An OMERACT Initiative Toward Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group

Monika E. Finger, Annelies Boonen, Thasia G. Woodworth, Reuben Escorpizo, Robin Christensen, Sabrina M. Nielsen, Amye L. Leong, Marieke Scholte Voshaar, Caroline A. Flurey, Nataliya Milman, Suzanne M. Verstappen, Rieke Alten, Francis Guillemin, Margreet Kloppenburg, Dorcas E. Beaton, Peter S. Tugwell, Lyn M. March, Daniel E. Furst, and Christoph Pohl

ABSTRACT. ***Objective.*** The importance of contextual factors (CF) for appropriate patient-specific care is widely acknowledged. However, evidence in clinical trials on how CF influence outcomes remains sparse. The 2014 Outcome Measures in Rheumatology (OMERACT) Handbook introduced the role of CF in outcome assessment and defined them as "potential confounders and/or effect modifiers of outcomes in randomized controlled trials." Subsequently, the CF Methods Group (CFMG) was formed to develop guidance on how to address CF in clinical trials.

Methods. First, the CFMG conducted an e-mail survey of OMERACT working groups (WG) to analyze how they had addressed CF in outcome measurement so far. The results facilitated an informed discussion at the OMERACT 2016 CFMG Special Interest Group (SIG) session, with the aim of gaining preliminary consensus regarding an operational definition of CF and to make a first selection of potentially relevant CF.

Results. The survey revealed that the WG had mostly used the OMERACT Handbook and/or the International Classification of Functioning, Disability and Health (ICF) definition. However, significant heterogeneity was found in the methods used to identify, refine, and categorize CF candidates. The SIG participants agreed on using the ICF as a framework along with the OMERACT Handbook definition. A list with 28 variables was collected including person-related factors and physical and social environments. Recommendations from the SIG guided the CFMG to formulate 3 preliminary projects on how to identify and analyze CF.

Conclusion. New methods are urgently needed to assist researchers to identify and characterize CF that significantly influence the interpretation of results in clinical trials. The CFMG defined first steps to develop further guidance. (First Release May 1 2017; J Rheumatol 2017;44:1734–9; doi:10.3899/jrheum.161200)

Key Indexing Terms:
CONTEXTUAL RHEUMATOLOGY OMERACT EFFECT MODIFIER
PATIENT-REPORTED OUTCOMES RANDOMIZED CONTROLLED TRIALS

From the Empowerment, Participation and Social Integration Unit, Swiss Paraplegic Research, Nottwil, Switzerland; Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre; CAPHRI Research Institute, Maastricht University, Maastricht; Department of Psychology, Health and Technology, University of Twente, Enschede; Department of Rheumatology, and Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, the Netherlands; Division of Rheumatology, David Geffen School of Medicine, University of California, Los Angeles; Bone and Joint Decade, the Global Alliance for Musculoskeletal Health, and Healthy Motivation, Santa Barbara, California; Department of Rehabilitation and Movement Science, The University of Vermont, Burlington, Vermont, USA; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark; Faculty of Health and Applied Sciences, University of the West of England, Bristol; Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, UK; Division of Rheumatology, Department of Medicine, University of Ottawa and Ottawa Hospital; Centre for Global Health, Institute of Population Health, University of Ottawa and Ottawa Hospital; Department of Clinical Epidemiology, Ottawa Hospital Research Institute; Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa; Musculoskeletal Health and Outcomes Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital; Institute for Work and Health, and Institute of Health Policy, Management and Evaluation, Rehabilitation Sciences Institute, and Departments of Occupational Science and Occupational Therapy, University of Toronto, Toronto, Ontario, Canada; Schlosspark-Klinik, University Medicine Berlin, Berlin, Germany; University of Lorraine, EA 4360 APEMAC, Nancy, France; Institute of Bone and Joint Research, University of Sydney; Rheumatology and Musculoskeletal Epidemiology, Sydney Medical School, Sydney; Department of Rheumatology, Royal North Shore Hospital, St Leonards, Australia.

