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Patient perspective on remission in rheumatoid arthritis: Validation of patient reported outcome instruments to measure absence of disease activity

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ABSTRACT

Objective: Patients have identified pain, fatigue and independence as the most important domains that need to be improved to define remission in rheumatoid arthritis (RA). This study identified and validated instruments for these domains and evaluated their added value to the ACR/EULAR Boolean remission definition.
Methods: Patients with a 28-joint Disease Activity Score (DAS28) ≤3.2 or in self-perceived remission (declaring their disease activity 'as good as gone') from the Netherlands, Portugal, Australia, and Canada, were assessed at 0, 3 and 6 months for patient-reported outcomes and the WHO-ILAR RA core set. Instrument validity was evaluated cross-sectionally, longitudinally and for the ability to predict future good outcome in terms of physical functioning. Logistic regression quantified the added value to Boolean remission.
Results: Of 246 patients, 152 were also assessed at 3, and 142 at 6 months. Most instruments demonstrated construct validity and discriminative capacity. Pain and fatigue were best captured by a simple numerical rating scale (NRS). Measurement of independence proved more complex, but a newly developed independence NRS was preferred. NRS for pain, fatigue and independence, in addition to or instead of patient global assessment did not add enough information to justify modification of the current Boolean definition of remission in RA.
Conclusion: Key elements of the patient perspective on remission in RA can be captured by NRS pain, fatigue, and independence. Although this study did not find conclusive evidence to improve the current definition of remission in RA, the information from these instruments adds value to the physician's assessment of remission and further bridges the gap between physician and patient.

Introduction

Rheumatoid arthritis (RA) is a chronic illness that is characterized by joint and systemic inflammation. Since the development of new treatment strategies, remission is increasingly becoming a realistic goal of treatment. The current definition of remission (2011) has been developed by the American College of Rheumatology (ACR) and

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European League Against Rheumatism (EULAR): the ACR/EULAR Boolean-based definition of remission (ACR/EULAR remission) requires that the 28-tender joint count (TJC), 28-swollen joint count (SJC), C-reactive protein (CRP; mg/dl), and patient global assessment (PtGA; 0–10 scale) are all ≤1 [1].

There is ongoing discussion on whether patient reported outcomes should be incorporated in the definition of remission: in oncology, remission is the absence of cancer; in dermatology, remission is the absence of skin lesions in psoriasis [2]. But remission in RA may not simply be the absence of inflamed joints. RA patients have expressed their dissatisfaction with the ACR/EULAR remission definition, because it contains only one patient reported outcome, the PtGA [3]. At the time this definition was developed, little information was available on potentially important aspects of remission from the patient perspective, but this situation has improved [4]. Also, the choice of PtGA as a tool to measure an overall disease activity state is controversial [5–9]. Therefore, the current remission definition may no longer include all relevant information.

To address this, patients and professionals joined forces in the Outcome Measures in Rheumatology (OMERACT) Working Group on the Patient Perspective on Remission in RA. At OMERACT 2010, the working group identified a lack of understanding regarding this issue and a lack of appropriate measures [3,10]. This resulted in the first phase of our study: a qualitative study involving nine focus group discussions performed in Amsterdam, Bristol and Vienna. It identified a total of 26 potential domains that inform remission from a patient perspective [11]. In the second phase, these qualitative results were refined through a survey that identified pain, fatigue, and independence as the three most important domains of remission as perceived by patients: pain and fatigue needed to be less, almost gone or gone to reflect remission, independence needed to be improved or maintained [12].

The current study focused on the measurement of the three identified domains. In the setting of minimal disease activity or remission, we aimed to:

1) validate patient reported outcome (PRO) instruments in the target population to measure the domains pain, fatigue, and independence;
2) explore whether the domains pain, fatigue and independence add information to the current definition of remission in RA, either in addition to, or instead of the PtGA.

Preliminary results of this study were presented at OMERACT 2016 and have been published previously [13]. At that conference, experts expressed a preference for working towards modification of the current remission criteria (rather than creating a new, patient-focused definition), either by adding PROs or by substituting the PtGA with one or more PROs.

Methods

Study population

In this validation study, RA patients from Netherlands (Amsterdam), Portugal (Coimbra), Australia (Adelaide), and Canada (Toronto) were included. At baseline, patients had to be in self-perceived remission (*"Would you say that at this moment your disease activity is as good as gone, yes or no?"*), or in a state of low disease activity defined as a Disease Activity Score of 28 joints (DAS28) ≤3.2 [14]. Self-perceived remission was the reference standard in this study, because we want to measure the performance of the instruments against patient perceived remission.

Patients completed at least one visit (baseline visit) for the cross-sectional validation to evaluate construct validity and discriminative capacity. Where possible, a follow up visit at 3 and 6 months (time window ± 2 months) was performed for the longitudinal validation to evaluate the sensitivity of instruments to change and the stability over time. All clinical data was gathered within the scope of daily clinical practice and existing clinical cohorts or trials; no additional clinical data were gathered specifically for this study. There was only a minor additional burden on the patients in terms of questionnaires. This study was approved by the local Ethics Committees and qualified as a study carrying no extra risk for the participants. All patients received written information about the study and provided informed consent for their participation.

Measurements

For each of the three domains pain, fatigue, and independence instruments were identified based on literature, feasibility, and experience of the research team as required by OMERACT [15]: i.e. all instruments were applied at every time point: Table 1.

Two instruments were selected for pain:

1) Pain numerical rating scale (NRS) – the international reference standard for pain as included in the RA core set. For feasibility we preferred the NRS over visual analogue scale; for practical reasons, we chose the version incorporated in the RA Impact of Disease questionnaire (RAID) [16,17];
2) Pain EQ-5D – the item on pain / discomfort of the EuroQol 5 dimensions questionnaire (EQ-5D).

