Defining Flare in Osteoarthritis of the Hip and Knee: A Systematic Literature Review — OMERACT Virtual Special Interest Group

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ABSTRACT. ***Objective.*** Beyond the exacerbation of pain in describing a flare in osteoarthritis (OA), patients and health professionals add other elements that deserve to be fully elucidated, such as effusion, swelling, and mobility limitation. To define and conceptualize the construct *flare* in OA, the objective was to identify the key variables, or symptoms, that worsen, and to clarify how these variables are described in the literature by patients and clinicians.

Methods. A systematic review of the literature was conducted in Medline and PsychINFO. In brief, the search terms used were "osteoarthritis," "knee," "hip," and "flare." Specific characteristics of included studies were identified, including the type of study design, type of flare assessed, how the flare developed, and what definition of flare was used, including whether the definition was based on qualitative or quantitative analysis.

Results. Pain was the major factor in the definition of flare within these studies. Four components of flare were identified: pain, other factors, composite criteria, and global assessment. While the majority of studies reported flare as an increase in pain using standardized outcome measures, only 1 study reported the antecedents and consequences of a pain flare using qualitative methods.

Conclusion. The use of flare as an outcome or inclusion criterion in rheumatology trials is a common occurrence; however, this review highlights the wide variation in the definitions of OA flare currently in use and the emphasis on the measurement of pain. This variation in definition does not allow for direct comparison between trials and limits interpretation of evidence. (J Rheumatol First Release July 1 2017; doi:10.3899/jrheum.161107)

Key Indexing Terms:
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To develop an evidence-based tool to measure "flare" in osteoarthritis (FLARE-OA), an Outcome Measures in Rheumatology (OMERACT) Working Group has been established and has held virtual Special Interest Group sessions. This is the first report from this group and we aim to use this information to develop interviews with those involved and the implementation of Delphi questionnaires.

With the development of clinical trials targeting hip and knee OA and short- and longterm treatment of symptoms, there is a need for a tool to identify the occurrence of flare in lower limb OA. Such treatments are currently under development, including slow acting or disease-modifying drugs, and will likely bring important changes in patient management. The development of a FLARE-OA tool is essential to identify the occurrence of flare. Indeed, 2 treatments may provide similar improvements over the longterm, but 1 may prevent more flare than the other in between the 2 assessments, therefore improving the patient's quality of life.

A definition of the construct of flare for OA is needed. The

term *flare* is used in most Westernized countries, including in French (*poussée*) and in English. Flares tend to be episodic, with a duration ranging from minutes to hours to days. The characteristic feature is that it requires a change in treatment or behavior. Beyond the exacerbation of pain, however, patients and health professionals add other elements that deserve to be fully elucidated, such as effusion, swelling, and mobility limitation.

Although frequently used in general and in patient descriptions, the term *flare* has not been largely used in the scientific OA literature. Some authors combine several criteria to define or rule out a flare, for example, sudden aggravation of knee pain causing nocturnal awakenings with clinical evidence of knee effusion[1]. A diagnosis score has been developed for knee OA flare based on a combination of morning stiffness, pain causing nocturnal awakenings, knee effusion, limping, joint swelling, and increased warmth over the knee[2]. This first interesting attempt, however, did not integrate the patient's perspective.

Many clinical trials in OA have used a flare design in which the flare is provoked by the temporary interruption of regular medication, resulting in patients with active and painful disease at baseline. Most clinical trials in OA use outcomes centered on exacerbation of pain and consequences regarding discomfort, activity limitation, and less frequently, participation restriction, as outlined in the International Classification of Functioning, Disability and Health framework[3]. Investigation of the definition of flare used would help document practices, and later serve to develop the FLARE-OA tool.

A definition of flare in rheumatoid arthritis (RA) has been developed by an OMERACT Working Group as "any worsening of disease activity that would, if persistent, in most cases lead to initiation of change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy"[4]. The signs and symptoms in RA are different in many aspects, but there may be some similarities that could inform the definition in OA. To define and conceptualize the construct "flare" in OA, our aim was to identify the key variables or symptoms that worsen, and to clarify how these variables are described in the literature by both patients and clinicians.

