Patient Reported Outcome Measures for Rheumatoid Arthritis Disease Activity: Rasch measurement theory to identify items and domains

Tim Pickles[1], Mike Horton[2], Karl Bang Christensen[3], Rhiannon Phillips[4], David Gillespie[1], Neil Mo[5], Janice Davies[6], Susan Campbell[6], Ernest Choy[7]

[1]Centre for Trials Research, Cardiff University, Cardiff, UK;

[2]Psychometric Laboratory for Health Sciences, University of Leeds, Leeds, UK;

[3]Section of Biostatistics, University of Copenhagen, Copenhagen, Denmark;

[4]Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, UK;

[5]Swansea Bay University Health Board, Port Talbot, UK;

[6]Patient and Public Involvement Stakeholders, UK;

[7]Division of Infection and Immunity, Cardiff University, Cardiff, UK;

Corresponding author details:

Tim Pickles

5th Floor, Neuadd Meirionnydd

Heath Park

Cardiff

CF14 4YS

PicklesTE@cardiff.ac.uk

Abstract

Objectives

Disease Activity (DA) monitoring is a standard of care in Rheumatoid Arthritis (RA). There is demand for achieving this through Patient Reported Outcome Measures (PROMs). The aim of this study was to determine which items could be used to measure the construct of RA DA, by analysing legacy PROMs, using Rasch measurement theory (RMT) analyses.

Methods

Questionnaires including 10 legacy PROMs were sent to people with RA to create original and validation datasets. Items were grouped according to OMERACT domains and analysed using Principal Components Analysis. By domain RMT analyses in original dataset, and domain-level testlets were assessed to determine which measure the construct of RA DA. The result was then replicated in confirmatory factor analyses bifactor models and RMT analyses in the validation dataset. Psychometric properties of legacy PROMs was assessed in the original dataset.

Results

The total sample size was 691 (original: 398, validation: 293). The *Patient Global* domain was split into *General health* and *Disease activity* domains under RMT. *General health* and *Fatigue* domain items measure a separate construct to the construct of RA DA. A set of 12 *Pain*, *Disease activity*, *Tenderness and swelling*, *Physical functioning* and *Stiffness* domain items can be used to measure the construct of RA DA. No legacy PROMs fully fit the Rasch measurement model.

Conclusion

General health and *Disease activity* domain items are not interchangeable. 12 items form an item pool that can be used to measure the construct of RA DA. Legacy PROMs should not be recommended for use.

Keywords:

Rheumatoid arthritis disease activity

Patient-reported outcome measures

Measurement properties

Key messages

General health and disease activity (DA) domain items are not inter-changeable

RA DA requires *Tenderness and swelling*, *Pain*, *Disease activity*, *Stiffness* and *Physical functioning* domain items

No legacy PROMs fully fit the Rasch measurement model

Introduction

Patient-reported outcome measures (PROMs) are critical to research and clinical care, as recognised by the U.S. Food and Drug Administration (FDA), who mandated PROMs to be captured in all randomised controlled trials. Additionally, they have published guidelines on how to develop and validate PROMs. (1, 2) Disease activity (DA) monitoring is a standard of care in Rheumatoid Arthritis (RA), and there is demand for achieving this through PROMs. Although there are many RA DA PROMs, (1) these are currently used as secondary outcomes in clinical trials of rheumatic diseases, but rarely in clinical care. All these PROMs were developed using classical test theory methods and often have various limitations. FDA (2, 3) and COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines (4-6) both recognise item response theory (IRT) and Rasch measurement theory (RMT) as suitable methods to assess the measurement properties of instruments. Validation using these methods requires PROMs to meet stringent measurement criteria, which include unidimensionality, internal consistency, targeting and lack of local dependence and differential item functioning. Thus, IRT and RMT provide a statistical framework where all these measurement criteria can be formulated as testable hypotheses. Specifically, RMT (7-9) allows for these attributes to be formally assessed, as it provides a template to determine PROM score validity.

A systematic review (10) of 10 legacy RA DA PROMS showed that none can be recommended for use according to COSMIN guidelines. (4-6) This justifies the need to collect further data to start the process of determining the domains, and items within those domains, that can be used to measure the construct of RA DA.

The overall aim of this study was to use RMT analyses to determine which items can form an item pool to measure the construct of RA DA to. A secondary aim was to examine the measurement properties of legacy RA DA PROMs and other relevant PROMs.

Methods

This research is reported in line with the Strengthening the reporting of observational studies in epidemiology (STROBE) framework (Supplementary Data S1). (11)

Study design

This was a cross-sectional study that took place in 2020 and 2021. In Cardiff and Vale and Swansea Bay University Health Boards (UHBs), potential participants were identified by NHS staff by searching the electronic health records of the Rheumatology Department for those at least 18 years old with

Rheumatoid Arthritis (RA). In Aneurin Bevan UHB, potential participants were identified by NHS staff as those at least 18 years old with an entry on the British Society for Rheumatology Biologics Registry for Rheumatoid Arthritis (BSRBR-RA) database, Paper questionnaires were sent out as part of study packs to these people living with RA (plwRA) In Cwm Taf Morgannwg UHB, potential participants were identified as those at least 18 years old with RA in clinic by NHS staff and handed the study pack. Inclusion criteria were: at least 18 years old; a diagnosis of RA and signed informed consent. Patients were excluded if they were unable to complete the questionnaire in English. The study was approved by the North West – Preston Research Ethics Committee (20/NW/0039).

