

# Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies

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**ABSTRACT. Objective.** During OMERACT 12, a workshop was held with the aim to endorse a core set of domains for 3 settings: clinical trials of symptom and structure modification and observational studies. Additional goals were to endorse a core set of contextual factors for these settings, and to define preliminary instruments for each core domain. Finally, an agenda for future research in hand osteoarthritis (OA) was to be proposed.

**Methods.** Literature reviews of preliminary instruments for each core domain of the proposed core set for hand OA in the settings described above. Literature review of radiographic scoring methods and modern imaging in hand OA were also performed. Proposed contextual factors for a core set were identified through 2 Delphi exercises with participation of hand OA experts, patient partners, and OMERACT participants.

**Results.** Results from Delphi exercises and systematic literature reviews were presented and discussed. It was agreed that a preliminary core domain set for the setting clinical trials of symptom modification should contain at least “pain, physical function, patient global assessment, joint activity and hand strength.” The settings clinical trial of structure modification and observational studies would in addition include structural damage. Preliminary instruments for the proposed domains were agreed on. A list of prioritized contextual factors was defined and endorsed for further research. A research agenda was proposed for domain instrument validation according to the OMERACT Filter 2.0.

**Conclusion.** Preliminary core sets for clinical trials of symptom and structure modification and observational studies in hand osteoarthritis, including preliminary instruments and contextual factors, were agreed upon during OMERACT 12. (J Rheumatol First Release xxxx; doi:10.3899/jrheum.141017)

*Key Indexing Terms:*

HAND

OSTEOARTHRITIS

OUTCOME MEASURES

INSTRUMENTS

CORE DOMAINS

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Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder involving all components of the joint<sup>1</sup>. All joints may be involved, but the hand is a predilection site. The phenotype hand OA warrants special attention, because hand OA is in itself polyarticular, making it complex to study. Moreover, hand OA is frequently accompanied by OA in other joint sites, such as the knees or hips<sup>2</sup>. Hand OA is not 1 phenotype, but comprises several subsets, such as nodal hand OA, thumb base OA, and erosive hand OA<sup>3,4</sup>, which are associated with different risk factors, requiring different treatment strategies. Currently, insight in underlying pathophysiologic mechanisms of hand OA is limited and insufficient treatment options exist<sup>5</sup>. Therefore, high-quality observational cohorts and clinical trials are warranted, requiring optimal sets of outcome measures for adequate assessment of hand OA.

In 2010 the Outcome Measures in Rheumatology (OMERACT) hand OA working group was assembled, comprising health professionals, researchers, and patient research partners (PRP), with interest and experience in hand OA, aiming at defining a set of core domains using the OMERACT framework<sup>6</sup>. Previously, 4 core domains (pain, function, patient global assessment, and imaging) for knee, hip, and hand OA trials of  $\geq 1$  year duration were defined for phase III clinical trials following the OMERACT III consensus conference<sup>7</sup>. An Osteoarthritis Research Society International taskforce added the following domains: mobility, deformity, inflammation, performance, stiffness, and esthetic damage<sup>8</sup>. However, the above-mentioned set of core domains has several shortcomings: only the clinical trial setting was addressed, patients were not involved in the process, and the core sets lacked incorporation of hand OA-specific aspects<sup>9,10</sup>.

First, the OMERACT hand OA group performed a Delphi exercise among hand OA group members and OMERACT participants to identify a set of core domains<sup>6</sup>. Potential domains were identified from a qualitative study with 10 focus groups among 56 patients with hand OA from 5 European countries<sup>11</sup>. This was done separately for 4 settings: clinical trials of symptom modification and structure modification, observational studies, and clinical record keeping. Results of the Delphi exercises were discussed in a special interest group (SIG) during OMERACT 11 and resulted in a proposed set of core domains<sup>6</sup>. Further, it was agreed during the SIG to apply the new OMERACT Filter 2.0 in the development process<sup>12</sup>. Further discussions were held at annual meetings of the American College of Rheumatology (ACR) in 2012 and 2013.

As a next step we proposed a workshop during OMERACT 12 with the following objectives: (1) to endorse a core domain set for 3 settings, clinical trials of symptom modification, of structural modification, and of observational studies, (2) to endorse a core set of contextual factors for the same settings, (3) to define a preliminary set of instruments

for each core domain, and (4) to propose a research agenda for domain instrument validation according to the OMERACT Filter 2.0.

