The OMERACT core domain set for clinical trials of shoulder disorders

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Running title: **OMERACT shoulder core domains**

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Abstract

Objective: To reach consensus on the core domains to be included in a core domain set for clinical trials of shoulder disorders using the OMERACT Filter 2.1 Core Domain Set process.

Methods: At OMERACT 2018, the Outcome Measures in Rheumatology (OMERACT) Shoulder Working Group conducted a workshop that presented the OMERACT 2016 preliminary core domain set and its rationale based upon a systematic review of domains measured in shoulder trials and an international Delphi involving patients, clinicians and researchers, as well as a new systematic review of qualitative studies on the experiences of people with shoulder disorders. After discussions in break-out groups, the OMERACT core domain set for clinical trials of shoulder disorders was presented for endorsement by OMERACT 2018 participants.

Results: The qualitative review (N=8) identified all domains included in the preliminary core set. An additional domain, cognitive dysfunction was also identified but confidence that this represents a core domain was very low. The core domain set that was endorsed by the OMERACT participants, with 71% agreement, includes four 'mandatory' trial domains: pain, function, patient global - shoulder and adverse events including death; and four 'important but optional' domains: participation (recreation/work), sleep, emotional wellbeing and condition-specific pathophysiological manifestations. Cognitive dysfunction was voted out of the core domain set.

Conclusion: OMERACT 2018 delegates endorsed a core domain set for clinical trials of shoulder disorders. The next step includes identification of a core outcome measurement set that passes the OMERACT 2.1 Filter for measuring each domain.

INTRODUCTION

Shoulder disorders, including rotator cuff disease (tendinopathy, impingement, subacromial bursitis, tears), adhesive capsulitis, instability, glenohumeral osteoarthritis, dislocation, proximal humeral or humeral head fractures, and unspecified shoulder pain, are highly prevalent disorders (7-26%),(1) and are associated with significant morbidity, disability and economic burden.(2-4) Despite increasing numbers of trials investigating the benefits and harms of treatments for these disorders, there is as yet no widely endorsed core domain set (for outcome domains) or core outcome measurement set (for instruments) that is advocated for clinical trials.

The Outcome Measures in Rheumatology (OMERACT) Shoulder Working Group was established in 2015 to develop these sets for clinical trials of shoulder disorders addressing all types of interventions.(5) Over the past three years, the Working Group has worked on several steps of this project in accordance with OMERACT methodology.(6, 7) This has included, firstly, a systematic literature review identified that across 409 trials, 32 outcome domains were assessed using 319 different measurement instruments.(8) Second, an international Delphi study that included 268 clinicians or researchers from 13 countries with experience in shoulder disorders and 67 patients with shoulder disorders.(9) This was followed by a pre-OMERACT meeting (including patient representatives) and subsequent Special Interest Group meeting at OMERACT 2016, in which a preliminary core domain set was presented and unanimously approved. In Table 1 the preliminary core domain set as well as the voting percentages of each of them from the Delphi are summarized.(10)

This preliminary core domain set consisted of four domains in the 'inner circle' of the OMERACT 'onion' (indicating mandatory domains for all trials of shoulder disorders): pain, physical function/activity, global perceived effect, and adverse events including death; three domains in the 'middle circle' (important but optional domains): emotional well-being, sleep and participation (recreation and work); and a research agenda required to inform the final core domain set in the 'outer circle'. The research agenda was comprised of clarifying the definition of physical function/activity, determining whether or not participation (recreation and work) should be in the inner circle, and determining whether to include pathophysiological manifestations in the core domain set and if it should be situated in the inner (mandatory) or middle (important but optional) circle. In the meantime, OMERACT nomenclature has been slightly updated as indicated later in the final core domain set.

