**JOURNAL OF RHEUMATOLOGY**

**TITLE PAGE**

**Title:** Uptake of the OMERACT-OARSI Hip and Knee Osteoarthritis Core Outcome Set: review of randomised controlled trials from 1997 to 2017.

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**ABSTRACT**

**Objective:** To assess the uptake of the OMERACT-OARSI core outcome set (COS) domains in hip and/or knee osteoarthritis (OA) trials.

**Methods:** 382 trials of hip and/or knee OA were identified from the ClinicalTrial.gov registry from 1997 to 2017. Frequency of COS adoption was assessed by year and per 5-yearly phase.

**Results:** COS adoption decreased from 61% between 1997-2001 to 38% between 2012-2016. Pain (95%) and physical function (86%) were most consistently adopted. Patient global assessment (48%) was the principal missing domain.

**Conclusion:** Limited adoption of the COS Domains indicates that further consideration to improve implementation is required to improved uptake.

**Keywords:** OMERACT; Core outcome set; domain; adoption; trial registration

**Word Count:** 1498/1500

**INTRODUCTION**

Clinical trials seek to determine whether a treatment is effective and safe for patients by comparing their relative effects on outcomes chosen to identify benefit or harm.(1) These can be used to make decisions on whether the treatment under investigation should be recommended or not.(2) It is therefore essential that outcomes reported in trials are those which are needed by decision-makers, and reflect meaningful outcomes for patients, clinicians and all stakeholders involved in the care of these patients.(3)

In 1997 OMERACT-OARSI presented the core outcome set (COS) for people involved in trials with hip and knee osteoarthritis (OA). They reported that four domains should be measured and reported in all future clinical trials including patients with hip or knee OA.(4) These were: pain; physical function; patient global assessment; and with an extra conditionally recommended domain for studies with a follow-up period of a year or longer with putative structure-modifying OA drugs, joint imaging (such as x-rays or MRI scans). Whilst these recommendations have been in the public domain for 20 years, it remains unknown whether they have changed the selection of outcomes used in trials with this population during this period.

The purpose of this study was to assess the uptake of a COS for hip and knee OA, and explore if specific study characteristics are associated with the failure of COS uptake.

**METHODS**

We adopted Kirkham et al’s (5)recommendations on the assessment of COS uptake. Through this, we searched the trials registry ClinicalTrials.gov on 6th July 2017 to identify all phase 3 or 4, drug or non-drug trials registered from January 1997 to July 2017, recruiting people with hip or knee OA. The following filters were applied to identify eligible trials: “conditions: osteoarthritis”, “study type: interventional studies”, and “phase: 3 and 4”. Only Phase 3 and 4 trials were included to reflect the Phase 3 and 4 recommendations made in the original OMERACT-OARSI COS.(4) We excluded trials which did not exclusively recruit people with OA, did not assess treatment benefit (i.e. effectiveness or efficacy) as endpoints (i.e. medication dosage or safety studies). We also excluded studies assessing outcomes following surgical intervention (principally joint replacement).

We extracted data on all planned trial outcomes and assessed whether the full OMERACT-OARSI hip and knee OA COS was adopted.(4) These were the assessment of pain, physical function, patient global assessment and, with a conditional recommendation for trials with a 12 month or greater follow-up period and for putative structure modifying OA drugs, imaging outcomes. We also assessed the uptake of ‘strongly recommended’ domains including: health-related quality of life (HRQOL) and physician global assessment. We assessed the frequency of use of outcomes which were recommended as ‘optional’, including: stiffness, biologic markers, inflammation, performance-based function, flares, time to surgery, analgesic count. If a trial had registered a composite outcome, all individual outcomes were considered in the composite, even when not listed separately.

Data also collected included: year of trial registration, anatomic location of OA participants presented with (hip, knee or hip and/or knee), country of origin, sample size, duration of follow-up at end-point, the intervention type under investigation (drug or non-drug trial) and phase of the trial.

All 382 trial registrations were extracted by one reviewer (TS). An independent reviewer (MM) verified 10% of the data collected to ensure accuracy of extraction from the trial registry, following Kirkham et al’s (5) approach. Disagreement between the reviewers was resolved through discussion. To assess the veracity of the ClinicalTrials.gov registry data, when a trial did not meet the full COS, with any of the core domains missing (n=230), the published full report was used to verify the data (n=74). When published reports were not available (n=156), the chief investigator or named contact on the trial registration was contacted via email to verify the data. Of these 14% (n=21) responded and provided additional data.