Three instruments were selected for fatigue:

1) Fatigue NRS – as implemented in the RAID [18].
2) FACIT-Fatigue Scale – Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-Fatigue), composed of 13 items [19];
3) BRAF-NRS – Bristol Rheumatoid Arthritis Fatigue questionnaire NRS (BRAF-NRS), consisting of three NRS scales that assess three different aspects of fatigue: level, effect and coping [20];

For the third domain of independence, the quotes from the focus group discussions [12] were studied to fully understand the meaning of this domain; it became clear that when discussing independence, patients referred to 'doing things physically, without the help of others, managing yourself'. As an instrument to exactly assess these components did not exist, we selected the following instruments to measure this domain. The first four focus on the physical component of independence, the fifth was newly composed by the research team in close consultation with patient research partners and based on the focus group discussions.

1) HAQ – the Health Assessment Questionnaire (HAQ);
2) RAND36 physical functioning and RAND36 role functioning physical – the dimensions on physical functioning with 10 items and role functioning physical with 4 items of the RAND-36 item Health Survey (RAND36);
3) EQ-5D mobility, EQ-5D self-management, EQ-5D usual activities – the items on mobility, self-management, and usual activities of the EQ-5D;
4) Functional disability assessment NRS, physical well-being NRS – functional disability assessment and physical well-being scales from the RAID;
5) Independence NRS – "*Over the last week, have you been able to do things as and when you want, without needing any kind of assistance?*", scoring 0 for no assistance to 10 for a lot of assistance.

The instruments RAND36, EQ5D and independence NRS were added when the study was already running, so the number of observations is limited.

Table 1
Instruments included in the validation study.

Measurements		Feasibility (ease of use)	Range questionnaire score
Domain: Pain	**N**	**type**	
NRS pain[1,2]	1	NRS	0–10
EuroQoL–5D: pain / discomfort question[2](part of a 6–item questionnaire)	1	multiple choice	0-4
Domain: Fatigue			
NRS fatigue[1,2]	1	NRS	0–10
FACIT Fatigue scale[3]	13	multiple choice	0–52
BRAF–NRS[4]: level[1], effect[2], coping[3]	3	NRS	0–10
Domain: Independence			
HAQ[2]	24	multiple choice	0–3
RAND36: physical functioning[3], role functioning physical[3] (part of a 36–item questionnaire)	36	multiple choice	0–100*
EuroQoL–5D: mobility[2], self–care[2], usual activities[2] (part of a 6–item questionnaire)	3	multiple choice	0–4
Independence NRS[2]	1	NRS	0–10
NRS functional disability assessment[1,2]	1	NRS	0–10
NRS physical well–being[1,2]	1	NRS	0–10
Other			
RAID complete	7	NRS	0–10**
Patient self–perceived remission[5]	1	NRS	Yes / no
Patient global assessment	1	NRS	0–10
Physician global assessment	1	NRS	0–10
Tender and swollen joint count (28 joints)	56	physical examination, joints	0–28
Diagnostic lab (IgM–RF, a–CCP)[6]	2	lab test (blood)	arbitrary units
C–Reactive Protein	1	lab test (blood)	0–200

1. Part of the RAID questionnaire:
◯ Pain NRS: "*Please check the number that best describes the pain you felt due to your rheumatoid arthritis during the last week*" (scoring 0 for non to 10 for extreme)
◯ Fatigue NRS: "*Please check the number that best describes how much fatigue you felt due to your rheumatoid arthritis during the last week*" (scoring 0 for no fatigue to 10 for totally exhausted)
◯ Phrasing of other single item instruments are available in the appendix (Table A)
2. Higher scores indicate worse outcome.
3. Higher scores indicate better outcome.
4. Translation of BRAF–NRS from English to Portuguese was done by three members of the own research team proficient in both languages, through translation into local language by one person, back–translation into English by a second person and a check for irregularities by a third person. A final translation was reached through consensus within the research team, including a patient research partner.
5. Question: "*Would you say that at this moment your disease activity is as good as gone, yes or no?*"
6. All measurements were performed at baseline, after 3 months and after 6 months, except for diagnostic lab that was only performed at baseline.
* Calculation of the RAND requires a two-step process: First, values were recoded to the percentage of the total possible score. Second, eight scales were created by the weighted sum of the questions in that scale, physical functioning and role functioning physical are two of those scales. Each question carries equal weight.
** Calculation of RAID score requires multiplication of the component NRS scores with weights before summing.
Abbreviations: N= number of items; NRS= numerical rating scale; EQ5D= EuroQol 5 dimensions questionnaire; FACIT Fatigue= Functional Assessment of Chronic Illness Therapy Fatigue scale; BRAF= Bristol Rheumatoid Arthritis Fatigue questionnaire; HAQ= Health Assessment Questionnaire; RAND36= RAND–36 item Health Survey; RAID= RA Impact of Disease questionnaire; IgM–RF= Immunoglobulin M–Rheumatoid Factor; a–CCP= anti–Cyclic Citrullinated Peptide.

In addition, at every time point patient assessment of remission was assessed by asking *"Would you say that at this moment your disease activity is as good as gone, yes or no?"* (patient self-perceived remission), and the full WHO-ILAR (World Health Organisation/International League Against Rheumatism) core set for RA [21] was assessed: PtGA and physician global assessment (PhGA), TJC, SJC, and CRP (patient's assessment of pain and physical function already represented above). DAS28 [14] and the Simple Disease Activity Index (SDAI) [22] were calculated. The proportion of patients in ACR/EULAR remission [1] and patients with minimal disease activity (defined as DAS28 <2.60 [23]) were calculated.

Analyses

General characteristics and demographics

General characteristics and demographics were summarized as mean (standard deviation), median [25th and 75th percentile], or percentage, as appropriate.

Feasibility

Feasibility of patient-reported outcomes was scored as '+' if it comprised a simple scale or addition of scales, and '–' otherwise.

1. Cross-sectional construct validity

Construct validity was assessed cross-sectionally by the linear correlation coefficient between disease activity (the construct, independent variable; DAS28 or SDAI) and the instrument scores for each domain (dependent variables pain, fatigue, independence). A Pearson correlation coefficient r of 0.2-0.39 was considered weak, 0.40-0.59 moderate, and an r of 0.60-0.79 was considered strong [24].