## MATERIALS AND METHODS

### Delphi Exercise

Prior to the OMERACT 12 meeting, we performed a Delphi exercise to reach consensus about the contextual factors that should be considered as mandatory in hand OA studies. In Delphi round 1 an initial list of 36 potential contextual factors was circulated to experts in hand OA, PRP, and OMERACT participants. The list was derived from hand OA experts, hand OA patient focus groups, OMERACT participants, and an International Classification of Functioning review<sup>13</sup>. Potential contextual factors, i.e., variables that are not outcomes of the study but need to be recognized (and measured) to understand the study results<sup>12</sup>, included demographics, OA-specific factors, physical health, mental health, physical fitness, and others. Participants were asked to divide 100 points among the contextual factors they considered important; participants were explicitly encouraged to include additional factors. Domains with high agreement (average  $> 6$  points) were kept, whereas domains with low agreement (average  $< 1$  point) were excluded. Factors with moderate agreement and suggested factors were voted on in Delphi round 2.

### Literature Reviews of Instruments to Assess Hand OA Outcomes

A systematic search of the medical literature up to January 2014 was performed to identify instruments measuring pain, physical function, patient global assessment, joint activity, and hand strength and to summarize their metric properties, i.e., discrimination (reliability, sensitivity to change), feasibility, and validity. Inclusion criteria required for studies to evaluate these aspects differed per item (Visser, *et al*, manuscript submitted)<sup>14</sup>.

Another systematic review of the medical literature up to November 2013 was performed to evaluate the use of radiography in hand OA and to assess the reliability, sensitivity to change, validity, and feasibility of the different available radiographic scoring methods<sup>15</sup>.

### OMERACT 12 Hand OA Workshop

A plenary session was held during which presentations were given: (1) On results of the Delphi exercises concerning core domains and later discussions (MK); (2) on the Delphi exercises concerning contextual factors (PB); (3) on systematic literature searches concerning instruments to assess pain, function, patient global, hand strength, and tender joints (AWV); (4) on searches to assess structural damage by radiography (AWV); and (5) on searches to assess joint activity or disease activity at joint level and structural damage using modern imaging techniques (IKH).

Subsequently, 4 breakout sessions took place to discuss (1) core domains in outcome measures, (2) contextual factors, (3) instruments to assess patient reported outcomes and performance measures, and (4) imaging instruments. Summaries of the breakout sessions were reported back during a plenary session. During this final plenary session, votes were taken; voters could "agree," "not agree," or "not know."

## RESULTS

### Endorsement of Domains for a Core Domain Set for 3 Settings

Based on results of the Delphi exercise and discussions during OMERACT 11, the proposed core domains included pain, physical function, patient global assessment, joint activity, health-related quality of life (HRQOL), reduced strength, pain medication, structural damage, and reduced mobility<sup>6</sup>. The proposed core domain set was widely discussed during a breakout session attended by 11 physi-

cians, 2 PRP, 1 representative from industry, 2 researchers, and 2 research fellows.

Discussions touched upon similarities and differences between “reduced strength” and “physical function,” and the term “hand strength” was proposed instead of “reduced strength.” HRQOL was included as a core domain. However, HRQOL contains different domains, and instruments are not available. Therefore, HRQOL was included as a non-mandatory domain until disease-specific instruments are available. After discussion, the proposed domain “pain medication” was incorporated as a potential contextual factor.

After the breakout session, it was proposed that in the setting of clinical trials of symptom modification, a preliminary set of core domains should at least contain pain, physical function, patient global assessment, HRQOL (although not mandatory as long as no disease-specific instruments are available), joint activity, and hand strength. In the final plenary, 47 (89%) of the voting participants agreed; 11% did not agree; and none responded “don’t know.”

For the setting of clinical trials of structure modification, the breakout group proposed to define subdomains as radiographic damage, esthetic damage, bony damage, and deformity. Further, “reduced mobility” was discussed: whether it is distinct from or similar to physical function, as well as the current lack of an appropriate instrument; “hand mobility” was suggested as a more appropriate term. Finally, it was agreed by 41 voting participants (76%) that a preliminary set of core domains for clinical trials of structure modification contain at least the domains endorsed for clinical trials of symptom modification *and* structural damage, and mobility; 13% did not agree and 11% did not know. Thirty-eight (72%) agreed that the preliminary set of endorsed core domains for the assessment of hand OA in observational studies is similar to that for structure modification; 11% did not agree and 17% did not know (Figure 1).

