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Evidence for Updating the Core Domain Set of Outcome Measures for Juvenile Idiopathic Arthritis: Report from a Special Interest Group at OMERACT 2016

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ABSTRACT. Objective. The current Juvenile Idiopathic Arthritis (JIA) Core Set was developed in 1997 to identify the outcome measures to be used in JIA clinical trials using statistical and consensus-based techniques, but without patient involvement. The importance of patient/parent input into the research process has increasingly been recognized over the years. An Outcome Measures in Rheumatology (OMERACT) JIA Core Set Working Group was formed to determine whether the outcome domains of the current core set are relevant to those involved or whether the core set domains should be revised.

Methods. Twenty-four people from the United States, Canada, Australia, and Europe, including patient partners, formed the working group. Guided by the OMERACT Filter 2.0 process, we performed (1) a systematic literature review of outcome domains, (2) a Web-based survey (142 patients, 343 parents), (3) an idea-generation study (120 parents), (4) 4 online discussion boards (24 patients, 20 parents), and (5) a Special Interest Group (SIG) activity at the OMERACT 13 (2016) meeting.

Results. A MEDLINE search of outcome domains used in studies of JIA yielded 5956 citations, of which 729 citations underwent full-text review, and identified additional domains to those included in the current JIA Core Set. Qualitative studies on the effect of JIA identified multiple additional domains, including pain and participation. Twenty-one participants in the SIG achieved consensus on the need to revise the entire JIA Core Set.

Conclusion. The results of qualitative studies and literature review support the need to expand the JIA Core Set, considering, among other things, additional patient/parent-centered outcomes, clinical data, and imaging data. (J Rheumatol First Release August 15 2017; doi:10.3899/jrheum.161389)

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Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease of childhood and a cause of acquired disability. Multiple outcome measurement sets are currently used in studies of JIA. These include the American College of Rheumatology (ACR) Pediatric Response criteria¹, the ACR Provisional Criteria for Defining Clinically Inactive Disease in Select Categories of JIA², and the Juvenile Arthritis Disease Activity Score (JADAS)³.

The ACR Pediatric Response criteria consider the current JIA Core Set items as recommended for JIA clinical trials since 1997. This core set was developed without patient/parent contribution and applies only to oligoarticular, polyarticular, and systemic categories of JIA, omitting enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (jPsA)⁴. The 6 JIA Core Set variables are the physician's global assessment of disease activity, parent's/patient's global assessment of overall well-being, physical function, joint count with active arthritis, joint count with restricted motion, and acute-phase reactants. A seventh variable, fever in the preceding week, was added posthoc for systemic JIA⁵. The current JIA Core Set has been used in evaluation of medications for selected categories of JIA, and several medications have been approved for JIA with its use^{6,7,8,9}. Some important features of ERA and jPsA (rash, inflammatory back pain, and enthesitis) are not incorporated in the current core set, limiting the applicability across populations and settings.

The Outcome Measures in Rheumatology (OMERACT) has long recognized the importance of patient/parent input into the research process. While the OMERACT filter has been applied in validation of clinical remission criteria for JIA¹⁰ and the JADAS, several factors warrant re-examination of the core set: lack of patient/parent input into the current core set, advances in the field of measurement, new patient-reported outcomes (PRO), and improved understanding of the pathophysiology of JIA.

MATERIALS AND METHODS

The OMERACT JIA Core Set Working Group was formed in 2015 with 24 members representing the United States, Canada, Australia, and Italy. Co-chairs (AC, EMM, JEM), an OMERACT fellow (MR), OMERACT Executive Committee mentors (COB, VS), and 2 patient representatives (JH, JEM) served leadership roles. The working group conducted monthly teleconferences, with additional ad-hoc working group members and organizations contributing to component projects discussed below.

Systematic review. The search strategy for the systematic review of the literature was developed by a health sciences information specialist with input from pediatric rheumatologists. It included terminology to identify all categories of JIA, was limited to citations published during and after 1992, and used the Clinical Queries Search String. Citations were reviewed by 2 reviewers, with at least 1 pediatric rheumatologist. Decisions regarding inclusion were made after abstract screening and full-text review, and using prespecified, standardized criteria. Primary and secondary outcome domains of included publications were abstracted and categorized according to OMERACT Filter 2.0 Core Areas¹¹.

Wide input. Multiple efforts were made to collect input from a wide group of participants to inform the JIA Core Set revision.

Web-based survey. A survey to gather perceptions on the domains considered important to measure in longitudinal registry studies was developed by pediatric rheumatologists, a patient, and the staff of an advocacy organization, with feedback from parents. Survey items focused on setting PRO, burden of illness, access to care, and goals of treatment as priorities. The Arthritis Foundation, a US-based advocacy group, distributed the survey to a JIA-targeted mailing list that included adults with a history of JIA and parents of children with JIA.

Disease Impact Idea Generation. Parents of patients with JIA at a clinic in Genoa, Italy, were provided a blank piece of paper and asked to list all problems caused by JIA in the child's general health and the difficulties for the child and his/her family in everyday life due to JIA. There was no limit on the number of items to be listed. Items were reviewed and grouped into domains.