2. Cross-sectional discriminative capacity

Discriminative capacity of the instruments to detect remission was evaluated cross-sectionally by studying the difference in scores on the selected instruments between patients in- and not in remission according to self-perceived remission; and according to the Boolean (ACR/EULAR) remission definition. For all measurements, the difference between patients in remission versus not in remission was tested with independent t-tests.

3. Longitudinal discriminative capacity: sensitivity to change and stability over time

Discriminative capacity was evaluated longitudinally by assessing the ability of instruments to detect meaningful changes in disease state, as well as the absence of change, i.e. a stable remission or minimal disease activity state. Two definitions of disease state were used: patients in self-perceived remission (3a) and patients with minimal disease activity (3b), and transitions (both from 'yes' to 'no' and from 'no' to 'yes') were defined as meaningful change. Minimal disease activity was chosen as a second cut-off as it was deemed to be close to self-perceived remission and reflect the intended setting of use. Originally, to extend the range of disease activity somewhat further, the analysis plan also included a third definition, patients with a DAS28 ≤3.20, but the number of transitions was too low for

meaningful analysis. The Boolean definition was not used to define transitions because this study was not aimed at validating measures associated with this definition.

Each patient could contribute to two observation periods: baseline to 3 months, and 3 to 6 months. Potential lack of independence of these observations was ignored, even though some patients contributed to both periods. For each disease state definition and each period, observations were grouped into three subsets: stable remission or minimal disease activity state, i.e. no change; change from 'yes' to 'no'; and change from 'no' to 'yes'. For example, a patient could make a change from 'yes' to 'no' between baseline and month 3 and a change from 'no' to 'yes' between 3 and 6 months; the patient would then contribute once to the 'change from yes to no' dataset, and once to the 'change from no to yes' dataset. Likewise, if a patient was stable in remission in the first period and then flared, the patient would contribute once to the 'no change' dataset and once to the 'change from yes to no' dataset. In each subset, the change scores of the instruments were tested for significance with the one sample t-test.

4. Prediction of future good outcome in terms of physical functioning

Logistic regression analysis identified domains that significantly predicted future good outcome in terms of physical functioning over a 6-month period: the instrument scores at baseline as the independent variable (X) were correlated with 'HAQ remission' at 6 months as dependent variable (Y). 'HAQ remission' was defined as a stable HAQ (change of $\leq$0) AND a low HAQ-score (consistently $\leq$0.5) [15]. Note that radiographic analysis along these lines was planned, but none of the centers was able to supply films or results of radiographic analysis.

5. Multivariable stepwise backward logistic regression analyses

Multivariable stepwise backward logistic regression analyses were performed to see if the patient perspective could add valuable information to the Boolean definition of remission, by testing which combination of criteria predicted HAQ remission best. The criterion for removal was set at $p<0.10$. In the multivariable backward analyses, the following sets were tested for their ability to predict HAQ remission:

- Presence of the separate elements of ACR/EULAR remission (TJC, SJC, CRP, and PtGA each at $\leq$1, yes or no) together with the results of instruments to measure pain, fatigue, and independence;
- Presence of the separate elements of ACR/EULAR remission together with presence of patient self-perceived remission (yes or no);
- Presence of ACR/EULAR remission (yes or no) together with the results of instruments to measure pain, fatigue, and independence;
- Presence of ACR/EULAR remission together with presence of patient self-perceived remission.

6. Selection of the best instruments to measure the domains

The results of the analyses of part 1 to 5 were used to identify the best instruments to measure the domains pain, fatigue and independence.

7. Does the patient perspective add valuable information to the definition of remission?

Fixed forward multivariable logistic regression analyses were performed to see whether one or more of the instruments to measure pain, fatigue, and independence added information when the separate criteria of ACR/EULAR remission were forced into the model; and secondly, to see whether one or more of these instruments could replace PtGA with the other three criteria forced into the model. This was assessed by the -2 log likelihood, the Cox & Snell R Square, and the Nagelkerke R Square (R^2).

To formulate our conclusion, we looked for arguments in the performed analyses to advise modification the ACR/EULAR remission criteria by adding or switching patient reported domain(s).

Analyses were performed in IBM SPSS Statistics, version 26. Statistical tests were used to rank performance of instruments, not for hypothesis testing. No corrections for multiple testing were applied.

Results

General characteristics and demographics

In total, 246 patients were included at baseline (Netherlands 133, Portugal 54, Australia 30, Canada 29), and follow up was available for 152 patients at 3 months (Netherland 127, Australia 25), resp. 142 patients (Netherlands 117, Australia 25) at 6 months. The other centers did not contribute to the follow up data. Patient characteristics showed heterogeneity in disease duration, biological treatment, prevalence of remission and comorbidities (Table 2).

Feasibility

We scored all NRS and the domains of the BRAF and RAID as feasible. FACIT, HAQ, RAND36, and EQ-5D were scored as less feasible because the end score requires more complex calculation.

1. Cross-sectional construct validity

Construct validity of the instruments selected to measure the three domains pain, fatigue, and independence was confirmed by the finding that all instruments mostly correlated moderately with disease activity (r between 0.33 and 0.50), except for BRAF coping (r slightly above 0.10) (Table 3). Interestingly, r's were higher for almost all instruments with the SDAI compared to DAS28.

2. Cross-sectional discriminative capacity

Discriminative capacity was confirmed for all instruments (Table 4). All instruments detected clinically relevant and significant differences between patients in remission and patients not in remission, for patient self-perceived remission as well as for ACR/EULAR

Table 2
General characteristics and demographics.