The Musculoskeletal Statistics Unit at the Parker Institute (SMN and RC) is supported by grants from the Oak Foundation.

M.E. Finger, PT, PhD, MPTSc, Empowerment, Participation and Social Integration Unit, Swiss Paraplegic Research; A. Boonen, MD, PhD, Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, and CAPHRI Research Institute, Maastricht

University; T.G. Woodworth, MD, Consultant, Division of Rheumatology, David Geffen School of Medicine, University of California; R. Escorpizo, PT, DPT, MSc, Empowerment, Participation and Social Integration Unit, Swiss Paraplegic Research, and Department of Rehabilitation and Movement Science, The University of Vermont; R. Christensen, PhD, MSc, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital; S.M. Nielsen, MSc, Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital; A.L. Leong, MBA, Bone and Joint Decade, the Global Alliance for Musculoskeletal Health, and Healthy Motivation; M. Scholte Voshaar, MSc, Department of Psychology, Health and Technology, University of Twente; C.A. Flurey, PhD CPsychol, Faculty of Health and Applied Sciences, University of the West of England; N. Milman, PhD, Division of Rheumatology, Department of Medicine, University of Ottawa and the Ottawa Hospital, and Department of Clinical Epidemiology, Ottawa Hospital Research Institute; S.M. Verstappen, PhD, Arthritis Research UK Epidemiology Unit, University of Manchester; R. Alten, MD, PhD, Schlosspark-Klinik, University Medicine Berlin; F. Guillemin, MD, PhD, University of Lorraine, EA 4360 APEMAC; M. Kloppenburg, MD, PhD, Professor, Department of Rheumatology, and Department of Clinical Epidemiology, Leiden University Medical Centre; D.E. Beaton, PhD, Musculoskeletal Health and Outcomes Research, Li Ka Shing Knowledge Institute, St. Michael's Hospital, and Institute for Work and Health, and Institute of Health Policy, Management and Evaluation, Rehabilitation Sciences Institute, and Department of Occupational Science and Occupational Therapy, University of Toronto, and Department of Epidemiology and Community Medicine, University of Ottawa, and Centre for Global Health, Institute of Population Health, University of Ottawa, and Ottawa Hospital; P.S. Tugwell, MD, Department of Epidemiology and Community Medicine, University of Ottawa, and Centre for Global Health, Institute of Population Health, University of Ottawa, and Ottawa Hospital; L.M. March, MBBS, PhD, Liggins Professor of Rheumatology and Musculoskeletal Epidemiology, Sydney Medical School, and Institute of Bone and Joint Research, University of Sydney, and Department of Rheumatology, Royal North Shore Hospital; D.E. Furst, MD, Division of Rheumatology, David Geffen School of Medicine, University of California; C. Pohl, MD, Schlosspark-Klinik, University Medicine Berlin.

Address correspondence to Dr. C. Pohl, Schlosspark-Klinik, Heubnerweg 2, 14059, Berlin, Germany. E-mail: christoph.pohl222@googlemail.com

Accepted for publication March 27, 2017.

The importance of contextual factors (CF) for appropriate, patient-specific care, especially in chronic conditions such as rheumatic diseases, is widely acknowledged[1,2,3,4]. CF may include sociodemographics, person-related factors, and physical and social environments[5]. However, despite logical arguments and clinical experience, evidence in clinical trials on how CF influence outcomes remains sparse[6]. Most researchers agree that CF, such as age, sex, and duration of disease, should be identified in rheumatic randomized controlled trials (RCT) to check whether an unequal distribution of CF, despite randomization, could confound the outcome. However, little is known concerning the influence of person-related factors or physical or social environment.