*Data Analysis*

We calculated the proportion of trials which reported each OA COS domain and the full domain set, and the percentage of core outcomes reported from the COS per year. These were assessed over the 20-year follow-up period to determine change over time.

Using a forced entry multivariate logistic regression model, we assessed the relationship between year of registration, sample size, country of origin, duration of follow-up interval, whether participants presented with isolated hip, isolated knee or hip and/or knee OA, phase of trial (Phase 3 or 4), whether it was a drug trial or non-drug trial and full COS domain uptake (yes/no). A forced entry method was adopted to ensure that all variables were included in the model. Data were presented as odds ratios (OR) with 95% confidence intervals (CI). A two-sided p-value <0.05 was deemed as indicating statistical significance. Analyses were undertaken using Stata version 14.0 (StataCorp LLC, Texas, USA).

**RESULTS**

In total, 382 Phase 3 or 4 trials registered in Clinicaltrials.gov were eligible for analysis. The eligibility assessment and reasons for exclusion of trials are presented in Figure 1. Trial characteristics are presented in Supplementary Table 1.

The assessment of COS uptake is summarised in Table 1 and Figure 2. There was a decrease in the adoption of the full COS from 61% between 1997 to 2001 to 38% between 2012 to 2016. The adoption of the full COS has largely plateaued between 2002 to 2017, within the ranges of 38% to 54% (Table 1; Supplementary Table 2). Whilst trials have consistently assessed pain (over 90%; Table 1) and physical function (over 80%; Table 1), there has been greater variability for patient global assessment (67% to 38%). As Figure 2 illustrates, the assessment of patient global assessment was the principal domain for COS not being fully reported from 1997 to 2017.

On assessment of domains which were ‘recommended’ but not ‘essential’ by the 1997 OMERACT-OARSI COS,(4) joint stiffness was most commonly assessed (58%) followed by HRQOL (26%) and analgesic consumption (27%). Least frequently assessed included swelling (7%), pain flares (2%) and time to surgery (3%) (Table 1).

On analysis of the factors which may be associated with a successful COS uptake, the phase of the trial was a significant factor, where Phase 3 trials were over twice as likely to have reported a full COS, compared to Phase 4 trials (OR: 2.32; 95% CI: 1.26 to 4.26; p=0.01). Drug trials were over three times as likely to have presented the full COS compared to non-drug trials (OR: 3.57; 95% CI: 1.12 to 5.37; p=0.03). The country of trial origin (p=0.99), year of registration (p=0.28), duration of the trial (p=0.07) and whether the trial recruited people with hip, knee or hip and knee OA (p=0.53) were not significant. Although statistically significant, there was no important difference in COS adoption based on sample size (OR: 1.00; 95% CI: 1.00 to 1.00; p<0.01).

**DISCUSSION**

This study has demonstrated that there has been limited uptake of the full OMERACT-OARSI COS domains in randomised controlled trials of hip and knee OA during the past 20 years. Whilst pain and physical function are consistently assessed, (over 90% and over 80% respectively), patient global assessment is less frequently evaluated and decreased from 67% to 38%, which is the principal reason for trials not satisfying the full COS uptake.

Of the three (conditionally four) components required to satisfy the COS, patient global assessment was the principal missing domain for trials not satisfying the full COS. There has been concern that patient global assessment scores may be influenced by social desirability bias.(6) This may therefore be a reason for the reported lower adoption of patient global assessment measures. Nonetheless, OMERACT and others have highlighted the importance of patient-reported outcome measures to measure the patient’s overall perceptions of their disease.(7) Accordingly, the diminishing inclusion of patient global domain warrants an update of the COS to ensure its relevance for OA trials.

