HHS Public Access

Author manuscript

Curr Rheumatol Rep. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Curr Rheumatol Rep. 2015 April ; 17(4): 501. doi:10.1007/s11926-015-0501-8.

Patient Reported Outcomes in Rheumatoid Arthritis Clinical Trials

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Abstract

Patient Reported Outcomes (PRO) are at the core of assessing RA treatment response with patient assessments of global health or disease activity, pain, and physical function included in the calculation of American College of Rheumatology (ACR) responses. Progress has been made in assessing PROs that include additional patient-valued aspects of disease in recent RA randomized clinical trials (RCTs), particularly fatigue. Importantly, the National Institute of Health (NIH) - Patient Reported Outcomes Measurement Information System (PROMIS) development of psychometrically advanced generic health measures that span the range of symptoms potentially affected in RA, with high precision across the entire range of a symptom are undergoing additional study in RA and other rheumatologic diseases to establish their construct validity, responsiveness, and clinically meaningful cutoffs. PRO measures that are currently used and widely available can provide important perspectives not captured in composite clinical response criteria with the potential of better informing treatment decisions in clinical practice.

Keywords

Rheumatoid Arthritis (RA); Patient Reported Outcomes (PRO); Patient Reported Outcomes Measurement Information System (PROMIS); Fatigue; Stiffness

Introduction

In recent years, there has been increasing emphasis from multiple groups to integrate outcomes that reflect the symptoms and life impact of disease of most relevance to patients as endpoints in clinical trials and as part of standard clinical assessments in practice (1–4). Patient Reported Outcomes (PROs) are outcomes assessed directly from the patient, without interpretation from the physician.

Some PROs have been included as part of Rheumatoid Arthritis (RA) composite outcome measures used in clinical trials (CTs) and clinical assessment for many years. Those

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routinely collected however reflect only global disease activity or general health, pain, and physical function, and may not encompass the spectrum of symptoms, health related quality of life, and disease impact experienced by patients. The Outcome Measures in Rheumatology Clinical Trials (OMERACT) group played a crucial role in this effort which led to development of the first core set for outcomes in RA CTs in 1994 (5, 6). There is now evidence from a systematic review that elements in the initial RA core set are increasingly being assessed in RA clinical trials; however, the use of the core set is frequently incomplete, and there is wide heterogeneity in terms of choices for outcome measures (7). Heterogeneity in CT outcomes and outcome measures make treatment effectiveness comparisons more difficult.

Evolution of PRO Development and Validation

The original OMERACT filter (of measure truth, discrimination, feasibility) and framework (8) for selecting and developing core outcome measures was recently revised to be applicable across diseases and conditions, and emphasized the importance of patient input in determining the domains of relevance to their health condition and improve generalizability of the process across diseases and study designs (9–12). Recognizing the importance of the patient perspective, OMERACT involved patients as research partners in outcome measure development beginning in 2002 (13).

The US National Institutes of Health (NIH) initiative, Patient-Reported Outcomes Measurement Information System (PROMIS®, www.nihpromis.org) is a multi-disciplinary effort to develop and standardize PRO measures across the spectrum of domains of health-related quality of life applicable for multiple chronic medical conditions. This system was developed based on item response theory to provide a population-normalized metric, with limited floor and ceiling effects, and improved precision compared to most PROs in common use (14). The NIH-PROMIS framework is based on the 2001 World Health Organization (WHO) International Classification of Functioning Disability and Health (ICF) framework (15) and encompasses item banks and instruments for physical, emotional, and social health, applicable across many chronic diseases, including RA. PROMIS measures are reported as a T-score, with the US population mean of 50 for all domains, and a change in 10 representing 1 standard deviation.

In part because of the variability of PROs currently in use and questions concerning their validation within the patient populations included in clinical trials, the US Food and Drug Administration (FDA) has put forward guidance for the drug industry on the use of PROs as end points in RCTs, which includes a requirement for patient input at early stages to develop a conceptual framework and ensure the content validity of draft instruments (16). More recently, there has been guidance toward validating PRO instruments in new populations, a process that may begin in phase II RCTs, to hypothesize on and test psychometric properties of PROs before engaging in larger scale trials (17). The Critical Path Institute (C-Path) brings together the FDA and industry in a partnership to enhance development of therapeutics resulting from medical research. Within C-Path, the PRO Consortium is concerned with developing PRO measures for use as endpoints in CTs. An RA working group was established in 2010 to focus on RA-related signs and symptoms (18).