Online discussion board (ODB). To gain a deeper understanding of the patient perspective than that provided by the survey or idea-generation study, 2 sets of paired ODB were conducted in the United States, 1 with parents (split by ages of their children) and 1 with patients (split by age). Each private 3-day ODB was facilitated by an experienced qualitative researcher (ST). The ODB sought to elucidate the effect of JIA on physical, mental, and social health, and the perceived differences in health between active and inactive JIA. The ODB format enabled elicitation, description, and prioritization of a comprehensive list of potential outcome domains relevant to patients and/or parents¹². Transcripts of respondents' typed answers were coded into domains regarding OMERACT Core Areas and analyzed using NVivo 11¹³.

The Web-based survey study protocol was reviewed by the Cincinnati Children's Hospital (CCHMC) Institutional Review Board (IRB) and is exempt from approval (study no. 2014-6575). The ODB with no collection of identifying information was determined to be non-human subjects research by the CCHMC IRB. The Disease Impact Idea Generation study was approved by the Istituto Giannina Gaslini IRB/Ethics Board.

At the OMERACT 13 meeting, a Special Interest Group (SIG) convened to establish consensus on 3 questions: (1) Is there a need for revision of the current JIA Core Set? (2) Should a new expanded core domain set be relevant for assessment of all JIA categories and include uveitis? (3) Are additional international qualitative studies required prior to a Delphi process to prioritize candidate core domains?

RESULTS

Systematic review. The MEDLINE search yielded 5956 citations for screening; 729 were assigned for full-text review. Data abstraction revealed 8 outcome domains that fall within

the OMERACT core areas, but are not completely covered by the current JIA Core Set (Table 1). Details will be published separately.

Web-based survey. Parents of children with JIA (n = 343) and 142 adults with JIA completed the survey. Many outcome domains not included in the current JIA Core Set were identified (Table 1). Patients prioritized outcome domains slightly differently from parents. For example, regarding physical health, patients prioritized the ability to manage self-care first, followed by pain control; parents prioritized pain control first.

Disease Impact Idea Generation. The study involved 121 parents. Twenty-one domains of disease effect were identified (Table 2), consisting of 10 domains within OMERACT Core Areas (Table 1).

ODB participation. Parent ODB had 10 participants each, the adolescent ODB had 11, and the young adult ODB had 13. Multiple outcome domains not included in the current core set were identified (Table 1). Participants characterized inactive disease as the absence of pain, stiffness, and swelling; increased activity/participation; ability to be more

independent; and improved mood and sleep quality. Table 3 reports themes expressed by patients in response to questioning about health features they notice when their disease is quiet, as well as to what factors they expect their healthcare provider to evaluate to measure disease activity.

Results of OMERACT SIG. Twenty-one individuals attended the JIA Core Set SIG at OMERACT, consisting of patient research partners, pediatric rheumatologists, adult rheumatologists, radiologists, researchers, regulatory officials, and industry representatives. After presentation of data and discussion of the key questions, all voted unanimously to endorse the SIG's conclusions. First, the SIG concluded that the entire core set should be considered for revision; rather than focusing only on addition of PRO, the SIG suggested consideration of imaging and other clinical data. Attendees suggested that the systematic review include publications prior to 1992 and that it search multiple databases. Second, the SIG concluded that the JIA Core Set should identify all JIA categories⁴. Attendees discussed the unique autoinflammatory features of systemic JIA, but reached consensus to include systemic JIA at this stage. The SIG also decided to

Table 1. Summary of domains identified by literature review and participant input.

Domains Organized by OMERACT Core Areas	Systematic Literature Review*	Web-survey of Pts	Web-survey of Parents	Disease Impact Idea Generation	ODB Teens	ODB Young Adults	ODB Parents of Young Children	ODB Parents of Older Children
Death								
Disease							✓	
Intervention								
Life effect								
ICF domains: activity and participation	✓	✓	✓	✓	✓	✓	✓	✓
Quality of life	✓	✓	✓	✓	✓	✓	✓	✓
Patient perception of health	✓	✓	✓	✓	✓	✓	✓	✓
Loss of ability to work				✓	✓	✓	✓	✓
Psychosocial impact	✓	✓	✓	✓	✓	✓	✓	✓
Secondary impact on family/caregivers				✓			✓	✓
Utility								
Resource use/economic effect								
Societal								
Individual				✓			✓	✓
Healthcare				✓	✓			✓
Direct/indirect (productivity)			✓			✓		
Intangible costs								✓
Pathophysiological manifestations								
ICF: body function and structure	✓	✓	✓	✓	✓	✓	✓	✓
Organ function	✓							
Reversible manifestations	✓	✓						
Irreversible manifestations	✓			✓			✓	
Biomarkers	✓							
Surrogate outcomes								

* Systematic literature review of juvenile idiopathic arthritis studies found domains/subdomains measured to include joint count, physician's global assessment, functional ability, inflammatory markers, patient's/caregiver's global assessment, biomarkers, health-related quality of life, adverse effects, adjustment/psychosocial health, flare, damage, fatigue, participation, ability to stop/decrease medications, growth/maturation, mental health, and bone health. Pts: patients; ODB: online discussion boards; ICF: International Classification of Functioning, Disability and Health.