This is, to our knowledge, the first attempt to examine the variation in definition of OA flare used in research studies and clinical trials. Comparison of outcomes is made difficult by this variability in definition. Our aim was to use the results of this review, in conjunction with patient involvement, to guide the development of a tool to measure flare in OA.

MATERIALS AND METHODS

A systematic review of the literature, following PRISMA guidelines (prisma-statement.org/documents/PRISMA%202009%20checklist.pdf), was conducted in Medline and PsychINFO during March 2017, without restriction on language or date of publication. A review protocol for our study has not been presented. Publications up until March 4, 2017, were eligible for inclusions. In brief, the search terms were "osteoarthritis," "knee," "hip," and "flare," with the full search shown in Table 1.

Studies were included in which participants had confirmed OA and if a specific definition of OA flare was reported, either in qualitative or quantitative methods. Screening of records was undertaken by 3 authors (MM, LD, FG) reviewing titles, abstracts, and full-text articles where necessary. Articles were then double-extracted independently by 2 authors (LD, MC). Consensus on final inclusion of articles was assessed, with a third reviewer (FG) available to resolve outstanding disagreements. Assessment of risk of bias within articles was not addressed because the definition of OA flare used within the study was the outcome of interest.

Specific characteristics of included studies were identified, including type of study design; type of flare such as flare as part of the study design, flare as an inclusion criterion, or flare as an outcome; how the flare developed; and the definition of flare used (based on qualitative or quantitative analysis).

Extracted data from each article allowed the description of the characteristics of the definition of the term *flare* in OA. Because our analysis was a review of published literature, ethics approval was not required, in accordance with the policy of the relevant institutions in France and Australia.

RESULTS

Results of the search are outlined in the study flowchart (Figure 1). Of the 1022 publications identified, 33 were included in the final review process.

Consensus discussions resulted in 23 articles considered for final inclusion. Initially, concordance was 79% good agreement, 15% intermediate, and 6% mismatched for study inclusion and definition used. Following discussion and involvement of the third reviewer, consensus was reached regarding definition of flare in included studies. Of the included studies, 15 were clinical trials including a metaanalysis; 3 were the development and validation of a diagnostic tool; and

Table 1. Search terms for Medline and no. results found.

Search Terms	Records Found
knee[MeSH Terms] OR knee[Title/Abstract] OR knees [Title/Abstract] OR hip[MeSH Terms] OR hip [Title/Abstract] OR hips[Title/Abstract]	231,642
osteoarthritis[MeSH Terms] OR arthrosis[MeSH Terms] OR osteoarthritis[Title/Abstract] OR osteoarthritides [Title/Abstract] OR arthrosis[Title/Abstract] OR "Degenerative joint disease"[Title/Abstract] OR "degenerative arthritis"[Title/Abstract]	320,969
1 AND 2	64,581
flare[Title/Abstract] OR flares[Title/Abstract] OR exacerbation[Title/Abstract] OR "osteoarthritis pain" [Title/Abstract] OR "tender joint"[Title/Abstract] OR "swollen joint"[Title/Abstract] OR "morning stiffness" [Title/Abstract] OR "nocturnal awakenings"[Title/Abstract] OR "inflammatory status"[Title/Abstract] OR "knee effusion"[Title/Abstract] OR "acute inflammation" [Title/Abstract]	52,135
3 AND 4	974
5 NOT ("arthritis, rheumatoid"[MeSH Terms] OR "rheumatoid arthritis"[Title/Abstract] OR "spondylitis, ankylosing"[MeSH Terms] OR "ankylosing spondylitis" [Title/Abstract])	730

