Harmonising data collection from osteoarthritis studies to enable stratification: recommendations on core data collection from an Arthritis Research UK clinical studies group. Rheumatology 55 (8), pp. 1394-1402. 10.1093/rheumatology/kew201 file

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Harmonising data collection from osteoarthritis studies to enable stratification: recommendations on core data collection from an Arthritis Research UK clinical studies group

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Abstract

Objective. Treatment of OA by stratifying for commonly used and novel therapies will likely improve the range of effective therapy options and their rational deployment in this undertreated, chronic disease. In order to develop appropriate datasets for conducting post hoc analyses to inform approaches to stratification for OA, our aim was to develop recommendations on the minimum data that should be recorded at baseline in all future OA interventional and observational studies.

Methods. An Arthritis Research UK study group comprised of 32 experts used a Delphi-style approach supported by a literature review of systematic reviews to come to a consensus on core data collection for OA studies.

Results. Thirty-five systematic reviews were used as the basis for the consensus group discussion. For studies with a primary structural endpoint, core domains for collection were defined as BMI, age, gender, racial origin, comorbidities, baseline OA pain, pain in other joints and occupation. In addition to the items generalizable to all anatomical sites, joint-specific domains included radiographic measures, surgical history and anatomical factors, including alignment. To demonstrate clinical relevance for symptom studies, the collection of mental health score, self-efficacy and depression scales were advised in addition to the above.

Conclusions. Currently it is not possible to stratify patients with OA into therapeutic groups. A list of core and optional data to be collected in all OA interventional and observational studies was developed, providing a basis for future analyses to identify predictors of progression or response to treatment.

Key words: osteoarthritis, clinical trials, stratification, prognosis, personalized medicine
Harmonizing data collection for OA studies

Rheumatology key messages
- Stratification of therapy is key to improving OA treatment.
- Development of OA stratification criteria requires harmonized data collection to enable analysis of pooled data.
- We developed a set of core and optional components for data collection across all OA studies.

Introduction
OA represents a considerable worldwide health and economic challenge [1]. Although OA is a heterogeneous disease driven by a variety of pathophysiologic factors, current therapy selection is largely arbitrary. In general, treatment is aimed at symptomatic relief rather than targeting pathology, and the choice of therapeutic agent is often based on potential toxicity without consideration of likely efficacy. As such, efficacy of these currently available treatments is poor in the majority of people with OA [2]. Stratification of patients towards targeting of commonly used as well as novel therapies will likely improve the range of effective treatment options and their rational deployment in this undertreated chronic disease.

The development of a stratification strategy for OA requires knowledge of both predictors of disease progression to identify patients requiring treatment and predictors of response to treatment, which together will allow the identification of subsets of patients within which treatments may have improved efficacy. Such data may be gathered prospectively in well-designed interventional and observational studies and retrospectively through post hoc analyses of single studies and linking or pooling of study data for meta-analyses. To ensure robust analyses and reliability of results, consistent data collection across studies is essential.

In order to develop appropriate datasets for stratification in OA, our aim was to develop advice on what minimum data should be recorded at baseline in all future OA interventional and observational studies.

Methods
The Arthritis Research UK Osteoarthritis and Crystal Diseases Clinical Studies Group conducted a literature review of systematic reviews and convened an expert consensus group to consider core data collection to allow post hoc stratification analyses to be conducted.

Literature review
A review of systematic reviews was conducted to identify prognostic factors of OA in general and more specifically for knee, hip and hand OA. Systematic searches were conducted across four electronic databases [Cochrane Library, Embase (OVID), Medline (OVID) and Web of Science] from inception to August 2015. The search strategy (supplementary Table S1, available at Rheumatology Online) was designed in OVID Medline using text words and MeSH and combining terms for OA, prognosis and systematic review. For the other databases, search terms were adapted to the search capabilities of the database. Non-English-language articles, letters, comments and editorials were excluded. Evidence was graded according to classifications in the included reviews, which were designated as conflicting, weak/limited, moderate and strong.

Consensus group discussion
A group of 32 stakeholders, including rheumatologists, physiotherapists, podiatrists, trialists, orthopaedic surgeons, primary care physicians, scientists and patient representatives who have a particular interest in OA, attended a meeting where the findings of the literature review were presented. The panel meeting started with a predefined objective presented by the chair (P.C.). The objective was to develop guidelines to harmonize data collection across all OA clinical studies.