	N	Total N = 246	Netherlands N = 133	Portugal N = 54	Australia N = 30	Canada N = 29
Age, years	246	54 (14)	51 (14)	56 (13)	62 (11)	57 (15)
Disease duration, years	243	0.5 [0.3;10.0]	0.2 [0.2;0.4]	11.0 [6.0;19.0]	7.8 [3.8;11.0]	20.0 [9.5;31.0]
Female. %	245	67	62	78	67	72
Biological use, %	246	23	0	65	13	62
Comorbidities, %	205	32	25	32	47	41
Patient self–perceived remission, %	239	60	65	39	83	48
ACR/EULAR Boolean remission, %	237	31	33	15	50	28
DAS28	242	2.3 (0.9)	2.4 (1.0)	1.6 (0.7)	1.5 (1.0)	2.3 (1.3)
Patient Global Assessment	240	2.0 [0.2;4.0]	1.0 [0.1;4.0]	3.5 [2.0;5.0]	1.0 [0.0;1.0]	2.0 [1.0;4.5]
Physician Global assessment	222	1.0 [0.0;2.0]	2.0 [0.8;3.1]	0.5 [0.0;1.0]	1.0 [0.0;1.0]	0.0 [0.0;0.5]
HAQ	232	0.3 [0.0;0.8]	0.3 [0.0;0.7]	0.8 [0.1;1.1]	0.0 [0.0;0.4]	0.2 [0.0;0.6]

Values are reported as mean (SD) for normally distributed data, as median [inner quartiles] for non–normally distributed data, or as percentage.

Table 3
Cross–sectional construct validity at baseline of the instruments selected to measure pain, fatigue, and independence: correlation with DAS28 and SDAI.

		DAS28		SDAI	
		N	r	N	r
Domain: Pain					
NRS	Pain	237	0.49	215	0.49
EQ5D	Pain/discomfort	147	0.39	136	0.47
Domain: Fatigue					
NRS	Fatigue	237	0.43	215	0.45
FACIT Fatigue scale		149	−0.40	138	−0.40
BRAF–NRS	Level	227	0.43	205	0.48
	Effect	232	0.41	210	0.45
	Coping	229	−0.15	208	−0.12
Domain: Independence					
HAQ		224	0.47	206	0.48
RAND36	Physical functioning	144	−0.40	134	−0.41
	Role functioning physical	144	−0.37	134	−0.38
EQ–5D	Mobility	147	0.35	136	0.42
	Self–care	147	0.33	136	0.34
	Usual acitivities	147	0.39	136	0.40
Independence NRS		146	0.47	137	0.47
NRS	Functional disability ass.	237	0.50	215	0.50
	Physical well–being	238	0.44	216	0.43
Other					
RAID	Complete	237	0.50	215	0.51
Patient Global Assessment		234	0.39	213	0.39

All correlations were significant at p<0.001, except BRAF-NRS coping: p=0.07 for DAS28, and 0.08 for SDAI.
Abbreviations: DAS28= Disease Activity Score of 28 joints; SDAI= Simple Disease Activity Index; N=number of observations; r= Pearson Correlation Coefficient.

remission. The largest effect size is observed for PtGA with ACR/EULAR remission, unsurprising as the PtGA is a component of the ACR/EULAR remission criteria.

3. Longitudinal discriminative capacity: sensitivity to change and stability over time

Sensitivity to change and stability over time for patient self-perceived remission and for minimal disease activity are displayed in *Tables 5A* and *5B* respectively.

For the domain pain, the NRS performs well: patients that changed from disease state in both directions, for both criteria, showed a relevant and significant change, whereas patients that did not change from disease state appropriately did not show such a change. The EQ-5D pain performed similarly.

For the domain fatigue, the NRS performs well with regards to sensitivity to change and stability over time for patient self-perceived remission. However, for minimal disease activity all instruments perform well for stability over time but none perform well enough to detect sensitivity to change in both directions: fatigue NRS and FACIT fatigue scales were only sensitive to detect favourable changes, whereas BRAF-NRS level was only sensitive to detect unfavourable changes.

For the domain independence, EQ-5D usual activities, functional disability assessment NRS, and physical well-being NRS perform well. The independence NRS was longitudinally administered only in a small subset of patients that changed activity status: it performs well on stability over time but wasn't sensitive to change. When we restricted the analyses to patients with data on the independence NRS, functional disability assessment NRS still performed better (data not shown). Interestingly, HAQ appeared overly sensitive as it showed small but significant changes over time in stable patients.

4. Prediction of future good outcome in terms of physical functioning

Table 6 shows the association between the instruments per domain and the prediction of future good outcome in terms of physical functioning over a 6-month period with HAQ remission. All instruments are significantly associated with 'HAQ remission', except BRAF-NRS coping (p=0.06).

5. Multivariable stepwise backward logistic regression analyses

Stepwise backward logistic regression of an initial model that contains the current criteria of ACR/EULAR remission as separate variables (TJC, SJC, CRP, and PtGA) and our selected instruments, shows that HAQ remission is best predicted by a single measure: independence NRS (β=-0.568, p=0.002). When patient self-perceived remission is added to the ACR/EULAR remission criteria instead of our selected instruments, TJC and PtGA remain significant in the model (β=-0.212, p=0.091 and β=-0.481, p <0.001 respectively).

Table 4
Cross–sectional discriminative capacity at baseline of the instruments selected to measure pain, fatigue, and independence: mean (SD) scores of patients in, or not in remission (self–perceived or ACR/EULAR Boolean).