Sample Size

To provide item calibrations within ± 0.5 logits within a Rasch measurement theory (RMT) analysis, the advised sample size is 250. (12) Given this, it was decided that a sample size of n ≥ 250 was required, for both an original dataset and a validation dataset.

Questionnaire creation

A questionnaire (see Supplementary Data S2) was created based on the items from 10 legacy PROMs identified and reviewed in a systematic review: (10)

- Rheumatoid Arthritis Disease Activity Index-5 (RADAI5); (13-15)
- Rheumatoid Arthritis Disease Activity Index (RADAI); (16, 17)
- RADAI-SF; (17, 18)
- Patient-based Disease Activity Score 2 (PDAS2); (19, 20)
- Patient Reported Outcome CLinical ARthritis Activity (PRO-CLARA); (21)
- Global Arthritis Score (GAS); (22)
- Patient Activity Score (PAS); (23)
- Patient Activity Score-II (PAS-II); (23)
- Routine Assessment of Patient Index Data 3 (RAPID3); (24)
- Routine Assessment of Patient Index Data 4 (RAPID4). (25)

Also included were the items from two PROMs measuring level of flare:

- Rheumatoid Arthritis Flare Questionnaire (RA-FQ) (26, 27);
- FLARE-RA (which includes FLARE-RA Old, FLARE-RA Arthritis and FLARE-RA General Symptoms). (28-31)

The items of The Rapid Assessment of Disease Activity in Rheumatology (RADAR), (32, 33) PROM-score (34) and the foot-specific RADAI-F5, (35) were included, as were fatigue items included on the

PAS and PAS-II assessments, the Health Assessment Questionnaire (HAQ) (PDAS2, PAS) and the multidimensional Health Assessment Questionnaire (MDHAQ) (used in RAPID3, RAPID4). The HAQ also has an additional pain item. RA-FQ has additional items about having a flare and how long it has been going on.

A draft questionnaire containing these items was discussed with two groups of plwRA: a meeting with J.D. and S.C. and a focus group convened by the National Rheumatoid Arthritis Society (NRAS). From these discussions, items on discomfort when walking, standing and exercising, plus fear of falling when walking were added. These four items used the Copenhagen Hip and Groin Outcome Score (HAGOS) (36) as a template. A focus group attendee also provided a pain scale, which was included. Thus, the total item pool contained 268 items (Supplementary Data S2, which states item codes).

Demographic items relating to current age, age at diagnosis, gender and sex assigned at birth, shielding during the COVID-19 pandemic, whether the participant completed the questionnaire themselves, ethnicity, education level, earlier and accompanying diseases, current or previous disease-modifying antirheumatic drug (DMARD) treatment are also included.

Item grouping

All items in the questionnaire, minus the two homunculi (`G01`, `A02`) and the aids and devices and help from another person items from HAQ (`H10`, `H11`, `H23`, `H24`), were grouped according to Outcome Measures in Rheumatology (OMERACT) domains for RA. (37, 38) 145 items were initially grouped by T.P. (researcher) and then checked by E.C. (Rheumatologist) to ensure correct grouping. Where necessary, additional domains were created (Table 1).

Analyses

Principal component analysis – original dataset only

Principal component analyses (PCA) (39) were undertaken on the 145 items described listed in Table 1. Two PCA were undertaken, one using a polychoric correlation matrix and another using Pearson's correlation coefficients. Within the PCA, the principal-component factor method was used and only factors with a minimum eigenvalue of 1 were retained. Oblique promax rotation was then applied. The purpose was to see if items within the identified domains loaded together onto factors that reflected those domains. If this was the case, the domain, and the items loading to that domain, were carried forward to further RMT analyses.

Rasch measurement theory – original and validation datasets

The Rasch Measurement Model (RMM) is a statistical model (7-9, 40) where the sum score of item responses contains all information about the underlying latent trait, here the construct of RA disease activity (DA), in a statistical concept known as sufficiency. The satisfaction of RMM assumptions therefore provides a prescription for what is necessary for a PROM to deliver fundamental measurement, (41) and therefore RA DA PROMs should be assessed on this basis.

Items were assessed by RMT analyses, which provides results on targeting and item locations, overall and individual item fit to the RMM, internal consistency, local dependency, uni-dimensionality and item threshold ordering. Differential item functioning was investigated by age group (18 to 54, 55 to 74, 75+), age at diagnosis (2 to 36, 37 to 56, 57+), sex (male, female), earlier and accompanying diseases (yes, no), previous DMARD treatment (yes, no), and highest educational qualification (Qualifications below university graduate, University graduate qualification as minimum). Grouping for age group and age at diagnosis were determined by the inter-quartile ranges for these variables.