Following the abovementioned initiatives, the Working Group proposed a Workshop for OMERACT 2018. In preparation for it, the Working Group performed a systematic review of qualitative studies that had explored the lived experience of shoulder pain. The purpose of this review was to determine whether any potentially relevant domains were missing from the preliminary core domain set and to further inform the research agenda.(11) The present paper summarizes the results of this work presented at the OMERACT 2018 Shoulder Core Set Workshop, the domains that were presented for endorsement, and the results of the

plenary and breakout discussions, and subsequent vote for endorsement of the core domain set for clinical trials of shoulder disorders.

MATERIALS AND METHODS

Review of qualitative studies

To ensure that all important patient outcome domains had been considered, we performed a systematic review of qualitative studies that had explored the experiences of people with a shoulder disorder.

The methods for our systematic review were pre-specified (PROSPERO ID: CRD42017082628) and the full findings are presented elsewhere.(11) Briefly, we searched for eligible studies indexed in Ovid MEDLINE, Ovid Embase, CINAHL (EBSCO), SportDiscus (EBSCO) and Ovid PsycINFO to November 2017. Studies in which the authors used qualitative methods (e.g. focus groups, Delphi methods, nominal group techniques, participant observation, interviews) to explore the experiences and perceptions of people living with a shoulder disorder were included.

The primary outcomes of interest for this review included the symptoms of people with shoulder disorders and the impact these symptoms have on their daily lives, and the outcome(s) of most importance to patients, as elicited by qualitative research methods. Two authors independently screened studies for inclusion, appraised their methodological quality (using the Critical Appraisal Skills Programme (CASP) checklist for qualitative studies)(12), coded text line-by-line to identify outcome domains (i.e. individual symptoms and perceived impacts on daily living) reported by participants, and assessed the confidence in each review finding (high, moderate, low, very low) using the GRADE-CERQual approach.(13)

Eight studies met the eligibility criteria and they included 133 participants (49 females and 84 males). Studies were conducted in the UK (four studies), Canada (two studies), Finland or New Zealand (one study each). Participants had diagnoses of rotator cuff disease (three studies), adhesive capsulitis (two studies), proximal humeral fracture, shoulder instability or unspecified shoulder pain (one study each).

Seven domains were identified across the eight qualitative studies: (1) pain; (2) physical function/activity limitations (difficulties performing activities of daily living such as dressing or bathing); (3) participation restriction (work disruption, limited recreation/leisure, and limited social interactions); (4) sleep disruption (difficulty falling, and subsequently staying, asleep); (5) cognitive dysfunction (poor concentration and memory); (6) emotional distress (frustration, anxiety and depression); and (7) pathophysiological manifestations (problems related to muscle functions, such as reduced range of motion and loss of muscle strength).

We mapped the outcome domains arising from our systematic review of qualitative studies against the domains included in the preliminary core domain set, to determine whether any important domains were missing. Only one domain, which we termed ‘cognitive dysfunction’,

referring to the reported experience that shoulder pain was so severe that it prevented the participant from being able to concentrate on anything else, had not been identified in our previous research.(8-10) Sleep deprivation due to shoulder pain was also reported to affect concentration and memory. However, we had very low confidence in these findings, because they were raised by only a few participants from only two studies, one of which had several methodological limitations. In contrast, we had greater confidence that the other outcome domains identified reflected the experiences of many people with shoulder disorders. For all the other domains the confidence in the findings was moderate, except for pathophysiological findings, for which confidence was also low (Table 1).

The review findings were discussed in the monthly teleconferences of the core members of the working group, in which convenors, fellows, patient representatives and representatives from the OMERACT technical advisory committee participated. Prior to OMERACT 2018 the final results were presented in a teleconference with all working group members. Members discussed potential modifications to the preliminary core domain set based on the findings of the review of qualitative studies. We decided to move condition-specific pathophysiological manifestations into the middle rather than inner circle, and added to the outer circle (research agenda) the question, "Should 'cognitive dysfunction' be in the Onion?". No other modifications were made before the OMERACT 2018 meeting (Table 1).

OMERACT 2018 Shoulder Core Set Workshop and Plenary

At OMERACT 2018 the Shoulder Core Set Workshop presented the steps that had been taken towards arriving at the proposed core domain set for clinical trials of shoulder disorders and the details of the domains that had been included.

