues [16]. In particular, we evaluated the following validity components: the first Likert assumption [mean and standard deviation (SD) equivalence]; the second Likert assumption or equal item–scale correlations (Pearson $r$; all items within a scale should contribute...
equally to the total score); third Likert assumption (item internal consistency or linearity for which each item of a scale should be linearly related to the total score that is 90% of the items should have Pearson $r \geq 0.4$); floor/ceiling effects (frequency of items at lower and higher extremes of the scales, respectively); internal consistency, measured by the Cronbach’s alpha, interscale correlation (the correlation between two scales should be lower than their reliability coefficients, as measured by Cronbach’s alpha); test–retest reliability or intra-class correlation coefficient (reproducibility of the JAMAR repeated after 1 or 2 weeks); and construct validity in its two components: the convergent or external validity which examines the correlation of the JAMAR subscales with the six JIA core set variables, with the addition of the parent assessment of disease activity and pain by the Spearman’s correlation coefficients ($r$) [17] and the discriminant validity, which assesses whether the JAMAR discriminates between the different JIA categories and healthy children [18]. Quantitative data were reported as medians with 1st and 3rd quartiles and categorical data as absolute frequencies and percentages.

The complete Estonian parent and patient versions of the JAMAR are available upon request to PRINTO.

**Results**

**Cross-cultural adaptation**

The Estonian JAMAR was fully cross-culturally adapted with two forward and two backward translations. The concordance rate between the original standard English version of the JAMAR and the two back-translations was 94.5% (115/123 lines) for the parent version and 97.5% (117/120 lines) for the child version.

All 123 lines of the parent version of the JAMAR were understood by at least 80% of the 10 parents tested (median = 100%; range 90–100%). Of the 120 lines in the patient version of the JAMAR, 113 (94%) lines were understood by at least 80% of the children (median = 100%; range 10–100%). Lines 3, 10, 29, 48, 94, 116, 119 of the child version of the JAMAR were modified considering patients’ suggestions.

**Demographic and clinical characteristics of the subjects**

A total of 110 JIA patients and 100 healthy children (total of 210 subjects) were enrolled at the paediatric rheumatology centre of Tartu University Hospital, Children’s Clinic. Two healthy children did not give the consent to use their data.

In the 110 JIA subjects, the JIA categories were 71.8% with oligoarthritis, 18.2% with RF-negative polyarthritis, 1.8% with RF-positive polyarthritis, 1.8% with psoriatic arthritis, 1.8% with enthesitis-related arthritis and 4.6% with undifferentiated arthritis. Notably, none of the enrolled JIA patients is affected with systemic JIA (Table 1).

All the 208 subjects had the parent version of the JAMAR completed by a parent (110 from parents of JIA patients and 98 from parents of healthy children). The JAMAR was completed by 192/208 (92.3%) mothers and 16/208 (7.7%) fathers. The child version of the JAMAR was completed by 205/208 (98.5%) children age 7.5 or older.

**Discriminant validity**

The JAMAR results are presented in Table 1, including the scores (median (1st–3rd quartile)) obtained for the PF, the PhH, the PsH subscales and total score of the HRQoL scales. The JAMAR components discriminated well between healthy subjects and JIA patients.

In summary, the JAMAR revealed that JIA patients had a greater level of disability and pain, as well as a lower HRQoL than their healthy peers. However, there was no significant difference between healthy subjects and their affected peers in psychosocial quality of life items and satisfaction with current health status.

**Psychometric issues**

The main psychometric properties of both parent and child versions of the JAMAR are reported in Table 2. “Results” refers mainly to the parent’s version findings, unless otherwise specified.