Developing the evidence towards qualified PROs requires considerable validation efforts and a rigorous process to ensure that measures are reflective of the intended concept, and are reliable, responsive, and interpretable in their intended setting. The COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) group had previously developed a checklist to ensure PRO properties and quality were standardized (19, 20). The International Society of Quality of Life Research (ISOQoL) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) have recently published standards for PRO development and validation (21–26).

The European League against Rheumatism (EULAR) (27) has also recognized the importance of patient involvement as partners in research and practice guideline development, and has developed new PROs for RA (28) and psoriatic arthritis (29) that are more inclusive of patient-valued domains of health than the current RA core set. EULAR has also established an outcome measure library (http://oml.eular.org/) where multiple PRO measures are available with information on source, development process, existing evidence for validation and available translations (30).

The Patient Centered Outcomes Research Institute (PCORI) in the US issued methods guidance for medical research (4, 31) to prioritize patient centered outcomes, in contrast to traditional comparative effectiveness research endpoints. PCORI methodology standards place emphasis on patient involvement in all stages of medical research, from decisions on prioritization of research agenda to dissemination and implementation of research findings.

There have been a number of new developments in PROs for RA since the last review on the topic in 2012 (32). RCTs of tofacitinib have been finalized and this drug gained FDA approval for RA treatment and including PRO endpoints (33–36). Head-to-head biologic (37–39) and medication tapering RCTs have also been conducted (40, 41) with information on PROs. Consensus on important patient-valued aspects of health-related quality of life for RA patients experiencing a flare has been reported that expands beyond the traditional RA Core set to include fatigue, stiffness, participation, and self-management (42–45). And as noted above EULAR has developed a new PRO, the RA Impact of Disease (RAID) to more comprehensively assess the range of patient-valued domains, including fatigue, sleep, physical/emotional well-being and coping. The introduction of fatigue as a core PRO represents a landmark in RA and is a direct consequence of patient involvement as research partners (12, 13, 46).

Patient Reported Outcomes in RA Clinical Trials

Methods

Prior reviews of PROs in RA have been published in 2012 (32) and 2013 (7), and evaluated measures used through 2011 and early 2012, respectively. It was our purpose to provide an update on PROs used in RA CTs performed in 2012 through present, and to discuss PROs recently developed or in development for RA.

We performed a literature search of PubMed on 8/25/2014 using terms ("Arthritis, Rheumatoid"[Mesh] OR "rheumatoid arthritis" OR "RA") AND ("Clinical Trial"

[Publication Type] OR "clinical trial" OR "RCT" OR "randomized" OR "clinical" OR "trial") and activated filters: clinical trial, publication date from 2012/01/01 to 2014/12/31 and humans. The following data were uniformly extracted from each paper: agent/intervention, study type, number of participants, primary endpoint, primary endpoint PRO (y/n) and specific PRO used, secondary endpoint PRO(s) (y/n) and specific PRO(s) used.

Results

The literature search yielded 879 entries. After review of titles and abstracts, 121 entries representing randomized controlled trials (RCTs) conducted in RA and reported in the English language were included and were retained for full text review. Based on full text review, 15 papers were excluded for the following reasons (number of entries): secondary analyses of RCT data (5); no full text available (5); focus was not RA (3); longitudinal observational study (1); phase I clinical trial (1). One hundred and six papers representing 96 unique RCTs were retained for data extraction and constitute the basis for this review.

Of 96 RCTs one was phase IV, 63 were phase III and 33 were phase II or proof of concept. There were 64 biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) (2 biosimilar), 8 traditional DMARDs (tDMARDs) and prednisone, 16 other agents (small molecules, other drugs/formulations); and 8 non-drug interventions. In 13 RCTs PROs were assessed as primary outcomes (6 phase III bDMARD, 1 tDMARD, 6 non-drug). In 44 RCTs PROs were assessed as secondary outcomes. Primary outcomes of the 96 RCTs are summarized in Table 1.