After discussion, it was agreed that development of recommendations for studies should be based on the predetermined principles explained here. Only clinically relevant domains should be included in the core list. These may be different for trials with structural or symptomatic endpoints. Domains would be based on existing recommendations for appropriate domains to be assessed (including those from the OMERACT).

For the data item to be recommended as a core component there should be evidence of either predicting response to treatment or as a risk factor for progression of OA. Where insufficient evidence currently exists, items should not be included in core components, but may be recommended as additional information to be captured at the study team’s discretion. Since an extensive literature review on the tools used to capture each component was not conducted, the use of a set tool would not be recommended. However, potential tools or mechanisms used to capture each component would be suggested. The choice of tool should depend on its extent of validation and psychometric robustness as well as feasibility issues, including costs. The core components should be revised as more data become available, with a maximum of 5 years before the next revision. Items may be generalizable to all anatomical sites of OA or specific to a particular joint. In trials designed with a primary structural endpoint, symptomatic domains should also be measured to assess the clinical relevance of structural change. Recommendations should apply to all types of OA clinical studies, including pharmacological and non-pharmacological interventional trials and observational studies.

The literature summarizing the current evidence for prognostic factors for OA was presented (N.C.). The panel was then prompted to identify the domains that were felt to be important for inclusion in the core data items and these were compiled. Once identified, each domain was discussed and considered in line with the presented evidence to determine whether they fulfilled the criteria for core data, and those with insufficient
evidence were excluded at this time. The discussion was separated by joint, with separate consideration of data collection for knee, hip and hand studies. Consensus on inclusion/exclusion of domains was defined where there was 100% verbal agreement from the panel. For each domain included, appropriate tools for assessment were discussed. Domains for which there was a consensus were included in a list of provisional domains. The provisional list was then transcribed and circulated 1 week after the consensus meeting. This was then refined and finalized following an iterative electronic discussion involving the entire panel.

Results

Literature review

A total of 35 systematic reviews were identified for inclusion. Thirteen reported on factors associated with structural/radiographic OA progression, 10 on functional/symptom progression and a further 15 on factors affecting outcomes of interventions for or associated with OA. These were categorized according to the location of OA, type of progression reported, level of evidence identified by the systematic review and whether an association was found or not.

Literature on structural progression

Knee OA

Eight systematic reviews reported on structural/radiographic progression of knee OA (Table 1) [3–10]. Two also reported on clinical outcomes and are therefore also included with respect to symptom progression. Strong evidence was found for significant associations of the following factors with structural progression: increasing age [3]; presence of generalized/multijoint OA [3, 4]; combined radiographic features including increasing osteophyte score, joint space width (JSW), joint space narrowing (JSN), Kellgren–Lawrence (KL) grade and chondrocalcinosis [3]; varus alignment [3, 6, 10]; baseline pain [10]; anterior cruciate ligament injury [8]; increasing serum hyaluronic acid [4, 10]; high levels of TNF-α [10] and increasing urinary C-telopeptide of type II collagen (uCTX-II) [7]. Strong evidence of no significant association was found for physical/regular sports activity or moderate exercise [3–5], radiological severity at baseline [4], baseline pain [4], quadriceps strength [4] and knee injury [4]. Conflicting evidence was reported for association of BMI, clinical/disease severity, leg length inequality and symptom duration with radiographic progression [3, 4].

Hand OA

One systematic review reported on structural/radiographic progression of hand OA [13]. No strong evidence was available for any factors with a relationship to progression. Limited evidence for association of baseline pain, early menopause, nodal OA and erosive OA with radiographic progression was reported [13].

General OA

Two systematic reviews reported on structural/radiographic progression of general OA (either hip OA or knee OA or both hip and knee OA), neither of which identified strong evidence for any factors related to progression [14, 15].