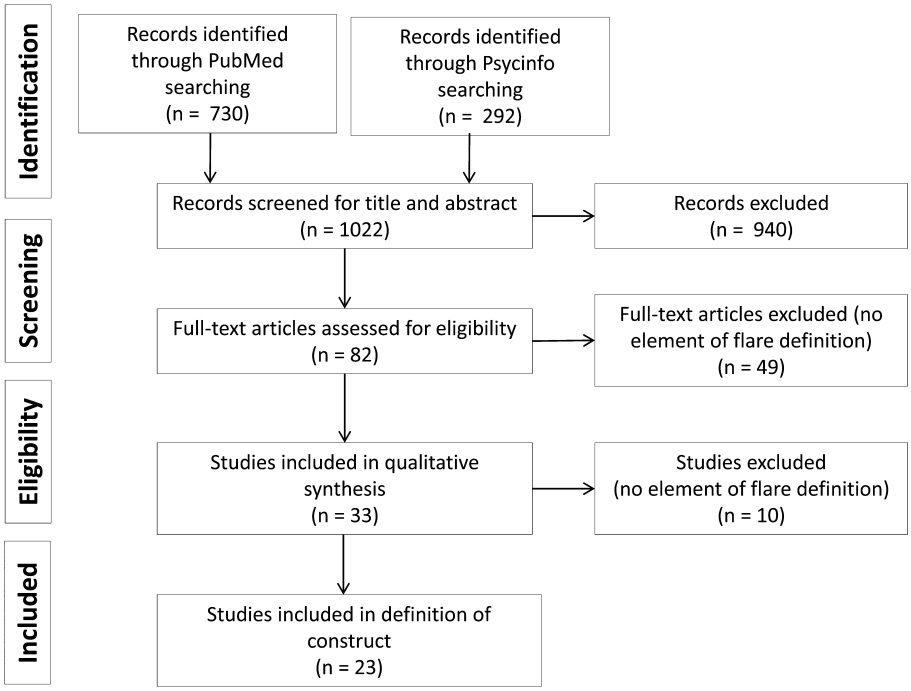

Figure 1. Results of literature search.

5 were prognostic studies including a literature review. Twelve studies were of flare design, 2 were of flare inclusion, and 8 of flare outcome. One study included both a flare inclusion and outcome (Table 2)[2,5–14,15–22,24,25,26,27].

While the majority reported flare as an increase in pain on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS), or global assessment, only 1 study reported the antecedents and consequences of pain flare, using qualitative methods, including the timing of the increase in pain, such as whether it was sudden or of short duration[5] (Table 2).

From the assessment of these publications, 4 components of the definition of flare have been identified:

1. Flare as a concept of pain (pain criteria): 19 items included at least 1 assessment of pain. Eleven reported increasing pain, 9 the need for minimal pain on VAS, and 3 increasing of pain on movement. Other items analyzed in qualitative analysis included timing, awakening at night, sudden increase in pain, increased pain on weight bearing, sharpness, intense pain, and short duration.

2. Flare as factors other than pain (other factors): 2 articles described joint effusion or swelling and 1 mentioned warmth. Other items analyzed the concept of prolonged morning stiffness, sensitivity/tenderness, limp, and resorting to medication.

3. Flare as composite factors (composite criteria): 10 articles described a change in the WOMAC score, others spoke of worsening disease status and deteriorating functional status. Qualitative analysis in 1 article investigated antecedents, such as increased activity or sitting for long periods and consequences of actions, such as using additional pain medication or resting until pain decreases.

4. Flare as a global evaluation (global assessment): 7 articles described a worsening of the overall assessment of the patient and 4 a worsening on the physician's global assessment.

DISCUSSION

The use of flare as an outcome or inclusion criterion in rheumatology trials is common; however, our review highlights the wide variation in definition of OA flare currently in use and the emphasis on the measurement of pain. This variation does not allow for direct comparison between trials and limits interpretation of evidence. Having a standardized methodology for the assessment of flare would facilitate comparison, underpinning the need for development of a new tool for this purpose.