RMT analyses in the original dataset were undertaken on items grouped by domain, with the purpose to identify potential items within each domain as candidate items for an item pool.

In the validation dataset, RMT analyses were undertaken on the potential items for each domain. Where discrepancies were found, these were reported. If suitable, items within domains were grouped together to form domain-level testlets, which operate as single items that represent a domain. These domain-level testlets were assessed together by RMT analyses to determine whether they could measure the construct of RA DA. If any evidence was found that this was not the case, iterative changes were made to achieve better fit to the RMM.

Structural validity – original and validation datasets

A confirmatory factor analysis (CFA) model is a statistical model used to test whether measures of a construct are consistent with a hypothesised measurement model based on theory and/or previous analytic research. (42, 43) CFA using Mplus (44) was used to calculate a X^2-test, root mean square error of approximation (RMSEA) along with an accompanying 90% confidence interval (CI), comparative fit index (CFI), Tucker-Lewis index (TLI), standardised root mean square residual (SRMR), Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

CFA was applied to the validation dataset to examine whether the solution determined by RMT analyses could replicated in CFA using bifactor models. (45)

Legacy PROMs – original dataset only

To assess construct validity, Mann-Whitney U tests (46) were performed to see if there was a difference between those identifying as having a flare and not having a flare, with a Hodges-Lehmann median difference and 95% CI calculated. (47) Spearman's ρ correlation coefficients (48) were calculated between legacy PROM scores, with the hypothesis that all $\rho \geq 0.5$. To assess internal consistency, Cronbach's α (49) values were calculated. In line with COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) guidelines, (4-6) internal consistency was indicated by $\alpha > 0.7$. Legacy PROMs in the original dataset were assessed using CFA. In line with COSMIN guidelines, (4-6) structural validity was indicated by RMSEA < 0.06, TLI > 0.95, CFI > 0.95 and SRMR < 0.08. RMT analyses were applied to the legacy PROMs in the original dataset to assess the measurement properties structural validity, internal consistency and measurement invariance.

Results

Descriptives

The total sample size was n = 691, with n = 398 in the original dataset and n = 293 in the validation dataset. Study packs were sent out in batches in September 2020 and June, October and November 2021. The mean current age was 63.8 (SD 12.82), mean age at diagnosis was 46.4 (SD 15.69) and mean disease duration was 17.3 years (SD 13.65). 67.4% (466/691) were female and all were the same as assigned at birth (Table 2). 15.5% (107/691) completed all demographic questions and legacy PROM items of the questionnaire.

Principal component analysis – original dataset

From the results of both principal component analyses, a set of 30 items loaded together with other items in the domains they were grouped in, a priori. These were taken forward for Rasch measurement theory (RMT) analyses. These items were in the *Tenderness and swelling*, *Patient global*, *Pain*, *Fatigue*, *Physical functioning* and *Stiffness* domains (Figure 1).

Rasch measurement theory – original dataset

Tenderness and swelling

The three items (`D02`, `T02`, `Q04`) in the *Tenderness and swelling* domain provided good fit to the Rasch measurement model (RMM) and were retained.

Patient global

Of the 10 *Patient global* domain items, five were general health items and five were disease activity (DA) items. There was evidence of local dependence between general health items and, separately, evidence of local dependence between DA items (Table 3). The residual principal components loadings also showed that all general health items loaded negatively, whilst all DA items loaded positively, on the first component (Table 3). Given this, two new domains were created: *General health* and *Disease activity*.

General health

For the five *General health* domain items, there were four item showing misfit, one item with differential item functioning (DIF) by sex and local dependence between three items. It was decided to retain the other two items alongside one of these locally dependent items and therefore three items (R05, P01, C01) were retained for the *General health* domain.

Disease activity

For the five *Disease activity* domain items, there were two item showing misfit and all items were locally dependent on other items. There was a distinction in local dependence between the three items with a six-month and those with shorter recall periods. These three items were the only items amongst the 30 with a six-month recall so it was decided to retain the other two items (PS1, A01) in the *Disease activity* domain.

Pain

For the eight *Pain* domain items, there were five items showing misfit and only one item was not locally dependent on another item. It was decided to retain three items (one with no local dependence (F01) and two with only minimal evidence of local dependence between them (R04 and P07)) and one of the five locally dependent items. Four items (F01, R04, P07, Q05) were retained in the *Pain* domain that provided the best fit to the RMM.

Fatigue

The four *Fatigue* domain items demonstrated three item showing misfit, and DIF by age group and gender for one item. On retaining the three items without DIF, the analysis showed only a minor issue for item misfit and therefore these three items (F03, PF1, RF1) were retained for the *Fatigue* domain.

Physical functioning

The two *Physical functioning* domain items (F02, F05) provided good fit to the RMM and were retained.

Stiffness

For the three items in the *Stiffness* domain, there was one item showing misfit, all items had disordered thresholds and one item displayed DIF by earlier and accompanying diseases. There were two duration items, one of which had entirely illogical threshold ordering, and one intensity items. Therefore, the single intensity item (F04) was retained in the *Stiffness* domain.