**Definition of a Preliminary Set of Instruments for Each Core Domain**

*Patient-reported outcomes and performance tests.* In the systematic literature review, 66 studies concerning hand OA were included, in which various questionnaires, performance-based instruments, and assessor-based instruments were applied. No major differences regarding metric properties were observed between the instruments, although the amount of supporting evidence varied.

The most frequently evaluated questionnaires were the Australian Canadian Hand OA Index (AUSCAN) pain subscale<sup>16</sup> and visual analog scale (VAS) or numerical rating scale (NRS) for pain assessment, and the AUSCAN function subscale and Functional Index of Hand OA (FIHOA)<sup>17</sup> for physical function assessment. Excellent reliability was shown for the AUSCAN and FIHOA and good sensitivity to change for all mentioned instruments; additionally, the FIHOA had good feasibility. No validation by comparing to a gold standard has been performed; however, good construct validity was suggested for all instruments. Grip and pinch strength to assess hand strength and palpation of tender joints to assess joint activity<sup>18</sup> were commonly applied. For these measures, good sensitivity to change and construct validity were established. Supporting evidence (Table 1) was presented and discussed in a breakout session, attended by 2 PRP, 1 representative from the pharmaceutical industry, 2 occupational therapists, 1 statistician, 1 epidemiologist, and several rheumatologists.

There was general agreement to use the VAS or NRS to assess pain. A single question was generally preferred over multiple pain questions. Further information is needed whether overall hand pain or joint pain specifically should be assessed, which joints should be assessed, how questions should be asked, and which anchors should be used. During voting, 49 participants (88%) agreed on either the VAS or

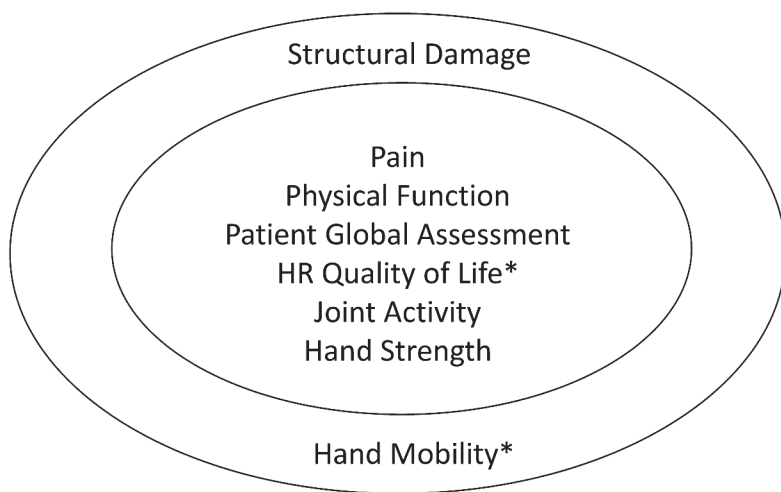


Figure 1. Preliminary set of endorsed core domains for hand osteoarthritis studies. Inner circle: Domains for all settings, i.e., clinical trials of symptom modification, clinical trials of structure modification, and observational studies. Outer circle: Domains for some settings, i.e., clinical trials of structure modification and observational studies. \*Domains not mandatory as long as no disease-specific instruments are available. HR: health-related.

Table 1. Supporting evidence from at least 3 studies for the most frequently applied instruments for evaluation of pain, physical function or patient global assessment. From Visser, *et al.* J Rheumatol (manuscript submitted)<sup>14</sup>.

	Reliability	Sensitivity to Change	Feasibility	Validity
Questionnaires				
AUSCAN	+	+	- #	+
FIHOA	+	+	+**	+
VAS pain		+		+
Performance-/assessor-based instruments				
Grip strength	+*	+		+
Pinch strength	+*	+		+
Tenderness/pain on palpation	+*	+		+*

+ Established evidence; \* supporting evidence in only 2 studies; \*\* supporting evidence in only 1 study; # not available in public domain. AUSCAN: Australian/Canadian Hand OA Index; FIHOA: Functional Index for Hand Osteoarthritis; VAS: visual analog scale; OA: osteoarthritis.