To date, there is no universally accepted, validated method for defining a flare in OA. The prior literature in this context has largely defined a flare using unidimensional constructs such as pain. While this might be an important component of flare, the specific characteristics of flare need to be devolved, both from the perspective of consumers and healthcare professionals. Much of the extant literature relies on 1 group and has not been developed in a systematic or methodologically sophisticated manner. Moreover, the concept of flare is likely to be more complex than a single unidimensional feature such as pain. The majority of studies found in our

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Table 2. Studies included in the analysis by type of study.

Study	Type of Study	Type of Flare Use: Design/inclusion/outcome	Flare Definition	Category of Flare Definition	Participant Criteria
Marty, *et al*[2]	Development and assessment of a diagnostic method	Outcome	Score ≥ 7 determined by presence of morning stiffness longer than 20 min (score = 1), nocturnal awakenings (= 2), effusion (= 2), limp (= 3), swelling (= 3), warmth (= 3; total = 14)	Quantitative	Referred by general practitioner and rheumatologist. Met clinical and radiological criteria for knee OA according to ACR criteria. Either had stable disease or were experiencing a flare-up according to the physician's assessment.
Murphy, *et al*[5]	Development and assessment of a diagnostic method	Outcome	INDIVIDUAL definition of "what pain flare means to you;" during the 7-day period; defined in terms of pain quality (e.g., sharp, increase in pain, intense), timing (e.g., sudden onset, short duration, or variable), and antecedents and consequences (specific activities, e.g., stairs, walking, sitting too long; resort to medication). INVESTIGATOR definition: inadequate pain relief for an episode of intense pain that is usually brought on by too much activity	Qualitative	Community-living adults > 50 yrs of age recruited from pain clinic; knee OA (ACR criteria)
Esen, *et al*[6]	Development and assessment of a diagnostic method	Outcome	Pain on a single knee for last 72 h with VAS > 30 mm; also uses WOMAC, but no definition of what level of pain, etc. constitutes flare	Quantitative	Pain on a single knee (for the last 72 h VAS > 30 mm); ACR criteria; ≥ 40 yrs of age; KL grade ≥ 2
Wise, *et al*[7]	Longitudinal, observational cohort	Inclusion/outcome	Interview: subject reported WOMAC score in the highest 30% of all WOMAC scores: yes or no	Qualitative	Age ≥ 50 years; males and females; physician-diagnosed hip and/or knee OA; pain in hip or knee on at least 15 out of the last 30 days at baseline; had at least 1 case period (flare) and at least 1 control period
Chapple, *et al*[8]	Observational/ review	Outcome	Progression of disease: deterioration in functional status or pain on WOMAC or VAS, or radiographic change as increase in KL grade or joint space narrowing score, increase in osteophytes, or decrease in joint space width	Quantitative	Adults aged over 18 years; males and females; any duration of symptoms; knee OA classified by clinical or radiographic reference standards
Makovey, *et al*[9], Zobel, *et al*[10], Ferriera, *et al*[11]	Observational	Outcome	Disabling increase in knee symptoms lasting longer than 8 h without settling. Increase in knee pain severity of 2 points from baseline on a NRS (0–10)	Quantitative	Aged ≥ 40 years; have active e-mail address and access to Internet; experience pain that fluctuates in intensity in at least 1 knee on most days in the past month; radiographic evidence of knee OA
Weaver, *et al*[12]	Subcategory of RCT	Inclusion	Pain, PtGA, and PGA. Defined as worsening of knee pain on motion or knee pain on weight-bearing and worsening of both the patient's and PGA to at least a score of 2, with a ≥ 1 grade worsening from screening	Quantitative	Adults, > 100 lbs with history of OA knee for at least 6 mos and radiographic evidence of OA
Zhao, *et al*[13]	Clinical trial	Design	Worsening of signs and symptoms of the disease after discontinuation of NSAID or other analgesics for 2- to 7-day washout period. Uncertain how measured	Quantitative	Men and women outpatients; ≥ 18 yrs; symptomatic OA; met ACR criteria for primary OA knee ≥ 3 mos, functional class I, II or III
Yocum, *et al*[14]	Clinical trial	Design	Worsening of disease activity from initial screening that included at least 1 grade deterioration in PGA of disease, increase of at least 100 mm on VAS for PtGA of disease activity, increase greater than 35 mm on patient overall assessment of pain	Quantitative	Current NSAID user; ≥ 40 yrs of age; at least 3-mos history of OA knee confirmed radiographically and by signs and symptoms; pain on movement in target joint; experienced flare after ceasing NSAID for 3 days from baseline visit

Table 2. Continued.