Rasch measurement theory – validation dataset

Discrepancies

There was evidence of DIF by earlier and accompanying diseases for two items in the *General health* domain. For the *Pain* domain, the original item over-discrimination issue remained, and another item also displayed misfit. A pair of items displayed local dependence and unidimensionality could not be evidenced. For the *Fatigue* domain, there was evidence of item misfit and also DIF by highest educational qualification.

There were no discrepancies for the analyses of the *Tenderness and swelling*, *Disease activity* and *Physical functioning* domains, with no analysis for the *Stiffness* domain (only one item retained).

Domain-level testlets

None of the above discrepancies led to any need for changes to be made, therefore seven domain-level testlets representing the *Tenderness and swelling*, *General health*, *Disease activity*, *Pain*, *Fatigue*, *Physical functioning* and *Stiffness* domains were created (using the 18 retained items) and analysed. The *Fatigue* domain-level testlet had an extremely high positive fit residual (indicating under-discrimination) and also displayed extremely large negative residual correlations with the *Tenderness and swelling*, *Disease activity*, *Pain*, *Physical functioning* and *Stiffness* domain-level testlets. This suggested that the *Fatigue* domain-level testlet did not measure the same construct as the other domain testlets (Figure 2; panel (a)) and it was therefore removed.

Analysis of the six remaining domain-level testlets provided a similar picture for the *General health* domain-level testlet: an extremely high positive fit residual (indicating under-discrimination, Figure 2; panel (b)) and also extremely large negative residual correlations with all of the domain testlets. This suggested that the *General health* domain-level testlet did not measure the same construct as the other domain testlets and it was therefore removed.

A final analysis of the five remaining domain-level testlets displayed issues but none that required further change. There was item misfit for the *Disease activity* domain-level testlet with a large negative fit residual (indicating over-discrimination) and a significant F-value. The *Physical functioning* domain-level testlet also had a large positive fit residual (indicating under-discrimination). However, the item characteristic curves did not suggest any issues, so these were determined to be non-problematic. For the *Disease activity* domain-level testlet to exhibit over-discrimination was logical, as this is the same wording as the construct of Rheumatoid Arthritis (RA) DA itself. The *Physical functioning* domain-level testlet is more of a functional status than a symptom status so may under-discriminate in comparison to the other domain-level testlets. There was evidence of local dependence between the *Disease activity* and *Tenderness and swelling* domain-level testlets and the *Physical functioning* and *Stiffness* domain-level testlets. Both of these combinations have conceptual sense in that RA DA inevitably causes tenderness and swelling, and greater levels of stiffness create issues with physical functioning. The *Pain* and *Physical functioning* domain-level testlets displayed DIF by age group, though this DIF was not evident graphically for the *Pain* domain-level testlet. For *Physical functioning* domain-level testlet, it was logical that those 75 and over were at higher levels across the continuum in comparison to the other two age group categories. Also, unidimensionality could not be proven.

The 12 items therefore retained across the *Pain*, *Disease activity*, *Tenderness and swelling*, *Physical functioning* and *Stiffness* domains have their item codes highlighted in green in Supplementary Data S2.

Confirmatory factor analysis – validation dataset

Confirmatory factor analysis (CFA) was used to assess and compare a 1-dimensional bifactor model and a 2-dimensional bifactor model, with a hypothesis that the 2-dimensional bifactor model would produce better summary statistics as it better represented the model created through RMT analyses. This hypothesis was confirmed as all summary values were better for the 2-dimensional bifactor model (Figure 3).

Legacy Patient Reported Outcome Measures – original dataset

For all legacy PROMs, the median of those having a flare was greater than the median of those not having a flare and, when compared through a Mann-Whitney U test, produce $p < 0.001$. (Supplementary Table S1). Spearman's ρ correlation coefficients were generally very high ($\rho \geq 0.833$ for RA DA PROMs) (Supplementary Table S2). Except for the PDAS2 variations, $\alpha \geq 0.802$ across the PROMs (Supplementary Table S3). Detail on discretised VAS items is shown in Supplementary Table

S4. The CFA results show that only RADAI5, RADAI-SF and RA-FQ could evidence structural validity (Supplementary Table S5). RADAI5, RADAI, RADAI-SF, PDAS2, PRO-CLARA, GAS, PAS, PAS-II, RAPID3, RAPID4, PROM-score, RADAI-F5 and FLARE-RA Old did not fit the RMM (Supplementary Table S6) and all had misfitting items. Local dependence, disordered thresholds and DIF were issues across the majority of legacy PROMs. Unidimensionality could only be evidenced for PROM-score, RADAI-F5, FLARE-RA Arthritis, FLARE-RA General Symptoms and RA-FQ. The Person Separation Index was high for all PROMs suggesting good levels of internal consistency. The measurement properties of the legacy PROMs are summarised in Supplementary Figure S1.

Discussion

We undertook a cross-sectional study in people living with Rheumatoid Arthritis (RA) (plwRA) to determine which items can form an item pool to measure the construct of RA disease activity (DA) and examine the measurement properties of legacy RA DA PROMs and other relevant PROMs.