The results contrast with the Kirkham et al (8)analysis of the uptake of the rheumatoid arthritis COS where uptake had increased within a 14-year period (from 2002) to 81% of eligible trials. This was attributed to the introduction of consistent guidance provided by regulatory authorities including the Food and Drug Administration (FDA) (9) and European Medicines Agency (EMA).(10) There is less consistency around COS domains in OA.(11) The OARSI-FDA Disease State Working Group12 recommended the assessment of pain, function, radiological measures and other wider patient experiences of illness including fatigue, mood, sleep and HRQOL.(12) The EMA guidelines recommend that pain, functional disability and structural damage should be assessed, but patient global assessment is recommended rather than mandatory.(13) Some of this discordance may account for lack of uptake, and therefore future work may be undertaken to standardise recommendations across regulatory authorities.

Trials were evaluated using their ClinicalTrials.gov registration, as recommended by Kirkham et al (5) to provide a more efficient means of assessing COS uptake compared to reviewing final trial reports or publications.(5,14) However, a disadvantage to the adopted approach was that we did not review additional registries such as the World Health Organization International Clinical Trials Registry Platform (ICTRP) or the Netherlands Trial Registry. However, since ClinicalTrials.gov demonstrates international coverage (Supplementary Table 1), we feel that the results were representative of trials on this population.

**ACKNOWLEDGEMENTS & DECLARATIONS**

**Acknowledgements:** None.

**Declarations:** This work was presented as a poster presentation at the OMERACT2018 meeting, 14th to 18th May 2018 at Terrigal, Australia.

**Funding:** Dr Toby Smith was awarded an Arthritis Action grant and a EULAR OMERACT Educational Bursary to support the Fellow’s (TS) attendance at the OMERACT2018 meeting.

TS is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre, Oxford and PGC is supported, in part, by the NIHR Leeds Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. The Parker Institute, Bispebjerg and Frederiksberg Hospital (RC) is supported by a core grant from the Oak Foundation (OCAY-13-309).

**Conflicts of Interest:** No author declares a conflict of interest in relation to this paper.

**Ethical approval:** No ethical approval was sought for this study design.

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**Figure 1:** Flow-chart of identification of trial registrations from ClinicalTrial.gov database

Reasons for non-eligible

* Joint replacement trials (N=211)
* Cohorts with mixed pathologies (i.e. OA, RA, AS, LBP, chronic pain) (N=53)
* Surgical trials (non-arthroplasty) (N=33)
* Trials on Hand OA (N=24)
* Location of OA not clearly documented (N=14)
* Trials on Shoulder Pain (N=7)
* Trials on Foot and Ankle OA (N=7)
* Trials on spinal OA (N=5)
* Not OA trials on full assessment (N=2)
* Diagnostic study, not interventional (N=1)
* Trials on TMJ pain (N=1)
* Solely safety trial, no symptom assessment (N=1)
* Cohort solely with RA (N=1)

Eligible trial registrations

(N=382)

All registrations relating to Phase 3 or 4 osteoarthritis intervention trials

(N=742)

Non-potentially eligible registrations (N=248,706)

All registrations in ClinicalTrials.gov on point of assessment

(N=249,448)

Trial completed or terminated

(N=276)

Trial ongoing, suspended or withdrawn

(N=69)

Trial of unknown status

(N=37)

**Figure 2:** Graph of uptake of core domain and individual domains for the osteoarthritis core outcome set from 1997 to 2017.



**Table 1:** Percentage frequency of domains reported and complete adoption of the Core Outcome Set in included trial registrations.

|  |  |  |
| --- | --- | --- |
| **Domain** | **Percentage Total Frequency****(N=382)** | **Percentage Frequency by Year** |
| **1997-2001****(N=18)** | **2002-2006****(N=94)** | **2007-2011****(N=133)** | **2012-2016****(N=123)** | **2017****(N=14)** |
| Core Domain |
| Pain | 94.8 | 100 | 91.5 | 96.9 | 94.4 | 92.9 |
| Physical function | 86.1 | 94.4 | 81.9 | 89.2 | 84.1 | 92.9 |
| Patient global assessment | 47.6 | 66.7 | 59.6 | 45.4 | 38.1 | 42.9 |
| Imaging\* | 75.0 | 71.4 | 40.0 | 79.2 | 89.5 | 85.7 |
| All core domains measured | 45.3 | 61.1 | 54.3 | 43.1 | 38.1 | 50.0 |
| Recommended Domains |
| HRQOL | 26.2 | 27.8 | 12.8 | 39.1 | 27.6 | 14.3 |
| Clinician global assessment | 23.0 | 44.4 | 36.2 | 16.5 | 20.3 | 14.3 |
| Optional Domains |
| Stiffness | 58.1 | 66.7 | 58.5 | 64.7 | 52.0 | 35.7 |
| Biological markers (i.e. relevant blood tests) | 18.8 | 22.2 | 17.0 | 23.3 | 15.4 | 7.1 |
| Swelling | 7.1 | 16.7 | 3.2 | 6.8 | 8.1 | 7.1 |
| Performance Assessment | 14.7 | 27.8 | 11.7 | 15.0 | 16.3 | 7.1 |
| Pain flares | 1.6 | 5.6 | 3.2 | 1.5 | 0.8 | 0.0 |
| Time to surgery | 2.6 | 16.7 | 0.0 | 0.0 | 4.1 | 7.1 |
| Analgesic consumption | 27.0 | 50.0 | 29.8 | 24.8 | 22.8 | 21.4 |