Study	Type of Study	Type of Flare Use: Design/inclusion/outcome	Flare Definition	Category of Flare Definition	Participant Criteria
Theiler, *et al*[15]	Clinical trial	Design	No definition of flare	—	Males and females ≥ 50 yrs, painful OA of the knee or hip according to ACR criteria; intake of NSAID for at least 5 days prior to study entry; pain intensity of 40 mm or more on the VAS in the previous 48 h when walking on a flat surface; be reluctant to continue on previous NSAID and be willing to change drug treatment; at least grade II to IV on the KL scale on a radiograph taken within the previous 12 mos
Cibere, *et al*[16]	Clinical trial	Design	Either the patient's perception of worsening of symptoms with a concomitant increase by at least 20 mm in WOMAC pain on walking (clinically important change), or a significant worsening in the PGA by at least 1 grade (1–5 scale)	Quantitative	(1) OA knee, met ACR criteria, (2) KL grade ≥ 2; (3) current daily use of glucosamine for at least 1 mo, (4) at least moderate improvement in knee pain since starting on glucosamine, measured on a 6-point scale of knee pain
Baer, *et al*[17]	Clinical trial	Design	Between screening visit (when therapy withdrawn) and baseline: an increase in total WOMAC pain subscale score of at least 2 and at least 25%, with a baseline total WOMAC pain score of at least 6 (out of a possible 20), and a score of ≥ 2 (out of a possible 4) on at least 1 of the 5 items in the WOMAC pain subscale	Quantitative	Men and women, age 40–85 yrs, radiologically confirmed primary OA knee and a flare of pain at baseline following discontinuation of prior therapy
Rother, *et al*[18]	Clinical trial	Design	(1) Pain in the index knee on walking > 40 mm on VAS, (2) increased by > 15 mm compared with pain on prestudy treatment (screening), and (3) PtGA score for OA of 3–5 and at least 1 grade increase from screening	Quantitative	Minimum 6-mos history of knee OA; met 2 of the following: (1) morning stiffness ≥ 30-min, crepitus on motion and age > 40 yrs; (2) rate knee pain > 3 on a 5-point Likert scale; and (3) taking oral NSAID at least 3 days/week for the past 3 mos or for 25 of the past 30 days
Boswell, *et al*[19]	Clinical trial	Design	A worsening in WOMAC pain Q1 from screening of ≥ 15 mm, and have ≥ 1 point worsening between screening and baseline for the PtGA of arthritis condition	Quantitative	Men and women ≥ 40 yrs of age; symptomatic primary knee OA ≥ 3 mos; met ACR criteria for OA knee; recent (≤ 12 mos) radiographic evidence of tibiofemoral OA (grade 2 or 3 on the KL scale); ARA functional class rating of I, II, or III
Hochberg, *et al*[20]	Clinical trial	Design	WOMAC pain score of ≥ 40 mm at baseline, mean change in WOMAC pain score from screening to baseline of ≥ 15 mm, worsening of PtGA by ≥ 1 point	Quantitative	≥ 50 years of age, 6-mos history of symptomatic, clinically diagnosed OA knee (meeting ACR criteria); ACR functional class rating of I, II, or III, receiving a stable dose of NSAID, COX-2–selective inhibitors, or other oral analgesic therapy for 6 weeks. Agreed to maintain physical activity at a stable level throughout the study
Essex, *et al*[21]	Clinical trial	Design	A flare was demonstrated if the physician's and PtGA of arthritis were both "fair," "poor," or "very poor" at the baseline visit, and if the baseline patient's assessment of arthritis pain VAS measurement was between 40–90 mm (on 100 mm scale; 0 = no pain and 100 = very severe pain), the PtGA of arthritis showed an increase of 1 or more grades and the PGA of arthritis showed an increase of 1 or more grades	Quantitative	African American patients aged ≥ 45 yrs, with OA of the knee (according to ACR criteria) in a flare state, and with a physician-classified functional capacity of I–III

Table 2. Continued.