		Patient self–perceived remission				ACR/EULAR Boolean remission			
		N (n/y)	No	Yes	t	N (n/y)	No	Yes	t
Domain: Pain									
NRS	Pain	95/142	4.0 (2.2)	1.7 (2.0)	8.3	162/73	3.4 (2.3)	1.1 (1.2)	10.1
EQ–5D	Pain / discomfort	70/ 79	1.9 (1.0)	0.9 (0.9)	6.2	110/40	1.6 (1.0)	0.7 (0.8)	5.0
Domain: Fatigue									
NRS	Fatigue	95/142	4.7 (2.7)	2.6 (2.7)	6.1	162/73	3.9 (2.7)	2.5 (3.0)	3.6
FACIT Fatigue scale		70/ 81	34.5 (9.0)	42.6 (8.1)	−5.9	109/42	36.8 (9.5)	43.8 (7.0)	−4.9
BRAF–NRS	Level	96/136	4.9 (2.7)	3.0 (2.6)	5.7	156/70	4.1 (2.6)	3.0 (2.9)	2.8
	Effect	96/141	4.5 (2.6)	2.8 (2.7)	5.0	159/72	3.9 (2.6)	2.7 (2.9)	3.1
	Coping	95/139	5.4 (2.6)	6.9 (3.1)	−4.0	157/71	6.0 (2.8)	7.1 (3.3)	−2.3
Domain: Independence									
HAQ		88/137	0.7 (0.6)	0.3 (0.5)	5.4	158/72	0.7 (0.6)	0.2 (0.2)	9.2
RAND36	Physical functioning	68/ 78	59.2 (24.8)	81.5 (20.1)	−5.9	106/41	64.7 (24.6)	86.8 (17.2)	−6.2
	Role functioning physical	68/ 78	43.0 (43.4)	71.4 (39.2)	−4.1	106/41	49.4 (44.3)	81.7 (31.1)	−5.0
EQ–5D	Mobility	70/ 79	1.4 (1.0)	0.7 (0.9)	4.9	110/40	1.2 (1.0)	0.5 (0.7)	4.9
	Self–care	70/ 79	1.0 (0.9)	0.5 (0.6)	4.1	110/40	0.9 (0.8)	0.3 (0.5)	4.8
	Usual acitivities	70/ 79	1.5 (1.0)	0.8 (1.0)	4.7	110/40	1.4 (1.0)	0.5 (0.7)	5.8
Independence NRS		70/ 78	3.1 (2.6)	1.0 (1.7)	5.7	108/40	2.6 (2.5)	0.4 (0.9)	7.7
NRS	Functional disability ass.	95/142	4.0 (2.6)	1.6 (2.1)	7.7	162/73	3.3 (2.6)	0.9 (1.5)	8.9
	Physical well–being	96/142	4.0 (2.1)	1.8 (2.0)	8.2	163/73	3.3 (2.3)	1.3 (1.7)	7.1
Other									
RAID	Complete	95/142	4.0 (2.1)	1.8 (1.9)	8.3	162/73	3.3 (2.2)	1.4 (1.5)	7.8
Patient Global Assessment		93/141	4.0 (2.2)	1.3 (1.6)	10.0	164/73	3.3 (2.3)	0.4 (0.5)	15.4

All differences between remission and non-remission were significant at p<0.001, except BRAF-NRS for Boolean remission: level: p=0.002, effect 0.001, coping 0.004.
Abbreviations: N(n/y)=number of observations for remission yes and remission no; t= Student-t statistic.

Table 5A
Longitudinal discriminative capacity for patient self–perceived remission over time: sensitivity to change of the selected instruments to measure the three domains pain, fatigue, and independence in patients that do or do not switch from disease state.

		Patient self–perceived remission											
		No change (in remission)				Change from yes to no				Change from no to yes			
		N	Change	95%–CI	p–value	N	Change	95%–CI	p–value	N	Change	95%–CI	p–value
Domain: pain													
NRS	Pain	128	−0.18	−0.51; 0.15	0.28	34	1.43	0.70; 2.17	<0.001*	30	−1.77	−2.60;−0.94	<0.001
EQ–5D	Pain / discomfort	62	−0.05	−0.21; 0.11	0.55	18	0.44	0.05; 0.83	0.03*	17	−0.47	−0.79;−0.15	0.01
Domain: fatigue													
NRS	Fatigue	128	−0.20	−0.54; 0.14	0.24	34	0.82	0.09; 1.55	0.03*	30	−1.53	−2.55;−0.52	0.004
FACIT Fatigue scale		63	0.78	−0.18; 1.74	0.11	19	−0.88	−2.96; 1.21	0.39	16	3.44	−1.99; 8.88	0.20
BRAF–NRS	Level	103	−0.12	−0.52; 0.28	0.57	24	0.67	−0.42; 1.75	0.22	28	−0.75	−1.65; 0.15	0.10
	Effect	112	−0.38	−0.72;−0.03	0.04	24	0.25	−0.84; 1.34	0.64	28	−0.39	−1.36; 0.58	0.41
	Coping	106	0.24	−0.45; 0.92	0.50	23	0.74	−0.65; 2.13	0.28	28	0.79	−0.59; 2.16	0.25
Domain: Independence													
HAQ		122	−0.06	−0.11;−0.01	0.01	35	0.11	−0.03; 0.24	0.12	28	−0.14	−0.23;−0.04	0.01
RAND36	Physical functioning	45	1.20	−1.29; 3.68	0.34	11	0.00	−8.09; 8.09	1.00	9	8.89	1.50; 16.28	0.02
	Role functioning physical	29	17.24	2.62; 31.86	0.02	8	−12.50	−39.87;14.87	0.32	5	0.00	−43.90; 43.90	1.00
EQ–5D	Mobility	62	−0.08	−0.16; 0.00	0.06	18	0.06	−0.26; 0.37	0.72	17	−0.06	−0.48; 0.37	0.77
	Self–care	62	0.00	−0.07; 0.07	1.00	18	0.00	−0.17; 0.17	1.00	17	−0.12	−0.29; 0.05	0.16
	Usual acitivities	62	0.02	−0.13; 0.16	0.82	18	0.39	0.09; 0.69	0.02*	17	−0.65	−1.19;−0.10	0.02
Independence NRS		46	−0.15	−0.35; 0.05	0.13	12	−0.08	−0.87; 0.70	0.82	12	−0.67	−1.83; 0.49	0.23
NRS	Functional disability ass.	128	−0.24	−0.52; 0.03	0.08	34	1.50	0.86; 2.14	<0.001*	30	−1.23	−1.81;−0.66	<0.001
	Physical well–being	130	−0.01	−0.33; 0.30	0.94	34	1.00	0.34; 1.67	0.004*	31	−1.31	−2.02;−0.59	0.001
Other													
RAID	Complete	128	−0.16	−0.41; 0.08	0.20	34	1.13	0.68; 1.59	<0.001*	30	−1.45	−1.91;−0.99	<0.001
Patient Global Assessment		131	−0.13	−0.36; 0.10	0.27	37	1.71	1.00; 2.42	<0.001*	30	−1.12	−2.08;−0.16	0.02

No Change = self–perceived remission was present and did not change between 0 and 3 months or 3 and 6 months.
Change from yes to no = self–perceived remission was present at the beginning of the period, but was lost between 0 and 3 months or 3 and 6 months.
Change from no to yes = self–perceived remission was absent at the beginning of the period, but was regained between 0 and 3 months or 3 and 6 months.
N = number of observed periods. Patients can contribute to two periods (0–3 and 3–6 months); these are regarded as independent observations.