Literature on symptom progression

Knee OA

Five systematic reviews reported on functional/symptomatic progression of knee OA (Table 1) [3, 5, 16–18]. Strong evidence was indicated for the association of the following factors with progression: increasing age [3]; presence of generalized/multijoint OA [3]; combined radiographic features including increasing osteophyte score, JSW, JSN, KL grade and chondrocalcinosis [3]; and varus alignment [3]. Physical activity was not associated with progression [3]. There was conflicting or limited evidence for associations with BMI [3, 17, 18], gender [3, 17, 18], symptom severity [3, 17, 18], mental health score [3, 17, 18], self-efficacy [3, 16, 17], clinical/disease severity [3], co-morbidity [17, 18] and baseline pain [3] with symptomatic progression.

Hand OA

There were no systematic reviews that reported on functional/symptomatic progression of hip OA.

Hip OA

Two systematic reviews reported on functional/symptomatic progression of hand OA [13, 19]. Kwok et al. [13] found no strong evidence available for the relationship of any factors to progression, while Nicholls et al. [19] concluded no information was available on the progression of hand pain and function over time. Limited evidence was reported for an association of age, baseline pain, number of painful joints and function with symptomatic progression, while limited evidence for no association with symptomatic progression was reported for nodal and erosive OA [13].

General OA

Three systematic reviews reported on functional/symptomatic progression of general OA (hip OA, knee OA or
both) [20], chronic musculoskeletal disease [21] and chronic disorders [22]. Strong evidence was indicated for lower self-efficacy as a predictor of disability in general OA [20]. However self-efficacy was not associated with pain in general OA [20].

Literature on response to interventions

Knee OA

Eleven systematic reviews reported on factors affecting outcomes of interventions for or including knee OA (Table 2) [23–33]. Strong evidence was indicated for association of the following factors with symptomatic outcomes? female gender was associated with pain while waiting for total joint replacement [28], worse preoperative mental health score was associated with lower function and greater pain >1 year after total knee arthroplasty (TKA) [25], increased pain catastrophizing was associated with postoperative pain within 1 year after TKA [25], postoperative self-efficacy was associated with short- and long-term outcomes [32] and co-morbidity was associated with TKA outcomes [30]. The following factors were found not to be associated with symptomatic outcomes? preoperative depression and anxiety was not associated with pain progression [28]. Limited or conflicting evidence was reported for association of age, BMI, baseline pain and pain duration with response to intra-articular steroid injection [23] and for association of BMI, age and health-related quality of life with TKA outcomes [29, 30, 33].

Hip OA

Nine systematic reviews reported on factors affecting outcomes of interventions for or including hip OA (Table 2)
Strong evidence was found for an association of female gender with pain while waiting for total joint replacement [28]. Co-morbidity was associated with total hip arthroplasty (THA) outcomes [30]. No association was found between wait for surgery (<180 days) and progression of pain or self-reported functioning [28]. Limited evidence was reported for association of age and health-related quality of life with THA outcomes and with response to intra-articular steroid injection [23, 29, 30].

Consensus group recommendation on structural progression

The recommended core items for inclusion in structural progression studies are outlined in Table 3. Injury is known to be an important risk factor for the onset of OA, but its role in progression is less clear and it was therefore not included in the core list. While collection of biological samples is highly desirable, especially for novel biomarker development, with only uCTX-II, serum hyaluronic acid and TNF-α showing evidence of association, it was agreed that their inclusion as a core item could not be justified based on current evidence. However, where study design and logistics allow, collection of biological samples is encouraged. The following items were not agreed for inclusion in the core components at this time due to insufficient evidence: clinical measures of inflammation, structural response to loading, joint circumference, joint laxity, patient-reported aetiology and patient expectation. Although there was conflicting evidence for an association of structural progression with BMI, including strong evidence for no association with hip OA, it was agreed that this should be included in the core data. Co-morbidity was not examined within any of the structural progression reviews, however, given the reported association of co-morbidity with THA and TKA outcomes and its association with symptom outcomes, it was agreed that this should be collected within the core items. Advice for hand OA was confounded by there being only a single systematic review that identified no strong associations with structural progression. On discussion it was agreed that hand surgery, hand dominance and menopausal age should be collected to inform future analyses.