NRS as a preliminary instrument for the self-reported pain domain; 4% did not agree; and 9% did not know. There was concern about the use of the FIHOA to assess physical function because of sex role-specific items (men use screwdrivers and women sew), cultural issues (e.g., handshake), and some items with low secular relevance, e.g., writing for a long period of time versus typing on computer. The alternative AUSCAN instrument had the disadvantage of limited access due to a mandatory fee. Therefore, it was voted by 31 participants (61%; 18% did not agree; 22% did not know) to use the FIHOA for the physical function domain for the time being. Research is warranted for a more contemporary instrument. To measure the hand strength domain, 43 participants (81%) agreed on use of grip/pinch strength as a preliminary instrument; 13% did not agree; and 6% did not know. Although it was agreed that more studies are needed, 43 participants (75%) agreed on use of the tender joint count on palpation as a preliminary instrument to assess joint activity; 11% did not agree, and 14% did not know.

**Radiographic scoring methods.** The domain structural damage includes the subdomain radiographic damage. The systematic literature review revealed 13 different scoring methods that evaluated radiographic hand OA; some scores were more extensively studied than others<sup>15</sup>. Data on reliability, validity, sensitivity to change, and feasibility were available. There were major differences between studies in the number of examined joints and the way scores were analyzed. The reliability of the assessed radiographic scoring methods was good for all evaluated scoring methods, although longitudinal performance was tested only for some methods. The validity of radiographic OA findings compared to that of clinical findings such as nodules and deformities was limited, but the association of radiographic findings with symptoms and hand function was better. The sensitivity to change was comparable for all evaluated scoring methods, as well as the

smallest detectable change. Few studies explored the feasibility of the radiographic scoring methods. Apart from time required for scoring (longer for individual features than for composite scores), no major differences between the evaluated scoring methods was shown. The metric properties are summarized in Table 2 for the most extensive studied scores.

The systematic review served as starting point in the breakout session (attended by 2 radiologists and 13 rheumatologists) discussing imaging instruments. The group supported that radiographs provide information on structural damage measures. There was consensus on including the most widely used and currently best-validated measures in a core set for structural damage. During voting it was agreed by 46 participants (87%) to use the Kellgren-Lawrence method, the OARSI atlas, the Verbruggen-Veys method, or the Kallman method as preliminary instruments for the structural damage domain; 6% did not agree; and 8% did not know.

**Modern imaging methods.** Updated literature overviews<sup>19</sup> of ultrasonography (US) and magnetic resonance imaging (MRI) scoring systems and metric properties were presented; the data were limited. US enables a dynamic image of joints and allows visualization of osteophytes, but also marginal erosions and synovitis. US studies of patients with hand OA have reported high prevalence of greyscale synovitis, while power Doppler activity is less frequent. One preliminary US scoring system has been developed for hand OA including assessment of synovitis (greyscale hypertrophy/effusion and power Doppler) and osteophytes on semiquantitative scales<sup>20</sup>. An US atlas for assessment of osteophytes was developed with excellent intra- and inter-reader reliability<sup>21</sup>. Preliminary studies have shown that validity and sensitivity in comparison with radiography of US seems good; however, more data are needed<sup>22</sup>.

MRI provides a multiplanar image of all joint components; it is the only imaging modality enabling the visualization of bone marrow lesions (BML). Synovitis, based on gadolinium enhancement, is frequent in patients with hand OA; the frequency of BML varies. A preliminary MRI scoring system, which includes assessment of osteophytes, joint space narrowing, erosions, cysts, malalignment, syno-

Table 2. Supporting evidence for most frequently applied radiographic scoring methods. Modified from Visser, *et al.* Osteoarthritis Cartilage 2014;22:1710-23<sup>15</sup>; with permission.

	Reliability	Sensitivity to Change	Feasibility	Validity
Composite score				
KL <sup>17</sup>	+	+	+	+
Individual features				
Anatomical phases <sup>18</sup>		+	+	+
OARSI <sup>19</sup>	+	+	+	+
Kallman <sup>20</sup>	+		+	+

+ Established evidence. KL: Kellgren-Lawrence; OARSI: Osteoarthritis Research Society International.

vitis, flexor tenosynovitis, BML, collateral ligament pathology and BML at insertion sites, has shown good reliability<sup>23</sup>. Lately, this scoring system was revised by OMERACT<sup>24</sup>. Knowledge about validity is limited.

In the breakout group, modern imaging techniques were discussed. The group noted that US and MRI provide information about inflammation and structural damage, with the benefit of multiplanar visualization and highlighting of the complex multitissue pathology in OA. It was felt that experience from rheumatoid arthritis could be transferred, although caution should be taken, especially, when evaluating very small joints. The group noted that knowledge is needed concerning metric properties of these modern imaging modalities. This notion was supported during voting: 98% of voting participants agreed to have US and MRI on the research agenda.