\* Imaging is a required core outcome set domain for trials of 12 month or greater follow-up in trials of structure modifying osteoarthritis drugs (Total N=68).

**APPENDIX: Supplementary Table 1:** Characteristics of included trials registered on ClinicalTrials.gov

|  |  |
| --- | --- |
| **Characteristic** | **Number (%) of trials (N=382)** |
| Location of Osteoarthritis |  |
| Hip | 17 (4.5) |
| Knee | 299 (78.3) |
| Hip and Knee | 66 (17.3) |
| Trial Phase |  |
| 3 | 253 (66.2) |
| 4 | 129 (33.8) |
| Intervention Type |  |
| Drug Trial | 348 (91.1) |
| Non-Drug Trial | 34 (8.9) |
| Trial duration |  |
| Mean duration (weeks; SD) | 27.2 (46.0) |
| <6 months | 254 (66.5) |
| 6-12 months | 95 (24.9) |
| >12 months | 29 (7.6) |
| Not documented | 4 (1.0) |
| Planned sample size |  |
| Mean sample size | 359.5 (537.1) |
| <100 | 100 (26.2) |
| 100-500 | 194 (50.8) |
| >500 | 88 (23.0) |
| Trial status |  |
| Complete | 259 (67.8) |
| Recruiting | 42 (11.0) |
| Terminated | 17 (4.5) |
| Not yet recruiting | 11 (2.9) |
| Active, not recruiting | 7 (1.8) |
| Withdrawn | 7 (1.8) |
| Enrolling by invitation | 2 (0.5) |
| Unknown status | 37 (9.7) |
| Principal continent of registration |  |
| Europe | 95 (24.9) |
| Asia | 80 (20.9) |
| North America | 177 (46.3) |
| South America | 22 (5.8) |
| Australasia | 8 (2.1) |
| Africa | 0 (0.0) |
| Antarctica | 0 (0.0) |
| Year of Registration |  |
| 1997-2001 | 18 (4.7) |
| 2002-2006 | 94 (24.6) |
| 2007-2011 | 130 (34.0) |
| 2012-2016 | 126 (33.0) |
| 2017 | 14 (3.7) |

**APPENDIX: Supplementary Table 2**: Frequency of domains reported and complete adoption of the Core Outcome Set in included trial registrations by year.