Consensus group recommendation on symptom progression

It was agreed that all of the core items recommended for structural progression should be included in the core list for symptom progression. The following additional core items were proposed to be included in symptom progression studies to ensure demonstration of clinical relevance: mental health score, self-efficacy and depression or anxiety (Table 3). The difference between the severity of symptoms and symptom progression was noted. In longitudinal cohorts, symptoms have been found to remain stable over years in many patients with knee OA, although different patterns of symptoms have been described [36, 37]. Further consideration is therefore required to define symptom progression, for example, how to define a patient with worse pain and unchanged X-ray compared with a patient with X-ray progression and unchanged pain.

Advice on choice of tools for data collection

While these recommendations did not set out to recommend a set tool to capture each domain, to ensure consistency in data collection and thus improve the opportunity for data to be pooled, it is suggested that,
where possible, items are captured using validated tools and with reference to other clinical studies that might provide an opportunity for later data pooling. Within the scope of these recommendations, we have therefore provided guidance on potential tools that may be considered during study design, but this does not represent a definitive list. For capturing multisite joint pain, use of a joint pain manikin is suggested, since joint counts do not reflect the distribution of joints. At a minimum, such a manikin should capture the joint region (e.g. hand, foot, ankle), although at the discretion of the investigator further differentiation may be captured (e.g. ball of the foot, mid-foot, hindfoot). In line with current IMMPACT guidelines, an 11-point numerical rating scale with a 1-week recall period is suggested for capturing baseline pain [38]. Other validated questionnaires may also be considered for assessing pain and function, including but not limited to joint-specific scales such as the Knee Injury and Osteoarthritis Outcomes Score, Hip Injury and Osteoarthritis Outcomes Score, WOMAC, Oxford Knee/Hand Score, Australian/Canadian Osteoarthritis Hand Index and Functional Index for Hand Osteoarthritis [39–43]. It is recommended that alignment should be captured at a minimum using a measure of varus/valgus deformity, but where possible, consideration should be made for inclusion of either a weight-bearing long leg X-ray, which would indicate static alignment in the sagittal plane, or gait assessment, to indicate coronal and sagittal alignment (varus/valgus), weight-bearing long leg X-ray or gait assessment.

### Discussion

For researchers undertaking clinical studies, these recommendations provide an important resource to underpin study design. Furthermore, as new studies are developed in line with these recommendations, a valuable resource will be established to inform future post hoc analyses of data pooled from multiple studies. Such analyses may include examining predictors of disease progression to identify patients requiring treatment and predictors of the response to treatment, informing the subsetting of patients within which treatments may have improved efficacy.

The distinction between the recommendations described herein and the work by OMERACT to develop core outcome sets for rheumatologic conditions must be noted. The aim of the OMERACT process is to develop core sets that specify, for each condition, the areas/domains (and associated measurement instruments) necessary to provide the best estimate of benefits of an intervention within the context of a clinical trial or observational study [50]. In contrast, the aim of the current recommendations is to harmonize data collection in order to enable pooling of data (using domains derived from the existing literature, which were influenced by the OMERACT OA core set) for future meta-analyses to examine predictors of response to an intervention and to identify patient phenotypes for stratified therapy. As such, we recommend that these components should be collected at baseline as a minimum, to enable definition of patient subgroups in future analyses, with inclusion in additional study visits at the discretion of the investigators and considered with respect to study design and time, expense and applicability to the study in question.

The consensus meeting identified a current relative paucity of data to allow stratification of patients with OA into therapeutic groups, highlighting the need for these recommendations in order to provide a foundation to enable stratified OA treatment. Part of the problem lies in the lack of standardisation of the data collected in clinical trials, with resultant limited ability to pool data from different trials to identify predictors of progression or of response to treatment. The harmonization of data
collected as recommended herein will allow these issues to be addressed and enable the treatment of OA to move into the era of personalized medicine. The consensus process identified a number of core components for which there is already some evidence of association with the progression of OA, either at a structural or a symptomatic level. Collection of these components, at baseline as a minimum, provides the starting point for efforts to develop stratification algorithms for OA treatment.