Table 5B
Longitudinal discriminative capacity for minimal disease activity state (DAS28 <2.6) over time: sensitivity to change of the selected instruments to measure the three domains pain, fatigue, and independence in patients that do or do not switch from disease state.

		Minimal disease activity state (DAS28 <2.6)											
		No change (DAS28 <2.6)				Change from yes to no				Change from no to yes			
		N	Change	95%–CI	p–value	N	Change	95%–CI	p–value	N	Change	95%–CI	p–value
Domain pain													
NRS	Pain	153	0.07	−0.21; 0.35	0.62	25	1.00	0.20; 1.80	0.02*	44	−1.09	−1.88;−0.31	0.01
EQ–5D	Pain / discomfort	88	0.00	−0.15; 0.15	1.00	11	0.36	−0.09; 0.82	0.10	15	−0.47	−0.82;−0.11	0.01
Domain fatigue													
NRS	Fatigue	153	−0.09	−0.39; 0.22	0.59	25	0.48	−0.61; 1.57	0.37	44	−0.91	−1.65;−0.17	0.02
FACIT Fatigue scale		87	−0.09	−1.47; 1.28	0.89	12	−0.10	−2.53; 2.34	0.93	14	4.26	1.27; 7.25	0.01
BRAF–NRS	Level	120	0.00	−0.38; 0.38	1.00	14	0.79	0.14; 1.43	0.02*	35	−0.31	−1.13; 0.50	0.44
	Effect	124	0.03	−0.32; 0.39	0.86	14	0.07	−0.70; 0.84	0.84	39	−0.49	−1.22; 0.24	0.18
	Coping	119	0.27	−0.32; 0.86	0.37	13	−0.23	−1.73; 1.27	0.74	38	0.66	−0.41; 1.73	0.22
Domain: Independence													
HAQ		142	−0.03	−0.06; 0.00	0.05	22	0.24	0.09; 0.40	0.004*	39	−0.13	−0.24;−0.01	0.03
RAND36	Physical functioning	56	0.75	−2.83; 4.33	0.68	5	0.00	−8.78; 8.78	1.00	10	9.17	3.38; 14.95	0.01
	Role functioning physical	36	−1.39	−12.45; 9.68	0.80	4	43.75	−24.19;111.69	0.13	10	30.00	−4.56; 64.56	0.08
EQ–5D	Mobility	88	−0.03	−0.14; 0.07	0.52	11	0.00	−0.52; 0.52	1.00	15	0.00	−0.42; 0.42	1.00
	Self–care	88	−0.01	−0.05; 0.03	0.57	11	0.00	−0.42; 0.42	1.00	15	−0.13	−0.42; 0.15	0.33
	Usual acitivities	88	0.03	−0.12; 0.19	0.66	11	0.27	−0.26; 0.80	0.28	15	−0.33	−0.68; 0.01	0.06
Independence NRS		62	0.02	−0.32; 0.35	0.92	5	0.20	−0.36; 0.76	0.37	11	−0.46	−1.21; 0.30	0.21
NRS	Functional disability ass.	153	−0.07	−0.33; 0.20	0.63	25	1.12	0.26; 1.98	0.01*	44	−0.98	−1.54;−0.42	0.001
	Physical well–being	156	0.05	−0.24; 0.35	0.73	25	0.43	−0.33; 1.19	0.26	44	−0.71	−1.34;−0.09	0.03
Other													
RAID	Complete	153	−0.03	−0.23; 0.17	0.79	25	0.66	0.10; 1.23	0.02*	44	−0.97	−1.45;−0.49	<0.001
Patient Global Assessment		160	0.17	−0.05; 0.39	0.14	27	1.03	0.09; 1.97	0.03*	45	−0.79	−1.54;−0.04	0.04

Minimal disease activity state yes (DAS28 <2.6) or no (DAS28 ≥2.6).
No Change = Minimal disease activity state was present and did not change between 0 and 3 months or 3 and 6 months.
Change from yes to no = Minimal disease activity state was present at the beginning of the period, but was lost between 0 and 3 months or 3 and 6 months.
Change from no to yes = Minimal disease activity state was absent at the beginning of the period, but was regained between 0 and 3 months or 3 and 6 months.
N = number of observed periods. Patients can contribute to two periods (0–3 and 3–6 months); these are regarded as independent observations.

Table 6
Logistic regression analysis between instrument value at baseline and subsequent HAQ remission

		HAQ remission				
		N	B	S.E.	p−value	95% CI
Domain: Pain						
NRS	Pain	71	−0.39	0.10	<0.001	0.56;0.82
EQ−5D	Pain / discomfort	36	−1.34	0.40	0.001	0.12;0.58
Domain: Fatigue						
NRS	Fatigue	71	−0.33	0.07	<0.001	0.63;0.83
FACIT Fatigue scale		36	0.08	0.03	0.009	1.02;1.16
BRAF−NRS	Level	68	−0.29	0.08	<0.001	0.65;0.87
	Effect	71	−0.31	0.08	<0.001	0.64;0.85
	Coping	70	0.12	0.07	0.065	0.99;1.29
Domain: Independence						
HAQ		−−−	−−−	−−−	−−−	−−−
RAND36	Physical functioning	37	0.08	0.02	0.001	1.03;1.13
	Role functioning physical	37	0.03	0.01	0.001	1.01;1.04
EQ−5D	Mobility	36	−0.86	0.34	0.011	0.22;0.82
	Self−care	36	−2.07	0.74	0.005	0.03;0.54
	Usual acitivities	36	−1.02	0.35	0.003	0.18;0.71
Independence NRS		35	−0.57	0.18	0.002	0.40;0.81
NRS	Functional disability ass.	71	−0.43	0.09	<0.001	0.54;0.78
	Physical well−being	71	−0.65	0.12	<0.001	0.41;0.67
Other						
RAID	Complete	71	−0.54	0.11	<0.001	0.47;0.72
Patient Global Assessment		71	−0.51	0.12	<0.001	0.48;0.75
Disease Activity						
Patient self−perceived remission		71	1.14	0.42	0.006	1.39;7.07
Boolean remission		70	1.08	0.43	0.012	1.27;6.87
SDAI		64	−0.17	0.05	<0.001	0.77;0.92
DAS28		70	−0.69	0.23	0.003	0.32;0.79

'HAQ remission' was defined as a stable HAQ (change of ≤0) AND a low HAQ-score (consistently ≤0.5)
Abbreviations: B= beta; S.E.= standard error; CI= confidence interval.