PROs used in RA RCTs, in order of frequency were: physical function (HAQ-DI), ACR core set PRO components (patient pain, patient global, physical function), fatigue (FACIT-fatigue, fatigue 100 mm VAS), HRQL (SF-36, SF-12, EQ5-D, RAQoL), morning stiffness duration, patient self-assessment of disease activity (RAPID3, RADAI), self-efficacy (RASE, ASES-D), depression/anxiety and sleep (Table 2).

ACR Core Set PROs

The ACR core set (6) is measured in RA clinical trials through the ACR20/50/70 composite responses which require assessment of 3 PROs (patient global assessment of disease activity, pain, and disability) in addition to physician and laboratory data (tender/swollen joint counts, physician global assessment and inflammatory markers) (47). Disability as measured by the HAQ-DI has also been reported separately as a secondary outcome in a majority of RA trials. Pain and patient global assessment are rarely reported as separate outcomes, although it was demonstrated in CT datasets these PROs are significant independent predictors of treatment response (48) and they should also be reported individually.

Physical Function—Health Assessment Questionnaire - Disability Index (HAQ-DI)

(49) a 41 item questionnaire (20 items for daily activities, 13 items assistive devices, 8 items for help from others), or its shortened 8 item version (M-HAQ) (50) have been almost universally assessed as secondary outcomes in RA RCTs according to the ACR core set (6). Recently the HAQ-DI was assessed as co-primary outcome with ACR20 responses and DAS

indices in tofacitinib (33, 34), golimumab (51) and traditional DMARD (52) RCTs. Even though the concepts of disability and physical function are related, the HAQ–DI is limited by a floor effect in the absence of disability (a normal score is 0 to 0.5; total range is 0 to 3) since it has limited ability to detect change within the range of normal physical function (53). The M-HAQ is further limited by floor and ceiling effects. As expectations for functional status in RA have improved over the past decades (54) measures that can discriminate changes within the normal and higher performance range of physical abilities are needed. A change of 0.22 – 0.25 in the HAQ-DI is currently accepted as the minimum clinically important difference (MCID) in RCTs, however a recent study suggests the minimum clinically important improvement (MCII) is larger: a decrease of 0.375 would be needed in the HAQ score (55).

Patient Reported Outcomes Measurement Information System (PROMIS) -Physical Function: PROMIS is an NIH-funded project consisting of a library of generic health measures developed using item response theory and normalized to the US general population to compare health status in chronic diseases. PROMIS measures are free to use through www.nihpromis.org and the Assessment Center (www.assessmentcenter.net), and international expansion is ongoing (56). The PROMIS physical function PRO has been reported to date for RA (57–59), osteoarthritis (60) and scleroderma (61). The responsiveness of the PROMIS - Physical Function was superior to SF-36 and HAQ-DI in a study of RA patients, and the suggested MCID from a longitudinal observational study in RA was 0.2 SD (57). In a recent study the PROMIS - Physical Function 10-item computer adaptive test (CAT) had the most desirable coverage across the range of physical function, with greatly improved precision, especially at lower levels of disability and improved physical function compared to HAQ-DI and SF-36 physical functioning scale (58).