A total of 95 participants (11 patients, 84 other stakeholders – including clinicians, other health professionals, researchers, regulators) were split into eight break-out sessions to facilitate in-depth discussions of the proposed core set. Each group had a facilitator, content expert and reporter. All domains of the proposed core domain set were discussed by all break-out groups. After reconvening, the reporter for each break-out summarized their group discussions to all OMERACT 2018 participants and this was followed by general discussion. The Shoulder Working Group collected detailed feedback from each breakout group for making further decisions regarding the naming and positioning of domains in the core domain set. In a final plenary session on the following day, a revised proposal of a core domain set was presented for final discussion and endorsement. To obtain endorsement 70% of the votes in favor of the proposed core set were required. In case consensus was not reached, revisions were discussed, a reformulation proposed and then re-voted on.

RESULTS

Break-out group discussions regarding each proposed domain and their definition

Pain: There was uniform agreement that pain, reflecting pain intensity, should be included as a mandatory domain within the inner circle.

Function: Function was also recognized as a mandatory domain. It was commented that function should not only reflect the ability to fulfil basic needs, so the definition was adjusted to reflect normal activities of daily living (see Table 3).

Adverse events including death: This was also considered to be a mandatory domain reflecting OMERACT principles.(6)

Global perceived effect: This domain elicited the most discussion. There were some concerns raised about whether this domain was redundant in view of overlap with the domains of pain and function. However, the results of the Delphi study were considered to justify its inclusion as a separate domain. Several participants raised the concern that as worded, this domain would include a change measure (for example, in relation to some treatment) while their preference was for a status measure (i.e., the patients' perception of their current state). Others argued that having a change measure in the core domain set could have a desirable effect as it could act as an anchor for other measures when analyzing outcomes in relation to each other. Following discussion, consensus was reached to change the name of this domain to 'patient global'. Consensus was also that this patient global should not be a measure of overall wellbeing, but a global rating of the shoulder, and therefore the name 'patient global – shoulder' was chosen. Whether or not this should be measured using a status or change measure will be reconsidered in the next phase of identifying suitable measures for this outcome.

Participation: There were proposals to adjust the definition of participation to ensure that it covers both paid and unpaid types of work, and to align the definition of participation to the International Classification of Functioning definition.(14) Both of these changes were adopted.

Emotional wellbeing: This domain was identified as having some overlap with the domains of patient global and function. However, given the results from the Delphi and the qualitative review, no changes to the domain were proposed.

Condition-specific pathophysiological manifestations: There were a range of divergent opinions regarding this domain and where it fits within the OMERACT core domain set for shoulder disorders. Arguments for inclusion of this domain within the inner circle focused on the fact that this was consistent with OMERACT rules for including at least one domain reflecting pathophysiologic manifestations in the inner circle. On the other hand, while pathophysiologic manifestations may be relevant for some trials, for example determination of fracture healing in a trial investigating treatment for proximal humeral fractures, it may not be of value to have a pathophysiologic manifestation included as a core outcome in *all* trials. In addition, there were also arguments for including this domain in the outer circle to reflect that more research was needed before this could resolved. For the purpose of voting, this domain was kept in the middle circle.

Sleep: Some discussion surrounded the idea that there are differing constructs that could be included within a sleep domain such as sleep quality and the interference/impact of sleep disturbance. However, there were no consistently recommended changes to the definition or position of sleep in the core domain set.

Cognitive dysfunction: This domain was considered to possibly overlap with other domains, such as sleep (i.e. lack thereof) or emotional wellbeing (e.g. depression can affect cognition). Some expressed it could be kept in the outer circle, while others recommended leaving it out of the core domain set altogether.

Results of the final vote

Seventy-one percent of OMERACT participants approved the inner core domains comprising pain, function, patient global and adverse events including death (Table 2). When considered individually pain was endorsed by 100% of participants, function by 99% and patient global by 80%. No vote was conducted for adverse events (including death) as this is a mandatory OMERACT domain.