In analysing the initial domains under Rasch measurement theory (RMT), *General health* and *Disease activity* were found to be separate domains within the *Patient Global* domain. By analysing domain-level testlets, it was found that 12 items across the *Pain*, *Disease activity*, *Tenderness and swelling*, *Physical functioning* and *Stiffness* domains can be used to form an item pool for a new PROM to measure the construct of RA DA. *Fatigue* and *General health* domain items were shown through RMT analyses to measure a separate construct to the construct of RA DA.

Additionally, whilst all legacy PROMs had good evidence for the internal consistency and hypothesis testing for construct validity, and that many had evidence for the structural validity from confirmatory factor analysis (CFA), no legacy PROMs could fully evidence fit to the Rasch measurement model.

The strength of this study is the novel and detailed strategy for analyses for the construct of RA DA. This was the first use of cross-validation (testing across two datasets) and RMT analyses for such items. This was the first use of CFA to complement RMT analyses, and the first use of bifactor models within CFA to confirm such an item structure. Equally, this was also the first time that RMT analyses were applied to assess the measurement properties of legacy PROMs with adequate sample size to obtain reliable estimates could be obtained through RMT analyses.

Patient and Public Involvement

J.D. and S.C., both plwRA, co-developed the participant information sheets, consent forms and questionnaires. The National Rheumatoid Arthritis Society (NRAS) organised a focus group of 15 plwRA to discuss this research ahead of application.

Limitations

The data collected were from a small, densely populated, area of South Wales, with an assumption that participants were able to understand the English language used in study documents and data collection forms. Collecting data from one geographical area meant that it was not possible to undertake simultaneous external validation with data from another area.

The paper questionnaire was very long at 18 pages: this and other factors contributed to only 15.5% providing a response to all demographic questions and legacy PROM items. These questionnaires were also sent out at varying stages of the lockdowns enforced in Wales as a result of the COVID-19 pandemic. This may have discouraged potential participants from responding to the questionnaire, and possibly in different ways across distinct demographic groups. Further detail is available in Supplementary Data S4.

Future research

The next step is to undertake cognitive interviews with plwRA to assess the content validity measurement property. This will determine whether plwRA believe these items have relevance, comprehensiveness and comprehensibility in order to measure the construct of RA DA. The 12 items have different recall periods, response formats and anchor wordings, so it will be important to explore preferences around these.

If this can be evidenced, then the item pool can be used to develop a computer adaptive test (CAT) or electronic PROM. However, there are only 12 items in the item pool so the CAT will only provide a marginal burden reduction for plwRA, as a minimum of five items must be asked to cover all domains.

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Data availability statement: Data can be made available on request to the Centre for Trials Research https://www.cardiff.ac.uk/centre-for-trials-research/collaborate-with-us/data-requests

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Table 1: Items grouped by OMERACT domain

OMERACT domain	Number of items
Tenderness and swelling	3
Patient global	15
Pain	11
Pain (area-specific)	53
Fatigue	5
Physical functioning	5
Physical functioning (specific)	40
Stiffness	5
Swelling	1
Discomfort/fear	4
Mood	3

OMERACT, Outcome Measures in Rheumatology

Table 2: Descriptives of the sample of people living with rheumatoid arthritis who responded to the questionnaire

		Dataset						Total		
		Original			Validation					
		n	%/Mean|SD		n	%/Mean|SD		n	%/Mean|SD	
Current age		397	63.6	13.25	292	64.0	12.23	689	63.8	12.82
Age at diagnosis		383	45.9	15.68	283	47.1	15.71	666	46.4	15.69
Disease duration		382	17.6	13.82	283	16.9	13.42	665	17.3	13.65
Gender	Male	122	30.7		103	35.2		225	32.6	
	Female	276	69.3		190	64.8		466	67.4	
	Prefer to self-describe	0	0.0		0	0.0		0	0.0	
	Rather not say	0	0.0		0	0.0		0	0.0	
Same gender as assigned at birth?	Yes	398	100.0		292	100.0		690	100.0	
	No	0	0.0		0	0.0		0	0.0	
	Rather not say	0	0.0		0	0.0		0	0.0	
Have you received a shielding letter from the Welsh Government or NHS?	Yes	325	81.7		216	74.0		541	78.4	
	No	70	17.6		75	25.7		145	21.0	
	Don't know	3	0.8		1	0.3		4	0.6	
	Rather not say	0	0.0		0	0.0		0	0.0	
Completed questionnaire on behalf?	Yes	19	4.8		25	8.6		44	6.4	
	No	376	95.2		266	91.4		642	93.6	
	Rather not say	0	0.0		0	0.0		0	0.0	
Best description of ethnic group or background	White	361	91.2		277	95.2		638	92.9	