**Descriptive statistics (first Likert assumption)**

There were no missing results for all JAMAR items since data were collected through a web-based system that did not allow to skip answers and input null values. The response pattern for both PF and HRQoL was positively skewed toward normal functional ability and normal HRQoL. All response choices were used for the different HRQoL items except for items 1 and 8, whereas a reduced number of response choices were used for all the PF items except for item 4. The mean and SD of the items within a scale were roughly equivalent for the PF and for the HRQoL items, except for HRQoL items 1 and 8 (data not shown). The median number of items marked as not applicable was 0% (0–0%) for the PF and 1% (1–1%) for the HRQoL.
Table 1 Descriptive statistics (medians, 1st–3rd quartiles or absolute frequencies and %) for the 110 JIA patients

| Oligoarthritis | RF – poly-arthritis | RF+ poly-arthritis | Psoriatic arthritis | Enthesitis-related arthritis | Undifferentiated arthritis | All JIA patients | Healthy |
|---------------|---------------------|-------------------|--------------------|-----------------------------|----------------------------|-------------------|---------|
| N = 79        | N = 20              | N = 2             | N = 2              | N = 2                       | N = 5                      | N = 110           | N = 98  |
| Female        |                     |                   |                    |                             |                            |                   |         |
| 43 (54.4%)    | 12 (60%)            | 2 (100%)          | 0 (0%)             | 0 (0%)                      | 3 (60%)                    | 60 (54.5%)        | 52 (53.1%)|
| Age at visit  |                     |                   |                    |                             |                            |                   |         |
| 13.7 (10.6–15.5) | 15 (13.1–16.8)  | 14.2 (13.3–15.1) | 15 (15.5–15.1)     | 16.5 (16.1–17)              | 13.1 (9.7–16)             | 14.3 (11.1–15.8) | 11.2 (9.3–14.2)* |
| Age at onset  |                     |                   |                    |                             |                            |                   |         |
| 9.9 (5.9–11.9) | 10.3 (7.5–13.4)    | 11.4 (9.9–12.8)   | 7.7 (6.2–9.1)      | 15.8 (15.4–16.2)            | 12.4 (8.6–14.3)          | 10 (6.4–12.1)    |         |
| Disease duration | 3.7 (1.9–5.8)  | 3.6 (2.8–5.1)     | 2.9 (2.3–3.4)      | 7.4 (6.8–8.8)               | 0.7 (0.6–0.8)             | 1.7 (1.6–1.9)    | 3.5 (1.9–5.6)* |
| ESR           | 4 (2–7)             | 5 (2.5–6)         | 3 (3–3)            | 2 (2–2)                     | 1.5 (1–2)                  | 3 (1–6.5)         | 4 (2–7) |
| MD VAS        | 3 (2–4)             | 3 (2–5)           | 5 (5–5)            | 0 (0–0)                     | 3 (2–4)                   | 2 (2–4)          | 3 (2–4) |
| No. of swollen joints | 1 (0–2)  | 0 (0–1.5)         | 0.5 (0–1)          | 3 (0–6)                     | 0 (0–0)                   | 0 (0–1)          | 0 (0–1)* |
| No. of joints with pain | 0 (0–1)  | 0.5 (0–3.5)       | 3 (3–3)            | 0 (0–0)                     | 3 (2–4)                   | 0 (0–1)          | 0 (0–1)* |