For the middle circle, 89% of participants endorsed inclusion of participation, 93% endorsed sleep and 82% endorsed emotional wellbeing. Inclusion of condition-specific pathophysiological manifestations in the middle circle was only endorsed by 44% of participants in the first voting round. After discussion a second vote recorded 35% preference for the inner circle, 35% for the middle circle and 29% for the outer circle. Of note the argument to move this domain to the inner circle was due to the OMERACT requirement for including at least one pathophysiological domain in the inner circle. As pain can be considered a condition-specific pathophysiological manifestation, and because 70% voted for either the inner or middle circle we elected to keep condition-specific pathophysiological manifestations in the middle circle as originally preferred by the OMERACT Shoulder Working Group.

Cognitive dysfunction was endorsed initially by 64% participants for remaining in the outer circle for further research. After further discussion which reminded participants of the results of the qualitative review, which had identified poor concentration and memory as relevant to the experience of people with shoulder pain, but that there was very low confidence that this cognitive dysfunction was truly a main issue, a second vote was conducted and 64% of participants endorsed removal of this domain from the core domain set altogether.

In response to discussions at OMERACT 2018, the OMERACT Onion was adjusted and approved. This adjustment adds another layer to the inner circle of the OMERACT Onion structure to allow specification of certain domains as mandatory in specific circumstances.

Currently, the OMERACT Onion includes the three circles comprising ‘mandatory’ domains (inner circle), including the domain adverse events including death; ‘important but optional’ domains (i.e., dependent on the design of the study or research question asked, middle circle); and ‘research agenda’ (domains of interest that need more research work but are

under consideration, outer circle). The final core domain set for clinical trials of shoulder disorders is shown in Figure 1.

DISCUSSION

We have outlined the final steps taken to reach OMERACT endorsement for a core domain set for clinical trials of shoulder disorders. It is likely that this core domain set will also be applicable for longitudinal observational studies. This core set development represents a major step forward in the harmonization of outcome measurement in this field of research. The core domain set comprises four 'mandatory' domains within the 'mandatory for all clinical trials' category: pain, function, patient global - shoulder and adverse events including death; and four 'important but optional' domains: participation (recreation/work), sleep, emotional wellbeing and condition-specific pathophysiological manifestations. Currently there are no items in the new 'mandatory in specific circumstances category' in the inner circle. There were no items remaining in the research agenda.

Potential limitations in the development of the shoulder disorders core domain set include the relatively low response rate in both Delphi rounds, particularly for some stakeholders. Furthermore, Delphi participants were asked to judge the importance of each domain, but not to rank or prioritize a pre-determined number of domains which may have contributed to overrating the importance of some domains and the inclusion of some overlapping domains. The review of qualitative studies was conducted after the Delphi which may have led to the inclusion of proposed domains (e.g. cognitive dysfunction) that may have been rated as unimportant during the Delphi exercise. On the other hand, strengths of the process include the high quality methods meeting OMERACT standards, and the engagement of patients, clinicians and other relevant stakeholders from the field of outcomes in rheumatology.

The next step will be to define a core outcome measurement set, which is a core set of instruments that should be used to measure each of the domains. The Working Group is already working towards determining which instruments pass the OMERACT 2.0 Truth, Discrimination and Feasibility filter. Results of this work will be presented at a future OMERACT conference to enable endorsement of specific measures for each domain to be included in the final core outcome measurement set and any priorities for future research.

After reaching widespread agreement of these core domain and outcome measurement sets via the OMERACT process, it will be important to implement them. While we work towards identifying which measurement instruments pass the OMERACT 2.1 Truth, Discrimination and Feasibility filter, researchers designing and conducting trials, observational studies and systematic reviews should already consider inclusion of the core domain set as a minimum. We will disseminate the OMERACT-endorsed core domain set in workshops at relevant meetings as well as use other methods for reaching relevant stakeholder groups (e.g. patients, trialists, researchers, clinicians, regulators). We will also ensure a web presence (e.g.