	(English/Welsh/Scottish/Northern Irish/British)						
	White – other	12	3.0	11	3.8	23	3.3
	Black/African/Caribbean/Black British	4	1.0	1	0.3	5	0.7
	Asian/Asian British	10	2.5	0	0.0	10	1.5
	Mixed/multiple ethnic groups	7	1.8	1	0.3	8	1.2
	Other	2	0.5	1	0.3	3	0.4
	Rather not say	0	0.0	0	0.0	0	0.0
Highest educational qualification?	Usual high school qualifications in your country at age 16 (e.g. GCSE, O-Level)	92	23.1	90	30.9	181	26.4
	Usual high school qualifications in your country at age 18 (e.g.AS Level, A-Level)	25	6.3	18	6.2	43	6.3
	A college or university diploma or degree	132	33.5	96	33.0	228	33.3
	A higher degree or professional qualification (e.g. Doctorate or Masters level degree)	54	13.7	32	11.0	86	12.6
	None of these qualifications	58	14.7	31	10.7	89	13.0
	Other	30	7.6	21	7.2	51	7.4
	Rather not say	4	1.0	3	1.0	7	1.0
Methotrexate – Previous treatment	Yes	154	39.0	118	41.0	272	39.8
Methotrexate – Current treatment	Yes	211	53.4	135	46.9	346	50.7
Sulfasalazine – Previous treatment	Yes	156	39.5	105	36.5	261	38.2
Sulfasalazine – Current treatment	Yes	85	21.5	63	21.9	148	21.7
Hydroxychloroquine – Previous treatment	Yes	83	21.0	49	17.0	132	19.3

Hydroxychloroquine – Current treatment	Yes	102	25.8	59	20.5	161	23.6
Leflunomide – Previous treatment	Yes	44	11.1	31	10.8	75	11.0
Leflunomide – Current treatment	Yes	19	4.8	10	3.5	29	4.2
Prednisolone – Previous treatment	Yes	121	30.6	94	32.6	215	31.5
Prednisolone – Current treatment	Yes	85	21.5	39	13.5	124	18.2
Enbrel/Benepali (Etanercept) – Previous treatment	Yes	45	11.4	51	17.7	96	14.1
Enbrel/Benepali (Etanercept) – Current treatment	Yes	38	9.6	33	11.5	71	10.4
Humira/Amgevita (Adalimumab) – Previous treatment	Yes	36	9.1	27	9.4	63	9.2
Humira/Amgevita (Adalimumab) – Current treatment	Yes	25	6.3	24	8.3	49	7.2
Cimzia (Certolizumab) – Previous treatment	Yes	16	4.1	5	1.7	21	3.1
Cimzia (Certolizumab) – Current treatment	Yes	11	2.8	1	0.3	12	1.8
Remicade/Inflectra (Infliximab) – Previous treatment	Yes	13	3.3	16	5.6	29	4.2
Remicade/Inflectra (Infliximab) – Current treatment	Yes	4	1.0	4	1.4	8	1.2
Simponi (Golimumab) – Previous treatment	Yes	0	0.0	2	0.7	2	0.3
Simponi (Golimumab) – Current treatment	Yes	0	0.0	0	0.0	0	0.0
Orencia (Abatacept) – Previous treatment	Yes	14	3.5	9	3.1	23	3.4
Orencia (Abatacept) – Current treatment	Yes	9	2.3	7	2.4	16	2.3
Mabthera (Rituximab) – Previous treatment	Yes	24	6.1	19	6.6	43	6.3
Mabthera (Rituximab) – Current treatment	Yes	26	6.6	16	5.6	42	6.1
Roactemra (Tocilizumab) – Previous treatment	Yes	13	3.3	12	4.2	25	3.7
Roactemra (Tocilizumab) – Current treatment	Yes	17	4.3	9	3.1	26	3.8
Kevzara (Sarilumab) – Previous treatment	Yes	1	0.3	0	0.0	1	0.1
Kevzara (Sarilumab) – Current treatment	Yes	2	0.5	0	0.0	2	0.3
Xeljanz (Tofacitinib) – Previous treatment	Yes	2	0.5	3	1.0	5	0.7
Xeljanz (Tofacitinib) – Current treatment	Yes	2	0.5	1	0.3	3	0.4
Olumiant (Baricitinib) – Previous treatment	Yes	11	2.8	12	4.2	23	3.4
Olumiant (Baricitinib) – Current treatment	Yes	15	3.8	22	7.6	37	5.4
Fibromyalgia	Yes	25	6.5	24	8.6	49	7.4