PROs of RA disease activity

Routine Assessment of Patient Index Data 3 (RAPID3) is a composite disease activity index consisting of the 3 PROs included in the ACR Core Set: disability, pain, and patient global assessment of disease activity (62). Disability is measured using the multidimensional HAQ (MD-HAQ) (63) a 10-item questionnaire that adds 2 items “(over the last week were you able to) walk 2 miles or 3 kilometers” and “participate in recreational activities and sports as you would like” to the 8-item MHAQ. For the calculation of RAPID3, MD-HAQ (range 0–3), patient global assessment of disease activity (DA) VAS (range 1–10) and pain intensity VAS (range 1–10) are entered into a total weighted score: (MDHAQ×3.33) + DA + Pain. RAPID3 scores range is 0–30, and disease activity categories are remission 0–3, low >3.1–6, moderate >6.1–12, and high >12. RAPID3 is currently used in clinical care by an estimated 29% of US rheumatologists and has been assessed in longitudinal cohorts (64). In a post-hoc analysis of a RCT of certolizumab, RAPID3 (computed using the original HAQ instead of the MDHAQ), had highest correlations with pain VAS (0.94) and patient global assessment (0.95) as might have been expected as they are components of the composite index. Correlations with DAS28 and with CDAI, which both include a patient global assessment, were 0.73 and 0.70 (65), respectively. In a longitudinal RA study, the correlation of RAPID3 with DAS28 and CDAI scores (averaged across 4 clinicians) was lower, 0.43 and 0.61 respectively (66). The MCID/MCII has not been defined for RAPID3.

Additional questions concerning sleep and coping with ("dealing with") anxiety/depression are included on the RAPID3 form suggested for use in clinical care, but are not included in the calculation of the value. Two RCTs with biologic agents included in this review assessed RAPID3 as a secondary outcome (Table 2). In the case of tocilizumab mean baseline RAPID3 scores were 5.2 and there was a statistically significant difference in RAPID3 mean decrease from baseline to 24 weeks ($p<0.0001$) between treatment arms: −2.33 in the tocilizumab arm versus −1.29 in the placebo arm (67). In a non-inferiority trial of abatacept versus adalimumab, RAPID3 scores at 52 weeks similarly decreased from baseline in both arms: −2.87 versus −2.74 respectively (37).

Rheumatoid Arthritis Impact of Disease (RAID) is a multidimensional PRO developed by EULAR with extensive patient involvement in selection of domains and domain weight attributions (28, 68). Domains assessed (highest to lowest weight as ranked by patients) are pain, functional disability, fatigue, sleep, physical/emotional well-being, and coping, measured as a separate numerical rating scale (NRS) for each concept measured. A simplified domain sum scoring has been proposed instead of the weighted score to increase feasibility (69).

Preliminary validation of RAID in RA has been performed in 1 multinational study (n=570 patients) where the highest correlations observed were with patient global assessment VAS (0.76), and DAS 28 (0.69) (28). Reliability in the same study was high (0.9, 95%CI: 0.96, 1.00), and the measure was sensitive to change after changes in treatment (standardized response mean 0.98, 95%CI: 0.96, 1.00)(28). The RAID was also examined in a cross-sectional study in the Oslo RA registry (n=1086) in which the highest correlations were observed with patient global VAS (0.82), pain VAS (0.80) and the Rheumatoid Arthritis Disease Activity Index (RADAI (0.82) (70). RAID thresholds for clinically significant change (minimally clinically important improvement, and patient acceptable symptom state) have been recently examined in one data set but require further study (71). While RAID is reflective of important domains and responsive to change, its utility as an endpoint in RCTs and clinical care has yet to be established, and its psychometric evaluation using modern measurement theory methods has not been reported. Importantly, RAID includes an assessment of fatigue, the third highest domain prioritized by patients in its derivation and also confirmed as important in many prior studies (46).

Health Related Quality of Life

Medical Outcomes Study Short Form – 36 (SF-36) is a generic 36-item HRQL measure that is frequently used in RA clinical trials with higher scores indicating better health (72). The measure is proprietary with a charge per use and its complex scoring algorithm severely limits its utility in clinical practice settings. The SF-36 has 8 component sub-scales (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health) and can also be scored into 2 summary scales: the physical health summary (PCS) and the mental health summary (MCS). The minimally important changes in these scales have been determined in RA at 4.4 for PCS and 3.1 for MCS (73, 74). There is a similar RAND-36 measure of HRQL (the original SF-36 used in the Medical Outcomes Study) that is free of charge, but its utility in clinical care is similarly limited by its complex

scoring algorithm (75). **SF-12** Health Survey is a generic 12-item short form derived from the original SF-36 items to increase feasibility of administration (76) (77). The SF-36 physical functioning scale has been compared to the HAQ-DI and to PROMIS physical function. The performance of the SF-36 physical functioning scale and HAQ-DI are largely dependent on the level of physical function with the SF-36 best identifying change in the normal physical function range and HAQ-DI in the lower physical function range, limiting the usefulness of either one for patients along the continuum of physical abilities or at higher levels of physical functioning (53, 58, 78). Variation in physical capacity is expected to occur during the course of rheumatologic disease, RA in particular where periods of flare and remission are part of the disease experience (9, 43).