Similar analysis of an initial model that contains ACR/EULAR remission as dichotomous variable (yes/no) in addition to our selected instruments, shows that HAQ remission is best predicted by independence NRS (β=-0.568, p=0.002) as well. By adding patient self-perceived remission instead of our selected instruments, a combination of dichotomous ACR/EULAR remission (β=0.878, p=0.051) and patient self-perceived remission (β=0.930, p=0.032) predict HAQ remission best.

Replacing the PtGA in the current definition of ACR/EULAR remission by our three selected instruments, shows that HAQ remission is again best predicted by independence NRS (β=-0.568, p=0.002). When PtGA in the current definition of ACR/EULAR remission is replaced by patient self-perceived remission, HAQ remission is best predicted by TJC (β=-0.333, p=0.007) and patient self-perceived remission (β=1.292, p=0.003).

6. Selection of the best instruments to measure the domains

Table 7 combines the results of the analyses of part 1 to 5 and adds feasibility of use as one of the criteria that are important when selecting valid measurement instruments. For the domain pain the *pain NRS* was selected as the best instrument, for the domain fatigue the *fatigue NRS* was selected, but for the domain independence no instrument was clearly superior. Given the strong association of most instruments with physical function, we selected the *independence NRS* for this domain, despite unclear results on the sensitivity to change.

7. Does the patient perspective add valuable information to the definition of remission?

As Table 8 shows, fixed forward multivariable logistic regression analyses resulted in a higher percentage of variance in HAQ outcome explained by the different elements of the remission definition when the patient perspective was part of the remission criteria: Nagelkerke R Square for the complete ACR/EULAR remission was 0.31 versus 0.10 without PtGA. Criteria that added one or more of the selected instruments to the complete ACR/EULAR remission criteria, or replaced the PtGA, also resulted in a higher R square. However, in these scenarios the increase in explained variance was incremental. Results of independence were promising: Nagelkerke R Square for the complete ACR/EULAR remission was 0.31 versus 0.43 when all three instruments for pain, fatigue and independence were added.

Discussion

Our study shows that numerical rating scales (NRS) for pain and fatigue are optimally valid and feasible instruments to describe patient-perceived remission. For independence, no instrument was clearly superior. The independence NRS, formulated by the research team in close consultation with patient research partners, was based on the focus group discussions, and emerged as the best predictor of HAQ remission; therefore this instrument was provisionally selected. In our opinion, the analyses in this study did not provide sufficiently convincing data to recommend a modification of the current definition of remission, either by adding or by replacing instruments.

The validation of instruments for the new domain of independence proved challenging. The SF36 scores low on feasibility, as it contains many questions, and is not easy to calculate. Functional disability assessment NRS, physical well-being NRS, and EQ-5D usual activities are possible alternatives. However, these instruments are strongly linked to physical function. Independence, as identified in our qualitative research [12], encompasses more than physical functioning alone: as no direct measurement instrument was available, we formulated the independence NRS with input of patient research partners, resulting in a good match with the concept of independence from the patient perspective. The independence NRS is easy to apply, but performed poorly in discrimination tests, albeit very low sample sizes. In contrast, it performed best in predicting HAQ stability. Therefore, we feel this measure is most acceptable as the instrument to measure independence for now. More research with sufficient sample sizes is required to confirm validity of the measure, and to explore

Table 7
Summary of the results: Combining the results of the analyses to rank the instruments for pain, fatigue and independence.

			Cross–sectional		Longitudinal				Sum of positive ratings[a]
		Feasibility (ease of use)	1. Construct validity	2. Discriminative capacity	3a. Discriminative capacity; self–perceived remission	3b. Discriminative capacity; DAS28<2.6	4. Prediction of HAQ remission	5. Added value for prediction	
Domain: Pain									
NRS	Pain	+	+	+	+	+	+	–	**6***
EQ5D	Pain/discomfort	–	+	+	+	–	+	–	**4**
Domain: Fatigue									
NRS	Fatigue	+	+	+	+	–	+	–	**5***
FACIT Fatigue scale		–	+	+	–	–	+	–	**3**
BRAF–NRS	Level	+	+	+	–	–	+	–	**4**
	Effect	+	+	+	–	–	+	–	**4**
	Coping	+	–	+	–	–	–	–	**2**
Domain: Independence									
HAQ		–	+	+	–	–	–	–	**2**
RAND36	Physical functioning	–	+	+	–	+	+	–	**4**
	Role functioning physical	–	+	+	–	+	+	–	**4**
EQ–5D	Mobility	–	+	+	–	+	+	–	**4**
	Self–care	–	+	+	–	+	+	–	**4**
	Usual acitivities	–	+	+	+	+	+	–	**5**
Independence NRS		+	+	+	–	–	+	+	**5*†**
NRS	Functional disability ass.	+	+	+	+	+	+	–	**6**
	Physical well–being	+	+	+	+	+	+	–	**6**

[a] Score for each instrument calculated by all the positive outcomes of the different analyses, one positive outcome is 1 point; += positive outcome; –= negative outcome; * Best instrument to measure the domain; † Given the strong association of most instruments with physical function, we selected the independence NRS for this domain, despite unclear results on the sensitivity to change.

the construct further. For instance, our current results are based on the total HAQ score, but in future research we want to analyze the subscores to examine the relation of independence with the availability of aids and assistive devices.