In addition, CF such as phenotypical subgroups (e.g., differences in disease subgroups, previous pharmacological management, or personal or environmental characteristics) can distort the net benefit (or harm), and thus have potential to act as "effect modifiers"[7]. Figure 1 illustrates a hypothetical RCT example where patients were randomized to either active intervention or placebo. The trial illustrates that these interventions are equally effective. However, reanalyzing the dataset and stratifying the analysis according to a potential CF revealed a divergent efficacy pattern in favor of the active intervention compared with the placebo in the CF-positive subgroup. For those who design trials, CF acting as effect modifiers can provide a quantitative perspective elucidating a difference in effect (i.e., net benefit) between subgroups. This has important implications for clinical practice and policymaking, such as calling for more individualized treatment strategies[8].

Acknowledging the need to integrate CF into the outcome measurement in rheumatic RCT, in 2012 the concept of CF was introduced for the first time in the Outcome Measures in Rheumatology (OMERACT) process in a preliminary version of the OMERACT Handbook. CF were defined as "variables that are not outcomes of studies, but need to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers"[9]. Several OMERACT working groups (WG; Worker Productivity[10], Hand-Osteoarthritis[11], Vasculitis[12], RA-Flare[13], and Health Literacy WG[14]), in consideration of input from patient research partners (PRP), started to include CF in their research. However, the research presented in OMERACT 2014 revealed great heterogeneity in understanding, approaching, and identifying CF. To address this confusion, the CF Methods Group (CFMG) was formed, representing "an entirely new work stream to address newly identified challenges"[15]. The mission of this group is to provide guidance to the OMERACT community and other researchers on the fundamental steps that should be implemented to identify CF that are essential for interpreting results in the setting of an RCT in rheumatology. The group consists of clinicians, statisticians, researchers, and PRP from the OMERACT WG already involved in CF research. The first objectives of the CFMG were:

1. To agree on the operational definition of CF (that can be applied to core sets or specific outcomes) among all stakeholders.
2. To inform the CFMG research agenda on how:
   a. To identify methods for the selection of relevant CF and for the statistical testing of its effect; and
   b. To understand whether the agreed definition can be applied to all settings (core sets, specific outcomes).

In its 2016 report, the CFMG highlighted the need to clarify the concept of "CF" in light of outcome measure development according to the OMERACT process. Based on the OMERACT CF definition and the International Classification of Functioning, Disability and Health (ICF) framework[16], an operational definition of CF was agreed on and a research agenda was formulated.

MATERIALS AND METHODS

In spring 2015, the CFMG analyzed the conceptualization of CF and previous research by OMERACT WG engaged in CF research in an e-mail survey. Ten questions were formulated by the CFMG members addressing the CF definitions used and the approaches to identify potentially important CF as well as strategies applied to measure and analyze the effect of CF (Table 1). The results were tabulated and the content summarized.

At the OMERACT 2016 CFMG Special Interest Group (SIG) session, a preliminary consensus on a potential operational definition of CF was estab-

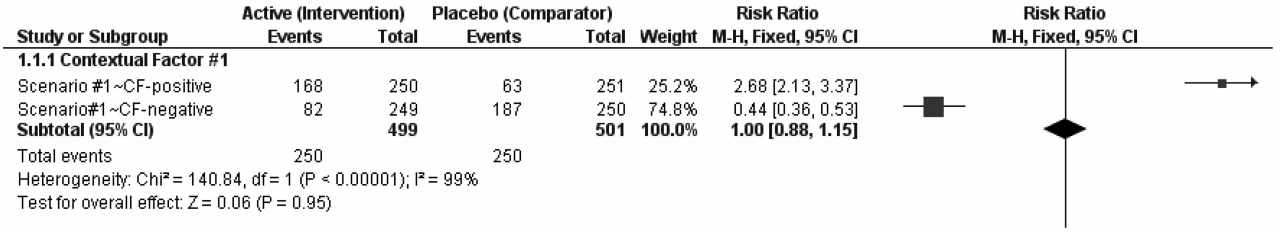

Figure 1. A hypothetical randomized controlled trial example in which 1000 patients were randomized (499 vs 501) to either active therapy or placebo and showing that both interventions are equally effective (RR SubTotal = 1.00). However, reanalyzing the dataset, stratifying the analysis according to a potential contextual factor, reveals that active intervention is more effective than placebo in the CF-positive category compared with the CF-negative (RRCF+ = 2.68 and RRCF– = 0.44, respectively). RR: risk ratio; CF: contextual factor; M-H: Mantel-Haenszel test.