Study	Type of Study	Type of Flare Use: Design/inclusion/outcome	Flare Definition	Category of Flare Definition	Participant Criteria
Sands, *et al*[22]	Clinical trial	Design	From original paper (Strand, *et al*[23]): reported a score ≥ 4 but < 9 on the pain NRS and an increase ≥ 1 grade on the PtGA of arthritis to "fair, poor, or very poor" between screening (visit 1) and flare (visit 2), and a score of "fair, poor, or very poor" on the PGA of arthritis at visit 2	Quantitative	Aged 18–80 yrs with knee or hip OA, determined by ACR criteria
Gibofsky, *et al*[24]	Clinical trial	Design	> 15 mm increase in WOMAC pain subscale score (on VAS) from screening to baseline	Quantitative	Men and women, clinically and radiographically confirmed hip and/or knee OA (KL grade II–III); ≥ 40 yrs of age, body weight ≥ 45 kg and a BMI < 40 kg/m^2
Liu, *et al*[25]	Clinical trial	Inclusion	ICOAP intermittent pain scale score > 0 + reporting unacceptable symptom state	Quantitative	Existing community cohort ≥ 45 yrs with hip or knee OA
Bartholdy, *et al*[26]	Exercise arm of clinical trial	Outcome	Knee pain above 5 on 0–10 NRS	Quantitative	Aged 40 yrs+, clinical diagnosis of knee OA confirmed by radiography, and BMI between 20 and 35 kg/m^2
Altman, *et al*[27]	Clinical trial	Design	≥ 15 mm increase in WOMAC Pain score after discontinuation of NSAID/acetaminophen	Quantitative	≥ 40 yrs of age; confirmed hip or knee OA; (KL grade II–III); chronic users of NSAID and/or acetaminophen; WOMAC pain score ≥ 40 mm

OA: osteoarthritis; ACR: American College of Rheumatology; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KL: Kellgren-Lawrence arthritis grading scale; NRS: numerical rating scale; PtGA: patient's global assessment; PGA: physician's global assessment; NSAID: nonsteroidal antiinflammatory drug; BMI: body mass index; ICOAP: Intermittent and Constant Osteoarthritis Pain score; ARA: American Rheumatism Association; COX-2: cyclooxygenase-2.

review used existing standardized measures to identify flare. While these cover aspects other than pain, such as WOMAC function or global assessment, the emphasis on pain remains with many using only the WOMAC Pain scale, varying also between the use of VAS or Likert scales and whether only baseline or change scores are assessed. In addition, describing flare in terms of effusion and warmth may be problematic because these factors may have limited reproducibility.

The OMERACT process highlights the importance of obtaining the patient's perspective in the development of outcome measures and clinical practice[28]. What constitutes a flare to health professionals may not be the same to patients. While pain is the most commonly reported feature of flare, other aspects may be important to patients, such as fatigue or activity restriction, and these factors are not currently included in definitions of OA flare. In addition, duration of the flare may vary from patient to patient. Some studies of flare include patients with pain symptoms lasting longer than 8 h[9] or for the previous 72 h[5]. Measuring only pain as specified by the study design may miss these important aspects, so the inclusion of patients' definitions of flare may offer a broader picture of its effect.