Rheumatoid Arthritis Quality of Life (RAQoL) is a RA-specific multidimensional 30-item questionnaire with dichotomous (yes/no) items. The questionnaire has data to support reliability, validity and sensitivity to change in RA, it is however infrequently used in RA clinical trials due to its impractical length as a single disease-specific measure and the inherent psychometric limitations of instruments containing only dichotomous response options (79).

Fatigue

Fatigue was first recommended for inclusion in RA clinical trials by OMERACT since 2007 (46, 80) and is increasingly is being assessed in RCTs; measures of fatigue were specifically reported in 17 of 96 RCTs in the past 2 years. The different fatigue measures used in RA have been previously reviewed (81) including a VAS and the Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F). New validation data concerning the use of the RA-specific Bristol Rheumatoid Arthritis Fatigue (BRAF) measure are available as well as preliminary data on use of PROMIS-Fatigue measures in osteoarthritis (60), scleroderma (61) and RA (82). As noted above the RAID includes a fatigue item within its calculation, but the independent fatigue scores have not been reported in clinical trials to date.

Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F) has commonly used in RA RCTs. FACIT-F is a 13-item PRO that covers multiple fatigue dimensions, initially developed in patients with anemia in oncology and subsequently adapted for use in other chronic conditions (83). Higher scores reflect less fatigue. FACIT-F has been used in RA and showed reliability, validity and sensitivity to change (84). A minimally important difference (MID) in RA has been confirmed at 3–4 points on a scale of 0–52 (84). Table 3 summarizes changes in FACIT-F in recent RCTs. In most RCTs, FACIT-F changes exceeded the MID with effective RA therapy and in many cases was able to discriminate between treatments (Table 3).

Fatigue visual analog scales (VAS)—These have also been used, with the caveats that fatigue VAS are not standardized, descriptions of the exact items and anchors are lacking, and therefore these measures may not be interchangeable when compared across interventions (85).

The Bristol Rheumatoid Arthritis Fatigue (BRAF) measures are RA-specific PROs developed using qualitative research with patients with RA to establish face and content

validity, followed by factor analysis and item debriefing. The measures consist of 3 unidimensional items (each available in standardized VAS and NRS format) for fatigue severity, effect, and coping respectively; and a multidimensional 20-item fatigue questionnaire (BRAF-MDQ) (86). Reliability and sensitivity to change with treatment (corticosteroid) have been shown in one study, and preliminary data on minimum clinically important difference for improvement and worsening have been suggested for each of the NRS and the BRAF-MDQ (87). The BRAF measures were recently compared to the SF-36 Vitality scale using item response theory with the finding that the BRAF-MDQ has highest discrimination in the high fatigue range and the SF-36 Vitality scale in the low-moderate fatigue range (88) due to preferential coverage of these extremes on the fatigue continuum. These results with fatigue are similar to HAQ-DI versus SF-36 physical functioning scale described above.

Stiffness

Morning stiffness duration was assessed in 8 RCTs (2 biologic, 2 DMARD, 1 modified release prednisone, 1 exercise training, 3 other) and was a key secondary outcome in the modified-release prednisone RCT (89). Morning stiffness duration is also a component of the RADAI questionnaire, assessed as co-primary outcome in 1 DMARD trial in this review (52). Duration of morning stiffness has not been a responsive tool in assessing treatment effect in RA possibly due to lack of standardization (heterogeneous assessment) or problems with the construct validity of the measure (6). Indeed, recent qualitative research with patients with RA confirmed stiffness as an important part of the RA experience with multiple aspects: impact on daily life choices, timing, location, severity, and also duration (90, 91). These studies would suggest that a single question concerning morning stiffness duration was inadequate in capturing the symptom as experienced and described by most patients. An assessment of stiffness severity was also included as an outcome in one previous delayed prednisone study (92).