Osteoarthritis	Yes	127	33.2	83	29.6	210	31.7
Cancer	Yes	48	12.5	32	11.4	80	12.1
Heart disease	Yes	49	12.8	32	11.4	81	12.2
Chronic Bronchitis	Yes	20	5.2	11	3.9	31	4.7
Depression	Yes	69	18.0	50	17.9	119	17.9
Diabetes	Yes	44	11.5	30	10.7	74	11.2
Stroke	Yes	15	3.9	13	4.6	28	4.2
Other medical condition	Yes	173	45.2	124	44.3	297	44.8
Site	Cardiff and Vale UHB	308	77.4	1	0.3	309	44.7
	Swansea Bay UHB	69	17.3	275	93.9	344	49.8
	Aneurin Bevan UHB	20	5.0	10	3.4	30	4.3
	Cwm Taf Morgannwg UHB	1	0.3	7	2.4	8	1.2
In addition to Sex (via Gender and Same as assigned at birth?), the following variables are used for the assessment of Differential Item Functioning under RMT							
Age Group	18 to 54	85	21.4	64	21.9	149	21.6
	55 to 74	240	60.5	170	58.2	410	59.5
	75+	72	18.1	58	19.9	130	18.9
Age at Diagnosis Group	2 to 36	109	28.6	72	25.4	181	27.3
	37 to 56	166	43.6	130	45.9	296	44.6
	57+	106	27.8	81	28.6	187	28.2
Earlier and accompanying diseases	Yes	292	76.2	214	76.4	506	76.3
	No	91	23.8	66	23.6	157	23.7
Previous DMARD treatment	Yes	292	73.9	215	74.7	507	74.2
	No	103	26.1	73	25.3	176	25.8

Highest educational qualification	Qualifications below university graduate	204	52.3	160	55.6	364	53.7
	University graduate qualification as minimum	186	47.7	128	44.4	314	46.3

SD, standard deviation
UHB, University Health Board
RMT, Rasch measurement theory

Table 3: Details from the *Patient global* domain RMT analysis: residual principal component loading and residual correlations

Item	Domain	Residual loading on first principal component	Residual correlations									
			T01	D01	Q03	PS1	A01	P01	R05	PS2	T04	C01
T01	*Disease activity*	0.768										
D01		0.749	0.548*									
Q03		0.694	0.573*	0.420*								
PS1		0.407	0.043	0.205*	0.022							
A01		0.264	-0.054	0.088	-0.100	0.426*						
P01	*General health*	-0.278	-0.323	-0.365	-0.284	-0.161	-0.157					
R05		-0.328	-0.307	-0.372	-0.393	-0.215	-0.196	-0.020				
PS2		-0.605	-0.430	-0.296	-0.375	-0.120	-0.171	-0.040	-0.145			
T04		-0.693	-0.398	-0.381	-0.347	-0.356	-0.213	-0.129	-0.033	0.467*		
C01		-0.717	-0.441	-0.449	-0.364	-0.326	-0.211	-0.048	-0.025	0.405*	0.565*	

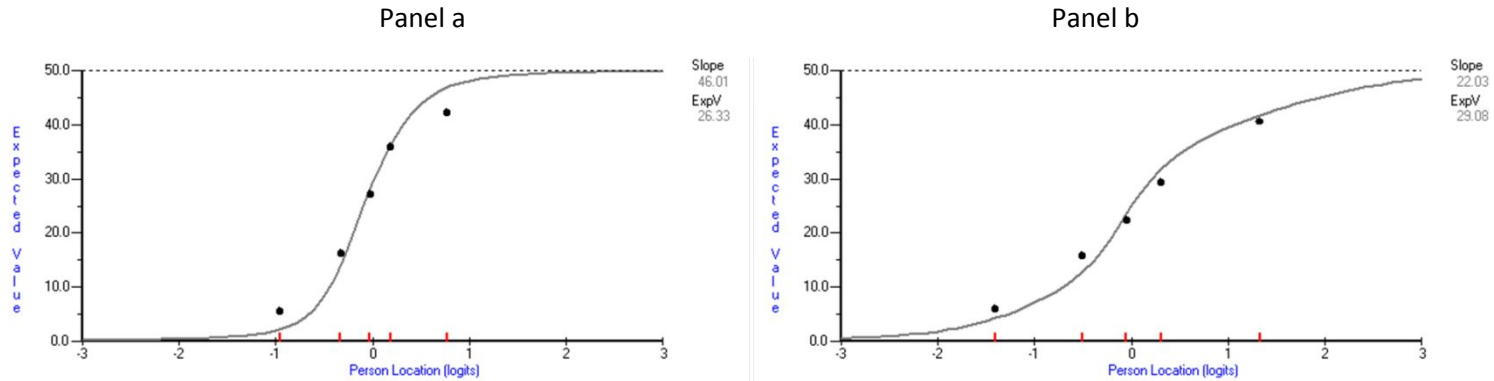
* indicates correlations above the threshold for local dependence of (mean residual correlation + 0.2) = (-0.1 + 0.2) = 0.1

Figure 1: Principal component analyses summary

Tenderness and swelling All 3 items carried forward	**Pain (area-specific)** All items discarded	**Physical functioning (specific)** All items discarded	**Discomfort/fear** All items discarded
Patient global 10 items carried forward; 5 items (from RADAI-F5 and FLARE-RA) discarded	**Fatigue** 4 items carried forward; 1 item (from FLARE-RA) discarded	**Stiffness** 3 items carried forward; 2 items (from RADAI-F5 and FLARE-RA) discarded	**Mood** All items discarded
Pain 8 items carried forward; 3 items (from FLARE-RA) discarded	**Physical functioning;** 2 items carried forward; 3 items (from RADAR and FLARE-RA) discarded	**Swelling** All items discarded	**Total** 30 items carried forward

ALT TEXT: Figure summarising within domain results of analyses that determine which domains, and which items within those domains, are taken forward for further analyses.