|  |  |
| --- | --- |
| Domain | Frequency (%) |
| 1997N=3 | 1998N=3 | 1999(N=7) | 2000(N=4) | 2001(N=1) | 2002(N=10) | 2003(N=28) | 2004(N=20) | 2005(N=19) | 2006 (N=17) | 2007(N=32) | 2008(N=24) | 2009(N=25) | 2010(N=22) | 2011(N=27) | 2012(N=16) | 2013(N=29) | 2014(N=24) | 2015(N=27) | 2016(N=30) | 2017(N=14) |
| Core Domain |
| Pain | 3 (100) | 3 (100) | 7 (100) | 4 (100) | 1 (100) | 10 (100) | 26 (93) | 19 (95) | 18 (95) | 13 (77) | 30 (94) | 24 (100) | 23 (92) | 22 (100) | 27 (100) | 16 (100) | 27 (93) | 22 (92) | 27 (100) | 27 (90) | 13 (93) |
| Physical function | 3 (100) | 3 (100) | 6 (86) | 4 (100) | 1 (100) | 9 (90) | 23 (82) | 15 (75) | 17 (90) | 13 (77) | 27 (84) | 23 (96) | 23 (92) | 21 (95) | 22 (81) | 15 (94) | 25 (86) | 18 (75) | 26 (96) | 22 (73) | 13 (93) |
| Patient global assessment | 0 (0) | 2 (67) | 5 (71) | 4 (100) | 1 (100) | 7 (70) | 20 (71) | 11 (55) | 11 (58) | 7 (41) | 17 (53) | 8 (33) | 16 (64) | 8 (36) | 10 (37) | 5 (31) | 12 (41) | 11 (46) | 12 (44) | 8 (27) | 6 (43) |
| Imaging\* | 3 (100) | N/A | 2 (100) | N/A | N/A | 0 (0) | 0 (0) | 2 (67) | 0 (0) | 2 (100) | 4 (100) | 5 (71) | 1 (33) | 3 (43) | 2 (33) | 1 (33) | 1 (25) | 1 (100) | 1 (33) | 4 (57) | 6 (86) |
| All core domains measured\* | 3 (100) | 2 (67) | 4 (57) | 4 (100) | 1 (100) | 7 (70) | 16 (57) | 10 (50) | 11 (58) | 7 (41) | 16 (50) | 8 (33) | 16 (64) | 7 (32) | 9 (33) | 5 (31) | 12 (41) | 10 (42) | 12 (44) | 9 (30) | 7 (50) |
| Recommended Domains |
| HRQOL | 1(33) | 2 (67) | 1 (14) | 1 (25) | 0 (0) | 1 (10) | 3 (11) | 0 (0) | 4 (21) | 4 (24) | 7 (22) | 12 (50) | 11 (44) | 7 (32) | 11 (41) | 5 (31) | 7 (24) | 7 (29) | 6 (22) | 8 (27) | 2 (14) |
| Clinician global assessment | 0 (0) | 1 (33) | 5 (71) | 1 (25) | 1 (100) | 2 (20) | 13 (46) | 8 (29) | 7 (37) | 4 (24) | 6 (19) | 1 (4) | 5 (20) | 5 (23) | 5 (19) | 6 (38) | 5 (17) | 5 (21) | 2 (7) | 4 (13) | 2 (14) |
| Optional Domains |
| Stiffness | 1(33) | 1 (33) | 5 (71) | 4 (100) | 1 (100) | 8 (80) | 16 (57) | 14 (50) | 10 (53) | 7 (41) | 22 (69) | 17 (71) | 18 (72) | 13 (59) | 11 (41) | 9 (56) | 16 (55) | 12 (50) | 17 (63) | 15 (50) | 5 (36) |
| Biological markers (i.e. relevant blood tests) | 0 (0) | 1 (33) | 1 (14) | 1 (25) | 1 (100) | 1 (10) | 8 (29) | 3 (11) | 2 (11) | 2 (12) | 6 (19) | 6 (25) | 7 (28) | 6 (27) | 5 (19) | 1 (6) | 5 (17) | 3 (3) | 5 (19) | 7 (23) | 1 (7) |
| Swelling | 0 (0) | 1 (33) | 1 (14) | 1 (25) | 0 (0) | 0 (0) | 1 (4) | 1 (4) | 1 (5) | 0 (0) | 1 (3) | 4 (17) | 1 (4) | 2 (9) | 2 (7) | 0 (0) | 2 (7) | 2 (8) | 2 (7) | 4 (13) | 1 (7) |
| Performance Assessment | 0 (0) | 1 (33) | 2 (29) | 1 (25) | 1 (100) | 2 (20) | 1 (4) | 3 (11) | 5 (26) | 0 (0) | 7 (22) | 5 (21) | 3 (12) | 3 (14) | 2 (7) | 3 (19) | 7 (24) | 3 (13) | 2 (7) | 4 (13) | 1 (7) |
| Pain flares | 0 (0) | 1 (33) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 2 (11) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Time to surgery | 2(67) | 0 (0) | 1 (14) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 3 (10) | 0 (0) | 1 (4) | 2 (7) | 1 (7) |
| Analgesic consumption | 2(67) | 1 (33) | 3 (43) | 2 (50) | 1 (100) | 3 (30) | 7 (25) | 6 (21) | 6 (32) | 6 (35) | 9 (28) | 6 (25) | 5 (20) | 6 (27) | 8 (30) | 4 (25) | 9 (31) | 4 (17) | 5 (19) | 7 (23) | 3 (21) |