*Endorsement of a preliminary core set of contextual factors for 3 settings.* The Delphi round 1 and 2 had 54 and 21 respondents, respectively. Age and sex as contextual factors reached high agreement across all settings in round 1, whereas hand OA subsets reached high agreement solely for the setting of symptom modification trials. Ethnicity, alcohol consumption, previous surgery for OA in locations other than hands, energy functions, control of voluntary movements, and effects of weather were excluded from further voting owing to low agreement. In round 2, body mass index (BMI), hand OA symptom duration, and hand OA subsets reached high agreement for all settings. Treatment for OA, comorbidities, OA in other specified joint sites, and fulfillment of the ACR Hand OA criteria reached high agreement for some settings and moderate agreement for others (Table 3).

Results of the Delphi exercise were discussed in a

Table 3. Candidate contextual factors for hand OA studies that resulted from Delphi exercises.

	Symptom Modification Trials	Structure Modification Trials	Observational Studies
Age	9.3*	9.3*	9.4*
Sex	8.3*	8.2*	8.3*
Body mass index	7.7	9.2	8.4
Handedness	5.6	5.6	5.5
Postmenopausal state	4.2	3.8	3.4
Socioeconomic status	3.1	2.4	3.8
Smoking	3.3	2.5	2.7
Current occupation	4.7	5.0	4.2
Work absenteeism/pension due to OA	2.0	1.8	1.8
Hand OA subsets	6.1*	16.5	8.3
Symptom duration	8.9	8.6	7.9
Disease duration	5.1	5.0	4.1
Secondary OA	0.7	2.0	1.9
Previous trauma of the hands	1.6	2.3	1.9
OA in other specified joint sites	6.5	5.2	6.7
Treatment for OA	8.3	6.5	5.8
Previous specified surgery for hand OA	3.1	3.5	2.7
Use of orthotics for hand OA	3.3	2.4	2.1
Previous surgery for OA other location	0.3	1.5	1.1
Family history of hand OA	2.2	2.8	3.8
Hand exercise	2.0	2.8	1.8
Comorbidities	6.8	4.9	5.2
Impairment of body functions due to comorbidities	2.5	NA	NA
Treatment for comorbidities	1.2	NA	NA
Sleep functions	1.2	0.2	0.7
Emotional functions	2.0	0.2	0.5
Coping and illness perceptions	3.2	0.7	2.8
Activities/hobbies requiring intensive use of the hands	2.7	3.5	1.7
Lower extremity exercise	0.2	0.3	0.2
Mental status	0.9	NA	0.6
Fulfilling ACR hand OA criteria	6.2	NA	4.1
Nutritional habits	NA	0.8	0.3
Degree of catastrophizing	1.7	NA	NA
Frustration	NA	0.2	NA
Use of stress management techniques	NA	NA	0.5
Activity limitation	NA	NA	1.6

\* Candidate contextual factors with high agreement from Delphi round. Dark grey shading: high agreement (average score > 6); light grey shading: moderate agreement (average score between 1 and 6); no shading: low agreement (average score < 1). OA: Osteoarthritis; ACR: American College of Rheumatology; NA: not applicable.

breakout session, among 6 rheumatologists, 1 occupational therapist, and 1 PRP. The group discussed generic issues regarding contextual factors and hand OA-specific issues. On a general level, there is a methodological need for validation of contextual factors. It was felt that a “core” contextual factor requires rigorous evidence that this factor influences the result of disease/drug on core outcome. However, there is no current consensus on the level of evidence required. Overall, the group held the opinion that the Delphi exercise was complex, with a large list of candidate contextual factors. The 100-point approach of the Delphi exercise and the choice of cutoff were debated. Although the results from the Delphi exercise were thought to be more informative than decisive, the breakout group agreed that the factors with high agreement from the Delphi exercise represent candidate contextual factors; i.e., age, sex, BMI, hand OA subsets, hand OA symptom duration, treatment for OA, OA in other specified joint sites, fulfillment of the ACR hand OA criteria, and comorbidities. The vast majority of voting participants [50 (93%)] agreed to continue research on the prioritized candidate contextual factors. Breakout group discussions and later voting supported the suggestion of 1 common set of contextual factors in hand OA across different settings [41 voting participants (75%) agreed; 9 (16%) did not agree; 5 (9%) did not know].