OMERACT website, links from other sites). In the future, we will also measure the success of our implementation strategies by monitoring whether the OMERACT-endorsed core domain and outcome measurement sets for clinical trials of shoulder disorders are being used in trials, as has previously done in other areas.(15, 16)

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Competing interests

The authors have no competing interests to declare.

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Statement of Contribution

In the current manuscript we have summarized all the preparatory work from the OMERACT Shoulder Working Group that has led to the presentation at a dedicated workshop at OMERACT 2018 of the proposed core domain set. This means summarizing the results of previously published studies, which consisted of a systematic review of domains measured in shoulder trials, an international Delphi involving patients, clinicians and researchers and a summary of the OMERACT 2016 Special Interest Group resulting in a preliminary core domain set. In the currently submitted manuscript the results of new systematic review of qualitative studies on the experiences of people with shoulder disorders were for the first time described. Furthermore, the discussions taking place at the Shoulder Workshop at OMERACT 2018, as well as the voting results are presented. In summary, the qualitative review (N=8) identified all domains included in the preliminary core set. An additional domain, cognitive dysfunction was also identified but confidence that this represents a core domain was very low. The core domain set that was endorsed by the OMERACT 2018 participants, with 71% agreement, includes four 'mandatory' trial domains: pain, function, patient global and adverse events including death; and four 'important but optional' domains: participation (recreation/work), sleep, emotional wellbeing and condition-specific pathophysiological manifestations. Cognitive dysfunction was voted out of the core domain set. OMERACT 2018 delegates endorsed a core domain set for clinical trials of shoulder disorders and this represents a major step forward in harmonization of outcome measurement in this field. The currently submitted manuscript has not been submitted elsewhere and includes only new data, clearly advancing the field of shoulder disorders and outcome measurement.

Table 1 – Phases of the development of the Shoulder core domain set and included domains

Circle	**Preliminary Core Set OMERACT 2016**	**Proposed Core Set OMERACT 2018**	**Final Approved Core Set OMERACT 2018**	**Delphi** § (9)	**Confidence in the evidence from qualitative evidence synthesis±**(11)
Inner	Pain	Pain	Pain	97%	Moderate
	Physical function/activity	Physical function/activity	Physical function/activity	94%	Moderate
	Global perceived effect	Global perceived effect	Patient global - shoulder	86%	NA
	Adverse events	Adverse events including death	Adverse events including death	NA	NA
Middle	Participation (Recreation and work)	Participation (Recreation and work)	Participation (Recreation and work)	NA Work ability 90% Recreation 71%	Moderate
	Sleep	Sleep	Sleep	70%	Moderate
	Emotional wellbeing	Emotional wellbeing	Emotional wellbeing	69%	Moderate/low *
	--	Condition-specific pathophysiological manifestations	Condition-specific pathophysiological manifestations	Voted out (<67%)	Low
Outer	Research agenda	Cognitive dysfunction		NA	Very low

NA – not available, i.e. not included in the Delphi or in the qualitative evidence synthesis

* Moderate for frustration and anxiety and low for depression

§ Percentage of votes from the Delphi second round agreeing with the inclusion of the domain(9)

± Confidence in each review finding (high, moderate, low, very low) using the GRADE-CERQual approach;(13) data from the qualitative evidence synthesis(11)