Table 1. Result and summary of the survey on work done previously on CF within OMERACT WG.

Definition of CF	Details	WG
OMERACT Handbook definition	"…variables that are not outcomes of studies, but need to be recognized (and measured) to understand the study results. This includes potential confounders and effect modifiers…"[9]	AS, HOA, RA-F, SDM, VA
ICF definition	Environmental factors make up the physical, social, and attitudinal environment in which people live and conduct their lives. Personal factors are the particular background of an individual's life and living, and consist of features of the individual that are not part of a health condition or health states[16].	AS, RA-F, VA, WP
No formal definition or group-specific definition		EG, HL, WP

Identification of CF	WG	Classification of CF	WG
ICF core set development	AS, HOA, VA	ICF-based grouping	AS, HL, VA, WP
Patient research partners/ patients	EG, HOA, HL, RA-F, VA, WP	Expert-based grouping	HL, RA-F, SDM, WP
Expert opinion	HOA, HL, RA-F, WP	OMERACT SIG-based grouping	WP
OMERACT SIG participants	HOA, HL, RA-F, SDM	Mandatory/nonmandatory to assess	HOA
Literature review	HL, RA-F, SDM, WP		

Measurement of CF	WG	Statistical analysis of CF	WG
CF instrument, specifically developed in WG	AS, EG, RA-F, VA	CF treated as confounders in regression analysis	HOA
Standard variables, e.g., age, sex	HOA, HL	Stratification for subgroup analysis	HOA
No measure	SDM, WP	IRT approach used to test interaction	HL

CF: contextual factors; OMERACT: Outcome Measures in Rheumatology; WG: working groups; ICF: International Classification of Functioning, Disability and Health; SIG: Special Interest Group; AS: ankylosing spondylitis; HOA: hand osteoarthritis; RA-F: rheumatoid arthritis flare; SDM: shared decision-making; VA: vasculitis; WP: worker productivity; EG: equity group; HL: health literacy; IRT: Item Response Theory.

lished based on an informed discussion. A preliminary list of candidate CF to be considered when interpreting an outcome in rheumatology clinical trials was collected in a group exercise and on individual written forms (post-SIG questionnaire). Then the CFMG requested recommendations to further develop the research agenda from the SIG participants.

RESULTS

Survey of OMERACT WG. Response to the survey was received from 8/10 OMERACT WG: Ankylosing Spondylitis, Equity, Hand-OA, Health Literacy, RA-Flare, Shared Decision-Making, Vasculitis, and Worker Productivity. The survey results are presented in Table 1 and Supplementary Table 1 (available with the online version of this article).

Five of the 8 groups used the OMERACT Handbook 2.0 definition[9], of which 3 groups also used the CF definition of the ICF, i.e., environmental and personal factors[16]. The Health Literacy group defined CF specifically as "a factor/variable that may modify the level or importance of the patient-reported outcome (PRO) measured."

Depending on the specific research focus, multiple methods were used to identify, refine, and categorize CF candidate categories including literature search, ICF or ICF core sets[17], expert discussions, patient interview and focus groups, and PRP and SIG participant discussions. This variety emphasized the great heterogeneity in approaching and identifying CF across OMERACT WG.

In their research, some WG identified potential

confounders or covariates specific to their research topic, e.g., "patient's ability to accurately complete a PRO," identified by the Equity group. As another example, self-management was identified initially as a domain to be measured by the RA-Flare WG, but when scoring was analyzed, variability of answers to questions designed to assess self-management resulted in determining that self-management is probably an effect modifier itself. The Assessment of Spondyloarthritis international Society Health Index identified 9 items of potentially relevant CF for testing in their new instrument, while others proposed factors used to identify phenotypical subgroups (Hand OA)[18].