While the current evidence has suggested a number of factors that are not associated with structural and/or symptomatic progression, this does not preclude their inclusion within a study. For example, while injury is known to be an important risk factor for the onset of OA, current evidence suggests that there is no relationship between knee injury and structural progression. However, analyses of association with progression are limited by the use of multiple mechanisms of assessment, and standardisation of individual tools or assessments used may reveal further elements associated with symptom or structural progression for inclusion. Furthermore, the assessment of association of injury with OA progression did not consider factors such as measurement of ongoing joint instability or accurate subanalysis of the type of injury, which may mediate the effect of any such association. Further measures that may be considered include patient-reported measures such as quality of life, serum and urine biomarkers and imaging biomarkers, including US and MRI. Although the latter were not examined within any of the reviews examined herein, with current efforts to develop disease-modifying OA drugs, including agents targeted at specific OA pathologies such as synovitis and bone marrow lesions, such data may prove highly valuable in determining patient phenotypes for individual therapies. Selection of additional components should remain at the discretion of the investigator and reflect appropriateness to the study in question as well as resource issues and patient burden. With inclusion of such components in studies, new evidence will enable further refinement of these recommendations and result in the addition of further domains to the core components.

There are a number of limitations to this work. The systematic literature review only included relevant systematic reviews and meta-analyses relating to the symptomatic and/or structural progression of OA and did not review primary papers or studies examining risk factors for the onset of OA. The dissemination plan was limited to presentation at national meetings and journal publication. The recommendations have not been piloted among users; however, there is a mechanism for updating the recommendations within the Clinical Studies Group framework. Finally, since we were unable to recommend a specific tool for each component, an element of variability will remain among studies designed according to these guidelines. Future work may seek to extend these recommendations with a robust review of the potential tools that may be used to assess each data component so as to improve uniformity further. We are aware of an ongoing EULAR project to detail the available psychometric properties of the commonly used OA outcome measures. Despite these limitations, we believe the work is strengthened by the breadth of stakeholders involved in the consensus process, and most importantly, inclusion of patient and public representation.

In summary, we recommend that in the design of new clinical studies, both interventional and observational, the data components to be captured should be carefully considered in light of these recommendations. Furthermore, care should be taken to include validated tools for all components, and where possible, to consider the design of similar studies that may provide the opportunity for future data pooling. Through considered, informed and unified study design we have the potential to provide a powerful substrate for future studies to underpin stratified treatment for OA. Such stratification of patients with OA may involve the use of clinical criteria, biomarkers or functional markers to target a treatment to a patient that is likely to progress with a phenotype that is driven by the pathway targeted by the treatment under investigation. Novel biomarkers may enable better application of a current treatment or the emergence of a new biomarker/treatment combination that would simultaneously develop a method of stratification and a new treatment. As new biomarkers become available, inclusion in the recommended core data will need to be considered.

**Acknowledgements**

The authors wish to thank Arthritis Research UK for convening the meeting as part of the Clinical Studies Group for Osteoarthritis and Crystal Diseases programme. The views of Arthritis Research UK have not influenced the content of this guideline.

**Arthritis Research UK Osteoarthritis and Crystal Disease Clinical Study Group working group:**

Prof Jo Adams, Faculty of Health Sciences, University of Southampton, UK; Dr Ian Appleyard, Department of Allied Health Services, London South Bank University, UK; Dr Fraser Birrell, Musculoskeletal Research Group, Newcastle University, UK; Mike Blank, Patient representative; Dr Michael J. Callaghan, Arthritis Research UK Epidemiology Unit, University of Manchester, UK; Jo Cumming, Arthritis Care, London, UK; Dr Graham J. Chapman, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK & Leeds National Institute for Health Research (NIHR) Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK; Dr Jill Halstead, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, UK & Leeds NIHR Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals Trust, Leeds, UK; Dr David F. Hamilton, School of Clinical Sciences, University of Edinburgh, UK; Prof Michael Hurley, School of Rehabilitation Sciences, Kingston University, London, UK; Dr Kathryn Martin, School of Medicine and Dentistry, University of Aberdeen, UK; Dr Deborah J. Mason, Cardiff School of Biosciences, Cardiff University, UK; Prof George Nuki, School of Molecular, Genetic and Population Health...
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Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: N.K.A. has received honoraria, held advisory board positions (which involved receipt of fees) and received consortium research grants from Merck (honorarium); Roche, Novartis and Bioiberica (grants); Smith & Nephew, Flexion Bioventus and Freshfields (personal fees) outside the submitted work. All other authors have declared no conflicts of interest.