Figure 2: Item characteristic curves for the *Fatigue* domain-level testlet (from the analysis of all seven domain-level testlets, Panel a) and for the *Patient global* domain-level testlet (from the analysis of six domain-level testlets minus *Fatigue,* Panel b)

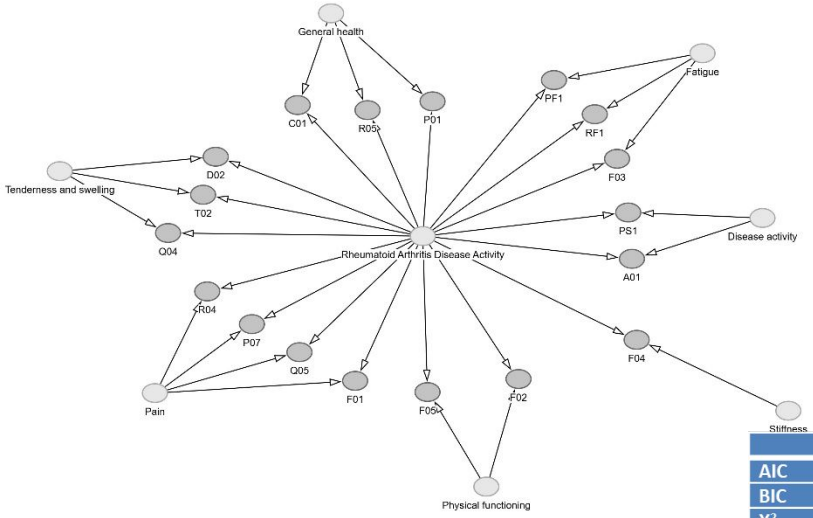


The observed data (dots) should follow the ogive hypothesised by the Rasch measurement model. The observed data patterns here are flatter than the hypothesised ogive indicating under-discrimination.

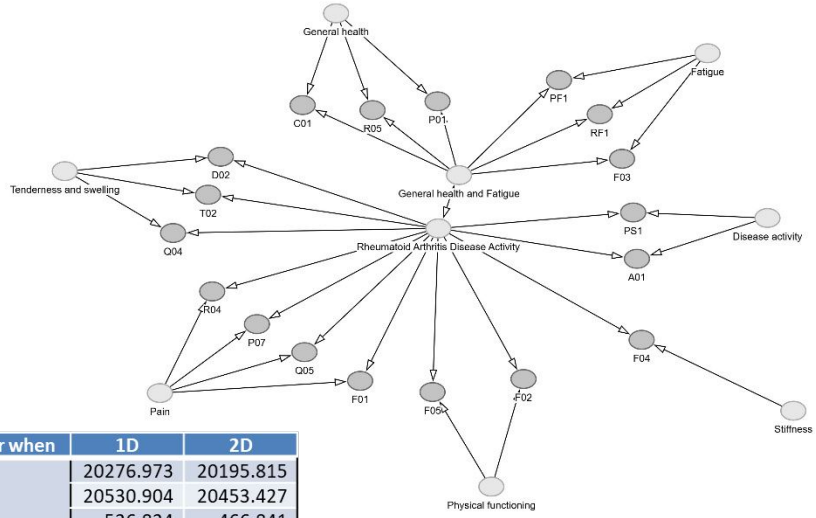
ALT TEXT: Graphs illustrating the lack fit of observed data to the Rasch measurement model, firstly for the *Fatigue* domain-level testlet secondly for the *Patient global* domain-level testlet.

Figure 3: Diagrammatical representations of the 1-dimensional and 2-dimensional bifactor models assessed by confirmatory factor analysis and results from these models

1-dimensional bifactor model (all items linked to construct of RA DA)



2-dimensional bifactor model (*Disease activity*, *Stiffness*, *Physical functioning*, *Pain* and *Tenderness and swelling* domain items linked to construct of RA DA; *General health* and *Fatigue* domain items linked to a separate construct to the construct of RA DA)



	Better when	1D	2D
AIC	Small	20276.973	20195.815
BIC		20530.904	20453.427
X^2		526.824	466.841
X^2/DF		4.390	3.923
RMSEA		0.108	0.100
SRMR		0.055	0.040
CFI	Large	0.929	0.940
TLI		0.910	0.922

AIC, Akaike information criterion
BIC, Bayesian information criterion
DF, degrees of freedom
RMSEA, root mean square error of approximation
SRMR, standardised root mean square residual
CFI, comparative fit index
TLI, Tucker-Lewis index

ALT TEXT: Diagrams representing two different bifactor models alongside confirmatory factor analysis results of these models. The first bifactor model has all items linked to construct of RA DA. The second has *Disease activity*, *Stiffness*, *Physical functioning*, *Pain* and *Tenderness and swelling* domain items linked to construct of RA DA, with *General health* and *Fatigue* domain items linked to a separate construct to the construct of RA DA.