| No. of joints with LOM | 0 (0–1)  | 0 (0–2)           | 0.5 (0–1)          | 0 (0–0)                     | 0 (0–0)                   | 0 (0–1)          | 1 (0–2) |
| No. active joints | 1 (0–2)  | 0 (0–2)           | 0 (0–2)            | 0 (0–0)                     | 0 (0–0)                   | 0 (0–1)          | 1 (0–2) |
| Active systemic features | 0 (0%)  | 0 (0%)            | 0 (0%)             | 0 (0%)                      | 0 (0%)                    | 0 (0%)            | 0 (0%)  |
| ANA status    | 4 (5.1%)            | 5 (25%)           | 1 (50%)            | 0 (0%)                      | 1 (50%)                   | 0 (0%)            | 11 (10%)|
| Uveitis       | 0 (0%)              | 0 (0%)            | 0 (0%)             | 0 (0%)                      | 0 (0%)                    | 0 (0%)            | 0 (0%)  |
| PF total score | 2 (0–4)             | 1.5 (0–6.5)       | 8.5 (5–12)         | 3 (2–4)                     | 5 (3–7)                   | 2 (0–7)          | 2 (0–4) |
| Pain VAS      | 2.5 (0–4.5)         | 2.3 (0.5–4)       | 4.3 (3.5–5)        | 2.3 (0.5–4)                 | 3.5 (1–6)                 | 4 (2–5)          | 2.5 (0.5–4) |
| Disease activity VAS | 2.5 (0.5–4) | 1.8 (0–5.4)       | 3.8 (3.5–4)        | 3.3 (1–5.5)                 | 3.3 (1–5.5)               | 2 (0.5–3)        | 2.3 (0.5–4) |
| Well-being VAS | 2.5 (0–4)          | 1.8 (0–4.3)       | 4.8 (3.5–6)        | 3.8 (3–0.6)                 | 3.8 (1–6.5)               | 3.5 (0–5)        | 2 (0.5–4) |
| HRQoL. PhH    | 3 (1–6)             | 3.5 (1–6.5)       | 4.5 (3–6)          | 4 (4–4)                     | 6 (2–10)                  | 4 (3–7)          | 3 (1–6) |
| HRQoL. PsH    | 2 (0–5)             | 3 (0–5)           | 3.5 (0–7)          | 3.5 (3–4)                   | 3 (1–5)                   | 5 (4–6)          | 2.5 (0–5) |
| HRQoL. total score | 6 (2–10)         | 6.5 (3–11)        | 8.3 (3–13)         | 7.5 (7–8)                   | 9 (3–15)                  | 8 (8–15)         | 6 (3–10) |
| Pain/swell. in > 1 joint | 43 (54.4%) | 12 (60%)          | 1 (50%)            | 1 (50%)                     | 1 (50%)                   | 3 (60%)           | 61 (55.5%)|
| Morning stiffness>15 min | 14 (17.7%) | 7 (35%)          | 0 (0%)             | 0 (0%)                      | 1 (50%)                   | 1 (20%)           | 23 (20.9%) |
| Subjective remission | 54 (68.4%) | 15 (75%)          | 2 (100%)           | 2 (100%)                    | 2 (100%)                  | 4 (80%)           | 79 (71.8%)|
| In treatment  | 78 (98.7%)          | 19 (95%)          | 2 (100%)           | 2 (100%)                    | 2 (100%)                  | 5 (100%)          | 108 (98.2%) |
| Reporting side effects | 18/78 (23.1%) | 6/19 (31.6%)     | 1 (50%)            | 1 (50%)                     | 1 (50%)                   | 2 (40%)           | 29/108 (26.9%) |
| Taking medication regularly | 71/78 (91%) | 18/19 (94.7%)   | 1 (50%)            | 2 (100%)                    | 2 (100%)                  | 5 (100%)          | 99/108 (91.7%) |
| With problems attending school | 15/48 (31.3%) | 5/13 (38.5%)     | 1 (50%)            | 0 (0%)                      | 0 (0%)                    | 1/2 (50%)         | 22/67 (32.8%) |
| Satisfied with disease outcome | 63 (79.7%) | 17 (85%)         | 2 (100%)           | 2 (100%)                    | 2 (100%)                  | 5 (100%)          | 91 (82.7%) |