Table 2. Twenty-one domains of JIA disease effect identified from the Italian Idea Generation Study.

Fatigue
Pain
Sleep disturbance
Reduction of functional ability
Restriction in autonomy and independence
Limited relations with peers
Difficulties in the relations with other members of the family
Difficulties in coping with a chronic disease
Difficulties in drug administration
Difficulties in interpreting disease symptoms
Dissatisfaction with physical appearance
Fear of disease relapses
Fear of medication side effects
Occurrence of disease complications
Uncertainty about longterm outcome of the disease
Restriction of possibilities and potentiality
Reduction of school/work attendance
Reduction of school/work performance
Costs and/or organizational problems with followup visits
Frequency of hospital admittance
Delay in vaccinations

include uveitis-related outcomes as a domain and to use the work of an international uveitis working group to identify the items to include¹⁴. Finally, the SIG agreed that additional qualitative input should be gathered in other countries, with an effort to include patients younger than 15 years, and to inform a Delphi process to prioritize domains.

DISCUSSION

An international collaboration between multiple participant has begun using the OMERACT process to develop an updated Core Domain Set for assessment of JIA in clinical trials. The preliminary data from working group projects and unanimous voting of the OMERACT SIG support the need to revise the current JIA Core Set. This working group has emphasized identification of patient/parent-valued domains because of the paucity of involvement in past JIA Core Set development and the absence of domains, such as pain, fatigue, and participation. The most informative of the qualitative approaches, the ODB, will be replicated outside the United States for cross-cultural validation of findings.

As a result of the JIA Core Set OMERACT SIG, the working group will expand to include additional international

participants. We will move forward a research agenda that addresses the knowledge gaps and priorities for revising the current Core Set within the OMERACT framework by expanding the systematic review, developing a conceptual model of patient/parent experience of JIA, and conducting a Delphi process to prioritize domains.

Unique challenges include eliciting input from young patients, reconciling perspectives between patients and parent-proxy respondents, and establishing content relevance across heterogeneous JIA subtypes in a single core set. The immediate goal is to advance this research agenda and return in 2018 as an OMERACT Workshop with a proposed draft JIA Core Domain Set. Ultimately, specific instruments for identified domains will be reviewed and/or developed to ensure that the new core set measures are able to discriminate between placebo and efficacious treatments in clinical trials.

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REFERENCES

1. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202-9.
2. Wallace CA, Giannini EH, Huang B, Irtter L, Ruperto N; Childhood Arthritis Rheumatology Research Alliance; Pediatric Rheumatology Collaborative Study Group; Paediatric Rheumatology International Trials Organisation. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res* 2011;63:929-36.
3. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al; Paediatric Rheumatology International Trials Organisation. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:658-66.
4. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for

Table 3. Patient views of disease remission assessment, from a North American online discussion board.

How does the patient know that the disease is inactive?	What is the doctor's role in determining whether disease is inactive?
No pain (less pain, or tolerable pain)	Joint examination (check for swelling, range of motion, warmth, redness)
Lack of stiffness (especially in morning)	Blood tests
No swelling	Listen to patient report (ask about pain, emotions/how happy they look)
Can participate in activities	Vision examination (uveitis screen)
Better sleep	Physical examination: e.g., range of spine, gait
More energy	Imaging (magnetic resonance imaging)
More capable/independent, everything is easier	

- Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.
5. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al; Paediatric Rheumatology International Trials Organisation PRINTO; Pediatric Rheumatology Collaborative Study Group (PRCSG). Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2015;74:1110-7.
 6. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al; Pediatric Rheumatology Collaborative Study Group; Pediatric Rheumatology International Trials Organisation. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810-20.
 7. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al; Paediatric Rheumatology International Trials Organization and the Pediatric Rheumatology Collaborative Study Group. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2010;62:1792-802.
 8. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763-9.
 9. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al; PRINTO; PRCSG. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2396-406.
 10. Wallace CA, Ravelli A, Huang B, Giannini EH. Preliminary validation of clinical remission criteria using the OMERACT filter for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2006;33:789-95.
 11. 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.
 12. Tates K, Zwaanswijk M, Otten R, van Dulmen S, Hoogerbrugge PM, Kamps WA, et al. Online focus groups as a tool to collect data in hard-to-include populations: examples from paediatric oncology. *BMC Med Res Methodol* 2009;9:15.
 13. NVivo qualitative data analysis Software, 11 ed. QSR International Pty, Ltd.
 14. Heiligenhaus A, Foeldvari I, Edelsten C, Smith JR, Saurenmann RK, Bodaghi B, et al; Multinational Interdisciplinary Working Group for Uveitis in Childhood. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. *Arthritis Care Res* 2012;64:1365-72.