Supplementary data
Supplementary data are available at Rheumatology Online.

References
1 Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014;10:437–41.
2 National Clinical Guideline Centre. Osteoarthritis. Care and management in adults. NICE Clinical Guideline 177. London, UK: National Institute for Health and Care Excellence. February 2014. http://www.nice.org.uk/guid ance/CG177.
3 Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: a systematic review of prognostic studies. Arthritis Care Res 2013;65:1115–25.
4 Belo JN, Berger MY, Reijman M, Koes BW, Bierma-Zeinstra SM. Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies. Arthritis Rheum 2007;57:13–26.
5 Bosomworth NJ. Exercise and knee osteoarthritis: benefit or hazard? Can Fam Physician 2009;55:871–8.
6 Tanamas S, Hanna FS, Cicuttini FM et al. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis Rheum 2009;61:459–67.
7 Saberi HF, Runhaar J, van Meurs JB, Bierma-Zeinstra SM. Biomarkers for osteoarthritis: can they be used for risk assessment? A systematic review. Maturitas 2015;82:36–49.
8 Ajued A, Wong F, Smith C et al. Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med 2014;42:2242–52.
9 Henriksen M, Creaby MW, Lund H, Juhl C, Christensen R. Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials. BMJ Open 2014;4:e005368.
10 Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SM. What are the prognostic factors for radiographic progression of knee osteoarthritis? a meta-analysis. Clin Orthop Relat Res 2015;473:2969–89.
11 Wright AA, Cook C, Abbott JH. Variables associated with the progression of hip osteoarthritis: a systematic review. Arthritis Rheum 2009;61:925–36.
12 Lievensen AM, Bierma-Zeinstra SM, Verhagen AP, Verhaar JA, Koes BW. Prognostic factors of progression of hip osteoarthritis: a systematic review. Arthritis Rheum 2002;47:556–62.
13 Kwok WY, Plevier JW, Rosendaal FR, Huizinga TW, Kloppenburg M. Risk factors for progression in hand osteoarthritis: a systematic review. Arthritis Care Res 2013;65:552–62.
14 Pearce F, Hui M, Ding C, Doherty M, Zhang W. Does smoking reduce the progression of osteoarthritis? Meta-analysis of observational studies. Arthritis Care Res 2013:65:1026–33.
15 Tanamas SK, Wijethilake P, Wluka AE et al. Sex hormones and structural changes in osteoarthritis: a systematic review. Maturitas 2011;69:141–56.
16 Marks R. Self-efficacy and its application in the treatment of knee osteoarthritis: a critical review. Rheumatol Rep 2012;4:34–45.
17 van Dijk GM, Dekker J, Veenhof C, van den Ende CH, Carpa Study G. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006;55:779–85.
18 Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. Arthritis Res Ther 2015;17:152.
19 Nicholls EE, van der Windt DA, Jordan JL, Dziedzic KS, Thomas E. Factors associated with the severity and progression of self-reported hand pain and functional difficulty in community-dwelling older adults: a systematic review. Musculoskeletal Care 2012;10:51–62.
20 Benyon K, Hill S, Zadurian N, Mallen C. Coping strategies and self-efficacy as predictors of outcome in osteoarthri- tis: a systematic review. Musculoskeletal Care 2010;8:224–36.
21 Loke YK, Hinz IW X, Rowlands G, Scott D, Salter C. Impact of health literacy in patients with chronic...
musculoskeletal disease—systematic review. PLoS One 2012;7:e40210.

22 Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007;29:147–55.

23 Hirsch G, Kitas G, Klocke R. Intra-articular corticosteroid injection in osteoarthritis of the knee and hip: factors predicting pain relief—a systematic review. Semin Arthritis Rheum 2013;42:451–73.

24 Maricar N, Callaghan MJ, Felson DT, O’Neill TW. Predictors of response to intra-articular steroid injections in knee osteoarthritis—a systematic review. Rheumatology 2013;52:1022–32.

25 Vissers MM, Bussmann JB, Verhaar JA et al. Psychological factors affecting the outcome of total hip and knee arthroplasty: a systematic review. Semin Arthritis Rheum 2012;41:576–88.