Data related to the JAMAR refers to the 110 JIA patients and to the 98 healthy subjects for whom the questionnaire has been completed by the parents.

*JAMAR* Juvenile Arthritis Multidimensional Assessment Report, *ESR* erythrocyte sedimentation rate, *MD* Medical doctor, *VAS* visual analogue scale (score 0–10; 0 = no activity, 10 = maximum activity), *LOM* limitation of motion, *ANA* anti-nuclear antibodies, *PF* physical function (total score ranges from 0 to 45), *HRQoL* health-related quality of life (total score ranges from 0 to 30), *PhH* physical health (total score ranges from 0 to 15), *PsH* psychosocial health (total score ranges from 0 to 15).

*p* values refer to the comparison of the different JIA categories or to JIA versus healthy. *p* < 0.05 **p < 0.001 *p < 0.0001
**Table 2** Main psychometric characteristics between the parent and child version of the JAMAR

| Missing values (1st–3rd quartiles) | Parent \(N=110/208\) | Child \(N=110/205\) |
|------------------------------------|----------------------|---------------------|
| Response pattern                    | No missing values    | No missing values    |
| Floor effect, median               |                      |                     |
| PF                                 | 86.4%                | 88.2%               |
| HRQoL PhH                          | 48.2%                | 55.5%               |
| HRQoL PsH                          | 51.8%                | 59.1%               |
| Pain VAS                           | 21.8%                | 24.5%               |
| Disease activity VAS               | 21.8%                | 23.6%               |
| Well-being VAS                     | 22.7%                | 33.6%               |
| Ceiling effect, median             |                      |                     |
| PF                                 | 0.0%                 | 0.0%                |
| HRQoL PhH                          | 1.8%                 | 0.9%                |
| HRQoL PsH                          | 1.8%                 | 0.9%                |
| Pain VAS                           | 0.9%                 | 0.9%                |
| Disease activity VAS               | 0.9%                 | 0.9%                |
| Well-being VAS                     | 1.8%                 | 0.9%                |
| Items with equivalent item–scale correlation | 80% for PF, 100% for HRQoL | 87% for PF, 80% for HRQoL |
| Items with item–scale correlation ≥ 0.4 | 80% for PF, 100% for HRQoL | 87% for PF, 80% for HRQoL |
| Cronbach’s alpha                   |                      |                     |
| PF-L                              | 0.79                 | 0.77                |
| PF-HW                             | 0.64                 | 0.77                |
| PF-US                             | 0.76                 | 0.72                |
| HRQoL-PhH                         | 0.84                 | 0.78                |
| HRQoL-PsH                         | 0.82                 | 0.77                |
| Items with item–scale correlation lower than the Cronbach’s alpha | 93% for PF, 100% for HRQoL | 100% for PF, 100% for HRQoL |
| Test–retest intraclass correlation |                      |                     |
| PF total score                    | 1.0                  | 0.99                |
| HRQoL-PhH                         | 1.0                  | 1.0                 |
| HRQoL-PsH                         | 1.0                  | 1.0                 |
| Spearman correlation with JIA core set variables, median |                      |                     |
| PF                                | 0.5                  | 0.4                 |
| HRQoL PhH                         | 0.4                  | 0.4                 |
| HRQoL PsH                         | 0.2                  | 0.3                 |
| Pain VAS                          | 0.1                  | 0.1                 |
| Disease activity VAS              | 0.2                  | 0.1                 |
| Well-being VAS                    | 0.1                  | 0.1                 |

*JAMAR* Juvenile Arthritis Multidimensional Assessment Report, *JIA* juvenile idiopathic arthritis, *VAS* visual analogue scale, *PF* physical function, *HRQoL* health-related quality of life, *PhH* physical health, *PsH* psychosocial health, *PF-LL* PF-lower limbs, *PF-HW* PF-hand and wrist, *PF-US* PF-upper segment

**Floor and ceiling effect**

The median floor effect was 86.4% (69.1–91.8%) for the PF items, 48.2% (23.6–53.6%) for the HRQoL PhH items, and 51.8% (46.4–52.7%) for the HRQoL PsH items. The median ceiling effect was 0% (0–0.0%) for the PF items, 1.8% (0.9–5.5%) for the HRQoL PhH items, and 1.8% (1.8–3.6%) for the HRQoL PsH items. The median floor effect was 21.8% for the pain VAS, 21.8% for the disease activity VAS and 22.7% for the well-being VAS. The median ceiling effect was 0.9% for the pain VAS, 0.9% for the disease activity VAS and 1.8% for the well-being VAS.
Equal item–scale correlations (second Likert assumption)

Pearson item–scale correlations corrected for overlap were roughly equivalent for items within a scale for 80% of the PF items, with the exception of PF items 9, 11 and 15, and for 100% of the HRQoL items.