The protocol of this study was drafted with contribution of the OMERACT Working Group on the Patient Perspective on Remission in RA. Preliminary results were presented at OMERACT 2016, and during that meeting, preferred future scenarios were discussed: a) modify ACR/EULAR remission criteria by adding or switching patient reported domain(s), i.e. adding pain, fatigue and/or independence to the current ACR/EULAR remission criteria or substituting the PtGA with pain, fatigue and/or independence; b) modify ACR/EULAR remission criteria by relaxing cut-off(s) of the existing patient reported domain within the current criteria; c) create separate set of patient perceived remission criteria [13]. Although all members realized that modification of the current ACR/EULAR remission criteria (scenario a) is a major undertaking and it can be questioned whether this is the best way forward, most members voted for this scenario (53%) [13].

However, in our opinion our analyses did not provide sufficiently convincing data to suggest a modification of the criteria, even though independence appeared promising and adding criteria also increased explained variance. It should be noted that adding criteria would make it harder for patients to be classified as being in remission.

Nevertheless, there is still need for a solution for the insufficient patient information in the current remission definition. Future research could be done by identifying domains that predict future good outcome in terms of radiological progression over a 12-month period, as this was not possible within this study. However, with low progression rates currently seen in practice, this is likely to prove challenging. Scenario b, especially relaxing cut-off(s) for the PtGA [6,25,26], was selected by a minority of working group members (10%) [13]. In the course of our study, we did find some results to

Table 8
Logistic regression analysis between the selected instruments per domain added to the current ACR/EULAR remission criteria as well as the selected instruments per domain replacing the PtGA in the current ACR/EULAR remission criteria, and HAQ remission.

	N (n/y)	–2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
Reference: Boolean remission complete (TJC, SJC, CRP, PtGA)	45/69	123	0.23	0.31
+ Pain	44/69	119	0.25	0.33
+ Fatigue	44/69	113	0.28	0.39
+ Independence	18/34	51	0.27	0.38
+ Pain and Fatigue	44/69	113	0.28	0.39
+ Pain and Independence	18/34	49	0.29	0.40
+ Fatigue and Independence	18/34	49	0.29	0.41
+ Pain, Fatigue and Independence	18/34	48	0.31	0.43
Boolean remission without PtGA (TJC, SJC, CRP)	45/70	146	0.07	0.10
+ Pain	44/69	127	0.20	0.27
+ Fatigue	44/69	122	0.23	0.31
+ Independence	18/34	51	0.27	0.37
+ Pain and fatigue	44/69	119	0.25	0.34
+ Pain and Independence	18/34	50	0.28	0.38
+ Fatigue and Independence	18/34	50	0.29	0.39
+ Pain, Fatigue and Independence	18/34	49	0.29	0.40

Abbreviations: N(n/y)=number of observations for HAQ remission yes and HAQ remission no; TJC= tender joint count; SJC= swollen joint count; CRP= C–reactive protein; PtGA= Patient Global Assessment. Pain, fatigue, independence all measured with numerical rating scales.

support this scenario, which will be documented in a separate paper (Rasch et al, in preparation). Scenario c was selected by 37% of the working group members and awaits possible future study [13].

Even though this study did not provide sufficiently convincing data to recommend a modification of the current definition of remission, either by adding or by replacing instruments, we did confirm the importance of the patient perspective in the remission criteria: remission without PtGA showed a Nagelkerke R Square of only 0.10, increasing to 0.31 when PtGA was added, and even to 0.43 when our three instruments for pain, fatigue and independence were added. Of course, adding criteria would make them more difficult to meet. There are votes to remove the PtGA from the current remission criteria [7,8], since no significant differences were found in joint damage progression between patients fulfilling the current definition of Boolean remission and patients fulfilling the criteria without PtGA. Opponents disagree [9], and also this study confirms the value of the patient perspective in defining remission in RA.

Our study is unique, since we are not aware of studies that attempted to adapt criteria such as these based on conceptual input from patients. We adopted a pragmatic stepwise approach for development and evaluation, using both qualitative and quantitative techniques, standard statistical methodology and clinically relevant contrasts. A strength of this study is the heterogeneity in disease duration and treatment and the geographical spread of the studied population, increasing generalizability of findings.

The methods were slightly changed over the course of the study. Originally, we wanted to use low disease activity (DAS28 $\leq$3.2) to study change between disease states, because this was one of the inclusion criteria. However, only a few patients changed from DAS28 $\leq$3.2 to DAS28 $>$3.2 or the other way around: for some instruments there were only four observations. With a lower cut-off of DAS28 $<$2.6 (minimal disease activity), more patients changed disease state. As minimal disease activity is a relevant disease state, we posit that our changed design still reflects what we want to measure, namely whether the instrument is sensitive enough to detect changes in such states. Furthermore, we planned to include radiological progression in the analyses, however, because of the missing radiographs we were not able to carry this out. All other analyses were performed as described in the original analysis plan.

This study has limitations. First, the selection of our instruments was based on literature, feasibility, and experience of the research team, but not on an exhaustive literature review. Nevertheless, most instruments are already validated extensively in RA; novel in this study is the validation in the setting of (near-) remission in RA.

Secondly, in this study, some instruments were only tested in a subset of patients, limiting our ability to draw conclusions. This is caused by the fact that most clinical data were gathered within the scope of daily clinical practice and existing clinical cohorts or trials, and some instruments had to be added during the course of the study. As a result, some analyses were hampered by limited numbers of observations, especially for RAND-36, EQ-5D, and the independence NRS.

Third, the instruments for independence are all strongly linked to physical function resulting in a high correlation with the HAQ (data not shown). However, our prior qualitative research [12] identified that independence is more than physical functioning alone. Because no direct measure was available, we formulated the independence NRS with input of patient research partners, so that it matches best with the concept of independence from the patient perspective.

To conclude, NRSs have the highest validity to measure the domains pain, fatigue, and independence in the setting of minimal disease activity to describe the patient perspective of remission in RA. Our study, with its limitations, does not suggest an urgent need to change the current remission definition. Future data collection should include NRSs on pain, fatigue and independence to further bridge the gap between the physician's and the patient's perspective on remission.

Declaration of Competing Interest

No conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2021.07.005.

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