| Non-Recommended Domains |
| Adverse events | 1(33) | 2 (67) | 2 (29) | 3 (75) | 1 (100) | 7 (70) | 14 (50) | 10 (36) | 5 (26) | 4 (24) | 11 (34) | 15 (63) | 15 (60) | 10 (46) | 8 (30) | 7 (44) | 14 (48) | 9 (38) | 12 (44) | 11 (37) | 7 (50) |
| Treatment adherence | 1(33) | 1 (33) | 2 (29) | 2 (50) | 1 (100) | 2 (20) | 9 (32) | 6 (21) | 5 (26) | 0 (0) | 5 (16) | 9 (38) | 7 (28) | 4 (18) | 4 (15) | 2 (13) | 7 (24) | 1 (4) | 2 (7) | 4 (13) | 2 (14) |
| Physical examination | 0 (0) | 0 (0) | 1 (14) | 1 (25) | 0 (0) | 1 (10) | 8 (29) | 3 (11) | 1 (5) | 4 (24) | 1 (3) | 7 (29) | 6 (24) | 8 (36) | 1 (4) | 1 (6) | 3 (10) | 5 (21) | 5 (19) | 5 (17) | 3 (21) |
| Vital signs (e.g. BP/HR) | 0 (0) | 0 (0) | 1 (14) | 0 (0) | 0 (0) | 1 (10) | 8 (29) | 2 (7) | 4 (21) | 3 (18) | 1 (3) | 4 (17) | 7 (28) | 5 (23) | 2 (7) | 2 (13) | 3 (10) | 2 (8) | 5 (19) | 4 (13) | 1 (7) |
| Work productivity | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 1 (6) | 1 (3) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 0 (0) | 1 (4) | 1 (3) | 0 (0) |
| Treatment response | 0 (0) | 0 (0) | 0 (0) | 1 (25) | 0 (0) | 1 (10) | 3 (11) | 5 (18) | 4 (21) | 2 (12) | 6 (19) | 2 (8) | 7 (28) | 5 (23) | 4 (15) | 1 (6) | 5 (17) | 3 (13) | 5 (19) | 5 (17) | 5 (36) |
| Sleep | 0 (0) | 0 (0) | 0 (0) | 1 (25) | 0 (0) | 2 (20) | 5 (18) | 1 (4) | 0 (0) | 4 (24) | 3 (9) | 1 (4) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 4 (15) | 0 (0) | 0 (0) |
| Mood and mental wellbeing | 0 (0) | 0 (0) | 1 (14) | 1 (25) | 0 (0) | 0 (0) | 2 (7) | 0 (0) | 0 (0) | 1 (6) | 2 (6) | 3 (13) | 5 (20) | 1 (5) | 2 (7) | 2 (13) | 2 (7) | 1 (4) | 2 (7) | 2 (7) | 0 (0) |
| Cost and economic evaluation | 1 (33) | 1 (33) | 2 (29) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 1 (6) | 1 (3) | 2 (8) | 0 (0) | 1 (5) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 1 (3) | 0 (0) |
| Biomechanical / kinematic assessment | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (10) | 0 (0) | 1 (4) | 0 (0) | 1 (6) | 0 (0) | 3 (13) | 0 (0) | 0 (0) | 0 (0) | 1 (6) | 2 (7) | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| Patient reported health status | 0 (0) | 0 (0) | 1 (14) | 0 (0.0) | 0 (0) | 1 (10) | 1 (4) | 0 (0) | 1 (5) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) |
| Falls | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) |
| Fatigue | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 0 (0) | 1 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Cognitive function | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Time to treatment response (pain) | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 1 (5) | 1 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Patient preference (to other treatment) | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Coping and self-efficacy | 0 (0) | 0 (0) | 0 (0) | 0 (0.0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

N/A – not applicable as respective trials did not met the threshold to require an imaging outcome in accordance with OMERACT recommendations (Bellamy, 1997).