Discussion

Qualitative studies in people living with RA have emphasized that multiple aspects of HRQL are important parts of the patient experience, and potentially amenable to therapy. Current composite response criteria in RA have limitations, namely heavier weighting of joint counts therefore underestimating patient reported improvement (93). It has been suggested that presenting a range of additional PRO results in clinical trials beyond the existing Core Set may provide better understanding of heterogeneous treatment responses within a particular sample (93). Assessment of additional PROs also becomes important to be able to differentiate between categories of non-responders: individuals with comorbidity such as depression, anxiety, and chronic musculoskeletal pain versus treatment-resistant RA (94, 95). PROs can also contribute information in setting treatment goals in clinical practice such as in targeting low disease activity versus remission (96). Clinically meaningful improvement (MCID/MCII), ideally anchored in long term outcomes, for each PRO must be known for correct interpretation of change within these measures (97).

Conclusion

PROs provide important complementary information to clinical disease activity measures used in clinical trials and for clinical practice. The growing emphasis on patient- centered outcomes and patient-centered care is providing additional impetus to expand PRO assessments to be more reflective of aspects of health most valued by patients. While some PROs are routinely collected as outcomes in RA, newer standards for PRO development and validation and advanced psychometric methods are demonstrating deficiencies of some of these in terms of their content and construct validity, responsiveness, and precision. This does not, however, negate the importance of those measures that are currently used and widely available as these can provide important perspectives not captured in composite clinical response criteria. But it does point to the opportunities for more robust PRO measures to better inform patient-level decision making in the future.

ACKNOWLEDGEMENT

Dr. Ana-Maria Orbai is supported by a Scientist Development Award from the Rheumatology Research Foundation (RRF).

Dr. Bingham was supported in part through a Patient-Centered Outcomes Research Institute (PCORI) Pilot Project Program Award (1IP2-PI000737-01).

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors, or Methodology Committee. Dr. Bingham is a member of the Executive Committee of OMERACT (Outcome Measures in Rheumatology), an international group that develops and evaluates health outcomes; OMERACT receives hands-off funding from more than 23 pharmaceutical and research companies.

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Table 1

Primary and co-primary outcomes assessed in RA randomized controlled trials (RCTs) conducted 2012–2014

RCT Outcomes	Primary (N=96)	Co-primary
Composite		
ACR20/50/70	45	2
ACR-N	2	-
DAS28	15	4
DAS44	1	-
EULAR response	3	-
Modified ACR remission	1	-
Patient Reported		
HAQ-DI	2	8
DASH	1	-
Pain VAS	1	-
RADAI	-	1
Clinician Reported		
DAS28CRP	7	-
TJC, SJC	2	-
Other		
Radiologic	8	7
Safety	5	-
NSAID requirement	1	-
Joint protection behavior	1	-
LDL reduction	1	-

Abbreviations in order of appearance in text:ACR20/50/70 American College of Rheumatology response indices; ACR-N American College of Rheumatology Index of Improvement; DAS28 disease activity index with 28 swollen/tender joint counts; EULAR European League Against Rheumatism;HAQ-DI Health Assessment Questionnaire Disability Index; DASH Disability of the Arm Shoulder and Hand; VAS Visual Analog Scale; RADAI Rheumatoid Arthritis Disease Activity Index; DAS28CRP DAS28 disease activity index with 28 swollen/tender joint counts and C reactive protein; TJC, SJC tender, swollen joint counts; NSAID nonsteroidal anti-inflammatory drug; LDL low density lipoprotein;

Table 2

Patient Reported Outcomes as Secondary Outcomes assessed in RA RCTs conducted 2012–2014