26 O’Connor MI. Implant survival, knee function, and pain relief after TKA: are there differences between men and women? Clinic Orthop Relat Res 2011;469:1846–51.

27 Singh JA, Kundukulam J, Riddle DL, Strand V, Tugwell P. Early postoperative mortality following joint arthroplasty: a systematic review. J Rheumatol 2011;38:1507–13.

28 Hoogeboom TJ, van den Ende CH, van der Sluis G et al. The impact of waiting for total joint replacement on pain and functional status: a systematic review. Osteoarthritis Cartilage 2009;17:1420–7.

29 Santaguida PL, Hawker GA, Hudak PL et al. Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. Can J Surg 2008;51:428–36.

30 Ethgen O, Bruyere O, Richy F, Dardenne C, Reginster JY. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. J Bone Joint Surg Am 2004;86A:963–74.

31 Markow MJ, Secor ER. Acupuncture for the pain management of osteoarthritis of the knee. Techniques Orthopaedics 2003;18:33–6.

32 Magklara E, Burton CR, Morisson V. Does self-efficacy influence recovery and well-being in osteoarthritis patients undergoing joint replacement? A systematic review. Clin Rehabil 2014;28:835–46.

33 Si HB, Zeng Y, Shen B et al. The influence of body mass index on the outcomes of primary total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2015;23:1824–32.

34 Haverkamp D, Klinkenbijl MN, Somford MP, Albers GH, van der Vis HM. Obesity in total hip arthroplasty—does it really matter? A meta-analysis. Acta Orthop 2011;82:417–22.

35 Montin L, Leino-Kilpi H, Suominen T, Lepisto J. A systematic review of empirical studies between 1966 and 2005 of patient outcomes of total hip arthroplasty and related factors. J Clin Nurs 2008;17:40–5.

36 Wesseling J, Bastick AN, Ten Wolde S et al. Identifying trajectories of pain severity in early symptomatic knee osteoarthritis: a 5-year followup of the Cohort Hip and Cohort Knee (CHECK) Study. J Rheumatol 2015;42:1470–7.

37 Nicholls E, Thomas E, van der Windt DA, Croft PR, Peat G. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: findings from the Knee Clinical Assessment Study and the Osteoarthritis Initiative. Osteoarthritis Cartilage 2014;22:2041–50.

38 Dworkin RH, Turk DC, Farrar JT et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19.

39 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.

40 Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) – validation and comparison to the WOMAC in total knee replacement. Health Qual Life Outcomes 2003;1:17.

41 Nilsdotter AK, Lohmander LS, Klassbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS)—validity and responsiveness in total hip replacement. BMC Musculoskelet Disord 2003;4:10.

42 Moe RH, Garratt A, Slatkowsky-Christensen B et al. Concurrent evaluation of data quality, reliability and validity of the Australian/Canadian Osteoarthritis Hand Index and the Functional Index for Hand Osteoarthritis. Rheumatology 2010;49:2327–36.

43 Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. J Bone Joint Surg Br 1998;80:83–9.

44 Hunt MA, Birmingham TB, Jenkyn TR, Giffin JR, Jones IC. Measures of frontal plane lower limb alignment obtained from static radiographs and dynamic gait analysis. Gait Posture 2008;27:635–40.

45 Buckland-Wright C. Which radiographic techniques should we use for research and clinical practice? Best Pract Res Clin Rheumatol 2006;20:39–55.

46 Helli Lo Graverand MP, Clemmer RS, Brunell RM et al. Considerations when designing a disease-modifying osteoarthritis drug (DMOAD) trial using radiography. Semin Arthritis Rheum 2013;43:1–8.

47 Dobson F, Hinnan RS, Roos EM et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. Osteoarthritis Cartilage 2013;21:1042–52.

48 Briggs KK, Kocher MS, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the Lysholm knee score and Tegner activity scale for patients with meniscal injury of the knee. J Bone Joint Surg Am 2006;88:698–705.

49 Martin KA, Rejeski WJ, Miller ME et al. Validation of the PASE in older adults with knee pain and physical disability. Med Sci Sports Exerc 1999;31:627–33.

50 Kirwan JR, Boers M, Hewlett S et al. Updating the OMERACT filter: core areas as a basis for defining core outcome sets. J Rheumatol 2014;41:994–9.