Table 2 – Voting Results from the OMERACT 2018 Shoulder Core Set Workshop

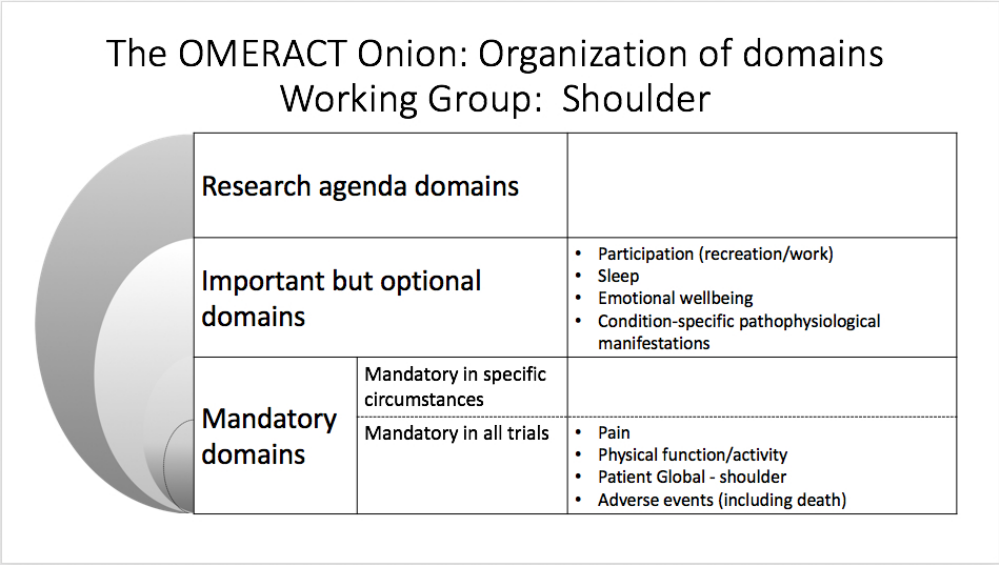
Domain	**Votes in favour n (%)§**
Inner Circle	67 (71%)
- Pain	94 (100%)
- Physical function	94 (99%)
- Patient Global - shoulder	75 (80%)
- Adverse events including death	No vote, mandatory domain
Middle Circle	
- Participation (recreation/work)	82 (89%)
- Sleep	85 (93%)
- Emotional wellbeing	75 (82%)
- Condition-specific pathophysiological manifestations	40 (44%)
Outer Circle	
- Cognitive dysfunction	58 (64%) -> 41 (36%)*

§Throughout the voting process, some participants did not vote for specific domains, so the total number of participants may vary for the different domains.

*In the first vote during the Workshop, 64% of the participants agreed with the proposal to keep cognitive dysfunction in the outer circle. It was thus unclear where it should be kept or removed, and therefore a second vote was conducted during the Plenary (n=115), in which only 36% of the participants indicated to keep it in the Core Domain Set. As a consequence, it was removed.

Table 3 – Definition of the domains included in the Core Domain Set for Shoulder Disorders

Domain	
Pain	How much a person's shoulder hurts, reflecting the overall magnitude of the pain experience (i.e., at rest, during and after activity, at night)
Physical function	A person's ability to carry out daily physical activities, ranging from self-care (e.g. bathing, combing hair) to more complex activities that require a combination of skills (e.g. driving a car)
Patient global - shoulder	Patient reported global rating of the status of the shoulder
Adverse effects including death	Any major or minor adverse event that occurs during the course of the trial, including any deaths
Emotional well-being	Effect on a person's emotions, including levels of depression, anxiety, or other types of psychological distress. Depression refers to negative mood, loss of self-confidence, loss of motivation, and enjoyment. Anxiety refers to fear, extreme worrying, and hyperarousal symptoms
Participation (Recreation and work)	A person's ability to engage in a life situation, in any form of play, recreational or leisure activity acts (e.g. sports of any kind or levels), and the ability to meet physical and/or psychological demands of work
Sleep	Sleep functions such as onset, maintenance, quality, amount of sleep, and functions involving the sleep cycle. This domain also includes the effect on perceptions of alertness and sleepiness during usual waking hours
Pathophysiological manifestations	Could be range of motion, muscle strength, radiographic outcomes, stability, fracture, mal-union, weakness



Core Domain Set for Shoulder Disorders
Shoulder disorders include rotator cuff disease (tendinopathy, impingement, subacromial bursitis, tears), adhesive capsulitis, instability, glenohumeral osteoarthritis, dislocation, proximal humeral or humeral head fractures and unspecified shoulder pain.

335x190mm (72 x 72 DPI)