Items’ internal consistency (third Likert assumption)

Pearson item–scale correlations were ≥ 0.4 for 80% of items of the PF (except for PF items 9, 10 and 15) and 100% of items of the HRQoL.

Cronbach’s alpha internal consistency

Cronbach’s alpha was 0.79 for PF-LL, 0.64 for PF-HW, and 0.76 for PF-US. Cronbach’s alpha was 0.84 for HRQoL-PhH and 0.82 for HRQoL-PsH.

Interscale correlation

The Pearson correlation of each item of the PF and the HRQoL with all items included in the remaining scales of the questionnaires was lower than the Cronbach’s alpha except for the PF item 8.

Test–retest reliability

Reliability was assessed in 10 JIA patients, by re-administering both versions (parent and child) of the JAMAR after a median of 1 day (0–5 days). The intraclass correlation coefficients (ICC) for the PF total score showed an almost perfect reproducibility (ICC = 1.0). The ICC for the HRQoL PhH and for the HRQoL PsH showed an almost perfect reproducibility (ICC = 1 for both).

Convergent validity

The Spearman correlation of the PF total score with the JIA core set of outcome variables ranged from 0.1 to 0.6 (median = 0.5). The PF total score best correlation was observed with the parent assessment of pain (r = 0.7, p < 0.001) and the PsH with the parent global assessment of well-being (r = 0.5, p < 0.001). The median correlations between the pain VAS, the well-being VAS, and the disease activity VAS and the physician-centred and laboratory measures were 0.1 (0.1–0.3), 0.2 (0.2–0.3), 0.1 (0.03–0.2), respectively.

Discussion

In this study, the Estonian version of the JAMAR was fully cross-culturally adapted from the original standard English version with two forward and two backward translations. According to the results of the validation analysis, the Estonian parent and patient versions of the JAMAR possess satisfactory psychometric properties. The disease-specific components of the questionnaire discriminated well between patients with JIA and healthy controls. Notably, there was no significant difference between the healthy subjects and their affected peers in the psychosocial quality of life and in the satisfaction with disease outcome variables. This finding indicates that children with JIA adapt well to the consequences of JIA.

Psychometric performances were good for all domains of the JAMAR with few exceptions: three PF items (open a door by lowering the handle, open and close a tap or open a previously open jar and bite a sandwich or an apple) showed a lower items internal consistency and the Cronbach’s alpha for PF-HW was questionable. However, the overall internal consistency for the remaining domains was good.

In the external validity evaluation, the Spearman’s correlations of the PF and HRQoL scores with JIA core set parameters ranged from very weak to moderate.

The results obtained for the parent version of the JAMAR are very similar to those obtained for the child version, which suggests that children are equally reliable proxy reporters of their disease and health status as their parents. The JAMAR is aimed to evaluate the side effects of medications and school attendance, which are other dimensions of daily life that were not previously considered by other HRQoL tools. This may provide useful information for intervention and follow-up in health care.

In conclusion, the Estonian version of the JAMAR was found to have satisfactory psychometric properties and it is, thus, a reliable and valid tool for the multidimensional assessment of children with JIA.

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Ethical approval
Son and Dr. Pruunsild have nothing to disclose.

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Compliance with ethical standards

Conflict of interest
Dr. Ruperto has received grants from BMS, Hoffman-LaRoche, Janssen, Novartis, Pfizer, Sobi, during the conduct of the study and personal fees and speaker honorarium from Abbvie, Aplysyn, AstraZeneca, Baxalta Biosimilars, Biogen Idec, Boehringer, Bristol Myers Squibb, Celgene, Eli-Lilly, EMD Serono, Gilead Sciences, Janssen, Medimmune, Novartis, Pfizer, Rpharm, Roche, Sanofi, Servier and Takeda. Dr. Consolaro, Dr. Bovis, Dr. Ilisson and Dr. Pruunsild have nothing to disclose.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent
Informed consent was obtained from all individual participants included in the study as per the requirement of the local ethical committee.

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