Participation of PRP. PRP initially focused on the influence of CF on transferability of study results to daily life. However, in discussions, PRP agreed to focus on CF influence on the interpretation of outcomes in RCT (not clinical care or daily life).

OMERACT SIG 2016. Forty-eight participants attended the CFMG SIG session, including 35 healthcare professionals, 6 fellows, 5 PRP, and 2 industry representatives.

After presenting the survey results to the participants, 28 variables were collected verbally and displayed, stimulating active discussion on the operational use of the OMERACT CF definition, the ICF framework, methods to identify CF, and approaches to select core CF. SIG participants acknowledged that research is complicated by the large number of CF. Further, depending on the setting, the study design, or research question, CF could be seen as potential confounders, effect modifiers, (co)-outcomes, or even as interventions. These findings were confirmed by 39 participants who provided written input to a post-SIG questionnaire (Data Supplement 1, available with the online version of this article), of which 11 listed the variables as potential core CF (Table 2A, Table 2B, and Table 2C).

Moreover, the CFMG SIG participants agreed that the OMERACT definition (focusing on effect modification in most settings) should be used as the main operational definition with the ICF as the conceptual framework. They confirmed the relevance of the CFMG as an OMERACT methods group to provide guidance to other groups in identifying, measuring, and characterizing important/core CF.

Further, the CFMG SIG participants made the following recommendations for the research agenda:

1. The CFMG should closely collaborate with other WG because these groups may develop measures for CF.
2. Statistical methods are needed to prove the effect of CF on effect modification. As a first step, identifying existing datasets that can be used for secondary analysis should be considered.

Based on these recommendations, the CFMG formulated 3 main projects as first steps toward providing guidance to identify and characterize CF that significantly influence the interpretation of results in clinical trials:

1. Delphi exercises (including experts and patients) to identify CF of importance within rheumatology with suspected effect modification.
2. Literature reviews to find evidence whether these CF are affecting the effect sizes in either RCT (using stratification or posthoc analyses) or in metaanalyses[19].
3. Investigation of how a CF should be (validly) measured.

Table 2A. Personal factors named by CF-SIG participants.

Personal Factor	Flip Chart	Individual Written Input	Both
Sex		X	
Ethnicity			X
Family living situation		X	
Social support			X
Social isolation	X		
Family/work relationship		X	
Education			X
Health literacy			X
Medical history		X	
Major life events			X
Socioeconomic status		X	
Financial situation, **poverty**			X
Lifestyle factors, physical activity, diet, **smoking**, alcohol			X
Nutrition/food security		X	
Self-management		X	
Adherence to treatment			X
Compliance/coping		X	
Psychological distress			X
Motivation		X	
Readiness to change		X	
Fear of side effects		X	
Mood		X	
Health expectations		X	
Health beliefs		X	
Illness beliefs			X
Regional effect on placebo response, South America		X	
Resilience/adaptability	X		
Assessment experience	X		
Failure of previous drugs, exclusion criteria for drug trials	X		
Comorbidities, depression, anxiety, obesity, **BMI**			X

Factors in bold face have been nominated by individual SIG participants in the written SIG CF questionnaire as candidate core CF. CF: contextual factors; SIG: Special Interest Group; BMI: body mass index.

DISCUSSION

In the context of outcome measurement in rheumatologic clinical trials, the OMERACT Handbook definition of CF, focusing on effect modification and using the ICF as a conceptual framework, was found to be pertinent. It is important to note that this definition depicts CF that are relevant to interpreting outcomes of clinical trials and may not cover the needs of clinical practice settings[20,21,22].

Despite the consensus on a CF definition, the characteri-

Table 2B. Health condition/symptom factors named by CF-SIG participants.

Health Condition/symptom	Flip Chart	Individual Written Input	Both
Duration of condition/disease		X	
Infection			X
Aspects of disease	X		
Side effects		X	
Genetics			X
Disease response biomarker		X	
Antibodies		X	
Serostatus		X	
ASO titers		X	

CF: contextual factors; SIG: Special Interest Group; ASO: antistreptolysin O.