## DISCUSSION

Discussions and voting during the consensus meeting at OMERACT 12 resulted in a preliminary set of core domains and subdomains, from which the majority was similar for 3

settings. The (sub)domains were distributed over the core area life impact and pathophysiological manifestations, according to the OMERACT filter 2.0, as depicted in Table 4. Preliminary instruments were identified for some (sub)domains. But for several others, research is needed to define disease-specific instruments. The results are summarized in Table 5. Candidate contextual factors have been identified, but need further investigation. Several items were introduced for further research (Table 6).

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*Table 4.* Preliminary core outcomes measurement set according to the OMERACT Filter 2.0.

Death	Life Impact	Resource Use	Pathophysiological Manifestations
Adverse event	<ul style="list-style-type: none"> <li>• Pain</li> <li>• Physical function</li> <li>• Patient global assessment</li> <li>• Hand strength</li> <li>• HRQOL*</li> </ul>		<ul style="list-style-type: none"> <li>• Pain</li> <li>• Physical function</li> <li>• Patient global assessment</li> <li>• Joint activity (tender joints, soft swollen joints*)</li> <li>• Hand strength</li> <li>• Structural damage (radiographic damage, aesthetic damage*, bony damage*, deformity*)</li> <li>• Hand mobility*</li> </ul>
Candidate contextual factors			
<ul style="list-style-type: none"> <li>• Age</li> <li>• Sex</li> <li>• BMI</li> <li>• Fulfillment ACR hand OA criteria</li> <li>• Hand OA subsets</li> <li>• Symptom duration</li> <li>• OA at other joint sites</li> <li>• Concomitant treatment for OA</li> <li>• Comorbidities</li> </ul>			

\* Domains not mandatory as long as no disease-specific instruments are available. HRQOL: health-related quality of life; ACR: American College of Rheumatology; OA: osteoarthritis.

Table 5. Preliminary set of core (sub) domains with preliminary instruments.

Domains	Subdomains	Instruments	
		Clinical Trials of Symptom Modification	Clinical Trials of Structure Modification and Observational Studies
Pain		Pain VAS/NRS	Pain VAS/NRS
Physical function		FIHOA	FIHOA
Patient global assessment		Research	Research
Joint activity	Tender joints	Tender joint count	Tender joint count
	Soft swollen joints	Research	Research
Hand strength		Grip/pinch strength	Grip/pinch strength
HRQOL*		Research	Research
Structural damage	Radiographic damage		Kellgren-Lawrence or Verbruggen-Veys or Kallmann or OARSI
			Research
			Research
			Research
Hand mobility*	Aesthetic damage*		Research
	Bony damage*		Research
	Deformity*		Research

\* Domains not mandatory as long as no disease-specific instruments are available. VAS/NRS: visual analog scale/numerical rating scale; FIHOA: Functional Index for Hand Osteoarthritis; OARSI: Osteoarthritis Research Society International.

Table 6. Future research for domain instrument validation according to the OMERACT Filter 2.0.

#### Research Agenda

- A definition for each contextual factor in hand OA should be formulated
- Performance of a literature review to assess the level of evidence for the different candidate contextual factors
- Identification or development of potential instruments to assess contextual factors, where applicable
- Disease-specific instruments have to be developed for the (sub)domains HRQOL, aesthetic damage, bony damage, deformity, and hand mobility
- Development and testing of VAS/NRS questions to measure the domain pain
- Development of a new measure for hand pain in analogy to knee and hip pain (Intermittent and Constant OA Pain for the hand)
- Evaluation of instruments that are commonly used by hand therapists, such as the DASH, PRWHE, and Michigan Hand Outcome Questionnaire, for use in hand OA.
- Investigation what hand OA contributes to grip strength or pinch strength relative to other conditions that affect hand strength or function
- Performance of qualitative interviews how to measure patient global assessment
- Investigation of the subdomain tender joints
- Further evaluation of the instrument to assess tender joints (Doyle index), with respect to validation in OA — e.g., what is the added value of joint count to other domains, like pain. How many joints and which ones should be incorporated in the tender joint count? How should the tender joint count be performed?
- Is there a floor effect?
- To develop instruments to assess soft swollen joints and bony damage
- Investigation of the value of patient-performed joint count (e.g., self-complete homunculus) versus physician-performed joint count
- Investigation of the metric properties of US and MRI
- Investigation of the value of CT

OA: osteoarthritis; VAS/NRS: visual analog scale/numerical rating scale; HRQOL: health-related quality of life; DASH: Disabilities of the Arm, Shoulder and Hand; PRWHE: Patient-rated Wrist Hand Evaluation; US: ultrasound; MRI: magnetic resonance imaging; CT: computerized tomography.

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