Patient Reported Domain	PROs (secondary outcomes, multiple outcomes per each RCT)	Number of RCTs (N=96)
Physical Function*	HAQ-DI	65
Patient Global*	VAS 100mm	27
Pain*	Pain 100mm VAS	30
	McGill Pain Questionnaire	1
	Brief Pain Inventory	2
	Morning pain intensity	1
Fatigue	FACIT-Fatigue	13
	Fatigue 100mm VAS	3
	RAQoL item #21	1
Health Related Quality of Life	SF-36	16
	RAQoL	4
	SF-12	3
	EQ5D	4
	EUROHIS-QUOL8	1
Patient Reported Disease	RAPID3	2
Activity	RADAI	1
Stiffness	Morning stiffness duration	8
Self-Efficacy	ASES	3
	RASE	1
Mood	Beck Depression Inventory	1
	HADS Depression	1
	HADS Anxiety	2
	STAI Anxiety	1
Work Limitations	WLQ	1
Sleep	MOS Sleep Scale	1

* PROs in the ACR RA core set(6)

Abbreviations in order of appearance in table: HAQ-DI Health Assessment Questionnaire - Disability Index;VAS Visual Analog Scale; FACIT-Fatigue Functional Assessment Chronic Illness Therapy-Fatigue; RAQoL Rheumatoid Arthritis Quality of Life; SF-36 Medical Outcomes Study Short Form-36; SF-12 Short Form-12; EQ5D EuroQoL 5D questionnaire; EUROHIS-QUOL8 EUROHIS (World Health Organization) Quality of Life 8-item index; RAPID3 Routine Assessment of Patient Index Data 3; RADAI Rheumatoid Arthritis Disease Activity Index; ASES Arthritis Self-Efficacy scale; RASE Rheumatoid Arthritis Self-Efficacy scale; HADS Hospital Anxiety and Depression Scale; STAI State-Trait Anxiety inventory; WLQ Work Limitations Questionnaire; MOS Sleep scale Medical Outcomes Study Sleep scale.

Table 3

Change in fatigue as measured by FACIT-Fatigue^ in RA RCTs

RCT (N=13)	Agent / Active comparator	Interval (wks)	Active Arm(s)- Mean change from baseline (SD,- not provided)	Placebo/MtTX* Arm- Mean change from baseline (SD)	P value
Phase IV					
Gabay C, 2013	Tocilizumab 8/	24	11.40 (−)	-	0.08
	Adalimumab		8.90 (−)		
Phase III					
Strand V, 2012	Ada*+Mtx*/	104	14.60 (−)	13.5 (−)	<0.001
	Adalimumab/		14.60 (−)		0.900
Bingham C, 2014	Golimumab iv	24	7.96 (10.8)	2.54 (10.2)	<0.001
Genovese M, 2012	Golimumabsc	24	7.23 (8.6)	2.16 (9.5)	<0.001
Butgereit F, 2013	MR-Prednisone	12	3.80 (−)	1.6 (−)	0.003
Yazici Y, 2012	Tocilizumab 8	24	8.43 (−)	5.89 (−)	<0.001
Strand V, 2012	Tocilizumab 8	24	8.83 (−)	4.22 (−)	0.015
	Tocilizumab 4		6.66 (−)		NS
Lee EB, 2014	Tofacitininb	24	*not provided*	*not provided*	
Kremer J, 2013	Tofacitininb 10	24	3.15** (1.27, 5.02)	-	
	Tofacitinib 5		2.85** (0.95, 4.74)		
Fleischman RM, 2012	Tofacitininb 10	12	8.00 (−)	2.80 (−)	<0.001
	Tofacitinib 5		6.70 (−)		
Phase IIB					
Weinblatt M, 2013	Fostamatinib 150	24	5.70 (1.0)	4.50 (0.9)	NS
	Fostamatinib 100		7.40 (1.0)		<0.050
Kremer J, 2012	Tofacitinib		*no improvement data not shown*	*data not shown*	
Fleischman RM, 2012	Tofacitinib 5/		*improvement vs placebo data not shown*		NS
	Tofacitinib 10/				<0.001

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RCT (N=13)	Agent / Active comparator	Interval (wks)	Active Arm(s)- Mean change from baseline (SD,- not provided)	Placebo/MtTX* Arm- Mean change from baseline (SD)	P value
	Tofacitinib 15/				NS
	Adalimumab				NS

^Higher scores reflect less fatigue, clinically meaningful change is ≥4 points (84)

*Methotrexate, Adalimumab

**Difference from placebo (95%CI)