Table 2C. Environmental factors named by CF-SIG participants.

Environmental Factor	Flip Chart	Individual Written Input	Both
Experience, researcher		X	
Experience of health provider	X		
Pooling patients into multicenter trials		X	
Study design characteristics			X
Proxy vs patient response, mode of data administration (paper, online, phone)			X
Assessor experience		X	
Type of healthcare	X		
Availability of medication		X	
Access to care		X	
Concomitant medication	X		
Job demands			X
Microbiotics	X		
Behavioral intervention		X	
Experience of researcher		X	
Shared decision making		X	

Factors in bold face have been nominated by individual SIG participants in the written SIG CF questionnaire as candidate core CF. CF: contextual factors; SIG: Special Interest Group.

zation of core CF remains a challenge, partially because the influence of most CF tends to vary according to the context[23]. Many CF have been identified as potentially relevant in interpreting outcomes of RCT, although only a few might fulfill the definition of effect modification[24].

As healthcare evolves toward person-centered medicine, CF might be key to optimizing treatment allocation. However, to even have the opportunity to prove the effect of a distinct CF, studies providing strong arguments for including that specific CF in RCT are needed first[19,25,26,27], and will provide a next step toward understanding the effect of CF on outcomes in clinical trials.

ACKNOWLEDGMENT

We thank all PRP, previous OMERACT fellows, and the participants of the CFMG Special Interest Group at OMERACT 2016, the pre-OMERACT meetings at the European League Against Rheumatism meeting 2014/15, and the multiple teleconferences for their valuable input. We also thank all OMERACT working groups who generously shared their work on CF with us, including also the Gout and Osteoarthritis-Flare group. Specifically, we thank Drs. Maarten de Witt, Peter Merkel, Will Taylor, Désirée M. van der Heijde, Sarah Legget, and Roxanne Cooksey for sharing their thoughts and providing valuable input to this project in many discussions and meetings.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Weiner SJ, Schwartz A, Weaver F, Goldberg J, Yudkowsky R, Sharma G, et al. Contextual errors and failures in individualizing patient care: a multicenter study. Ann Intern Med 2010;153:69-75.
2. Fosco GM, Van Ryzin M, Stormshak EA, Dishion TJ. Putting theory to the test: examining family context, caregiver motivation, and conflict in the Family Check-Up model. Dev Psychopathol 2014;26:305-18.
3. Zou K, Wong J, Abdullah N, Chen X, Smith T, Doherty M, et al. Examination of overall treatment effect and the proportion attributable to contextual effect in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis 2016;75:1964-70.
4. Tomoaia-Cotisel A, Scammon DL, Waitzman NJ, Cronholm PF, Halladay JR, Driscoll DL, et al. Context matters: the experience of 14 research teams in systematically reporting contextual factors important for practice change. Ann Fam Med 2013;11 Suppl 1:S115-23.
5. Sorensen G, Emmons K, Hunt MK, Barbeau E, Goldman R, Peterson K, et al. Model for incorporating social context in health behavior interventions: applications for cancer prevention for working-class, multiethnic populations. Prev Med 2003;37:188-97.
6. Ovretveit JC, Shekelle PG, Dy SM, McDonald KM, Hempel S, Pronovost P, et al. How does context affect interventions to improve patient safety? An assessment of evidence from studies of five patient safety practices and proposals for research. BMJ Qual Saf 2011;20:604-10.
7. Christensen AW, Tarp S, Furst DE, Døssing A, Amris K, Bliddal H, et al. Most trial eligibility criteria and patient baseline characteristics do not modify treatment effect in trials using targeted therapies for rheumatoid arthritis: a meta-epidemiological study. PLoS One 2015;10:e0136982.
8. Hingorani AD, Windt DA, Riley RD, Abrams K, Moons KG, Steyerberg EW, et al; PROGRESS Group. Prognosis research strategy (PROGRESS) 4: stratified medicine research. BMJ 2013;346:e5793.
9. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
10. Tang K, Boonen A, Verstappen SM, Escorpizo R, Luime JJ, Lacaille D, et al. Worker productivity outcome measures: OMERACT filter evidence and agenda for future research. J Rheumatol 2014; 41:165-76.
11. Kloppenburg M, Boyesen P, Smeets W, Haugen IK, Liu R, Visser W, et al. Report from the OMERACT Hand Osteoarthritis Special Interest Group: advances and future research priorities. J Rheumatol 2014;41:810-8.
12. Merkel PA, Aydin SZ, Boers M, Cornell C, Direskeneli H, Gebhart D, et al. Current status of outcome measure development in vasculitis. J Rheumatol 2014;41:593-8.
13. Bykerk VP, Lie E, Bartlett SJ, Alten R, Boonen A, Christensen R, et al. Establishing a core domain set to measure rheumatoid arthritis flares: report of the OMERACT 11 RA flare Workshop. J Rheumatol 2014;41:799-809.
14. O'Neill J, Rader T, Guillemin F, Boonen A, Christensen R, Lyddiatt

A, et al. Including health equity considerations in development of instruments for rheumatology research: an introduction to a novel OMERACT paradigm. J Rheumatol 2014;41:150-2.
15. Boers M, Kirwan JR, Gossec L, Conaghan PG, D'Agostino MA, Bingham CO 3rd, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. J Rheumatol 2014;41:1025-30.
16. World Health Organization. International classification of functioning, disability and health: ICF. Geneva: WHO; 2001.
17. Boonen A, Braun J, van der Horst Bruinsma IE, Huang F, Maksymowych W, Kostanjsek N, et al. ASAS/WHO ICF Core Sets for ankylosing spondylitis (AS): how to classify the impact of AS on functioning and health. Ann Rheum Dis 2010;69:102-7.
18. Kiltz U, van der Heijde D, Boonen A, Braun J. The ASAS Health Index (ASAS HI) - a new tool to assess the health status of patients with spondyloarthritis. Clin Exp Rheumatol 2014;32 Suppl 85: S-105-8.
19. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Ann Intern Med 2012;157:429-38.
20. Parslow R, Patel A, Beasant L, Haywood K, Johnson D, Crawley E. What matters to children with CFS/ME? A conceptual model as the first stage in developing a PROM. Arch Dis Child 2015;100:1141-7.
21. Boonen A, Boone C, Albert A, Mielants H. Understanding limitations in at-work productivity in patients with active ankylosing spondylitis: the role of work-related contextual factors. J Rheumatol 2015;42:93-100.
22. Pousada Garcia T, Groba González B, Nieto Rivero L, Pereira Loureiro J, Díez Villoria E, Pazos Sierra A. Exploring the psychosocial impact of wheelchair and contextual factors on quality of life of people with neuromuscular disorders. Assist Technol 2015;27:246-56.
23. Staalesen Strumse YA, Nordvåg BY, Stanghelle JK, Røisland M, Winther A, Pajunen PA, et al. Efficacy of rehabilitation for patients with ankylosing spondylitis: comparison of a four-week rehabilitation programme in a Mediterranean and a Norwegian setting. J Rehabil Med 2011;43:534-42.
24. Petkova E, Tarpey T, Su Z, Ogden RT. Generated effect modifiers (GEM's) in randomized clinical trials. Biostatistics 2017;18:105-18.
25. Alexander ES, Martin LJ, Collins MH, Kottyan LC, Sucharew H, He H, et al. Twin and family studies reveal strong environmental and weaker genetic cues explaining heritability of eosinophilic esophagitis. J Allergy Clin Immunol 2014;134:1084-92.e1.
26. Gadallah MA, Boulos DN, Gebrel A, Dewedar S, Morisky DE. Assessment of rheumatoid arthritis patients' adherence to treatment. Am J Med Sci 2015;349:151-6.
27. Frederiksen P, Karsten MM, Indahl A, Bendix T. What challenges manual workers' ability to cope with back pain at work, and what influences their decision to call in sick? J Occup Rehabil 2015;25:707-16.