An OMERACT group has undertaken a similar project in defining flare in RA to develop an evidence-based, consensus-driven standard definition that incorporates the patient's perspective[4], and a similar methodology has been used in France by the Strategy of Treatment in Patients with Rheumatoid Arthritis group for flare in RA[29]. The involvement of patients in the process of developing a standard definition of RA flare includes constitutional, physical, functional, psychological, and time-oriented elements.

The recent focus on chronic care programs and self-management strategies for OA heightens the need for a patient-reported outcome measure of OA flare. There is a need for an instrument that identifies comprehensive aspects of flare in OA that does not only summarize exacerbation of pain, but also encompasses other functional aspects described by patients. The ultimate aim of the FLARE-OA group is to develop a tool for the use in clinical trials and observational studies to identify the occurrence of flare in hip and knee OA.

REFERENCES

1. Conrozier T, Mathieu P, Vignon E, Piperno M, Rinaudo M. Differences in the osteoarthritic synovial fluid composition and rheology between patients with or without flare: a pilot study. Clin Exp Rheumatol 2012;30:729-34.
2. Marty M, Hilliquin P, Rozenberg S, Valat JP, Vignon E, Coste P, et al. Validation of the KOFUS (Knee Osteoarthritis Flare-Ups Score). Joint Bone Spine 2009;76:268-72.
3. World Health Organization. International classification of functioning and health. WHO: Geneva; 2001.
4. Bingham CO 3rd, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, et al. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol 2009;36:2335-41.
5. Murphy SL, Lyden AK, Kratz AL, Fritz H, Williams DA, Clauw DJ, et al. Characterizing pain flares from the perspective of individuals with symptomatic knee osteoarthritis. Arthritis Care Res 2015;67:1103–11.
6. Eşen S, Akarırmak U, Aydın FY, Unalan H. Clinical evaluation during the acute exacerbation of knee osteoarthritis: the impact of diagnostic ultrasonography. Rheumatol Int 2013;33:711–7.
7. Wise BL, Niu J, Zhang Y, Wang N, Jordan JM, Choy E, et al. Psychological factors and their relation to osteoarthritis pain. Osteoarthritis Cartilage 2010;18:883-7.
8. 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 2011;63:1115–25.
9. Makovey J, Metcalf B, Zhang Y, Chen JS, Bennell K, March L, et al. Web-based study of risk factors for pain exacerbation in osteoarthritis of the knee (SPARK-Web): Design and rationale. JMIR Res Protoc 2015;4:e80.
10. Zobel I, Erfani T, Bennell KL, Makovey J, Metcalf B, Chen JS, et al. Relationship of buckling and knee injury to pain exacerbation in knee osteoarthritis: a web-based case-crossover study. Interact J Med Res 2016;5:e17.
11. Ferreira ML, Zhang Y, Metcalf B, Makovey J, Bennell KL, March L, et al. The influence of weather on the risk of pain exacerbation in patients with knee osteoarthritis - a case-crossover study. Osteoarthritis Cartilage 2016;24:2042-7.
12. Weaver A, Rubin B, Caldwell J, McMahon FG, Lee D, Makarowski W, et al. Comparison of the efficacy and safety of oxaprozin and nabumetone in the treatment of patients with osteoarthritis of the knee. Clin Ther 1995;17:735-45.
13. Zhao SZ, McMillen JI, Markenson JA, Dedhiya SD, Zhao WW, Osterhaus JT, et al. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. Pharmacotherapy 1999;19:1269–78.
14. Yocum D, Fleischmann R, Dalgin P, Caldwell J, Hall D, Roszko P. Safety and efficacy of meloxicam in the treatment of osteoarthritis: a 12-week, double-blind, multiple-dose, placebo-controlled trial. The Meloxicam Osteoarthritis Investigators. Arch Intern Med 2000;160:2947-54.
15. Theiler R, Bischoff HA, Good M, Uebelhart D. Rofecoxib improves quality of life in patients with hip or knee osteoarthritis. Swiss Med Wkly 2002;132:566-73.
16. Cibere J, Kopec JA, Thorne A, Singer J, Canvin J, Robinson DB, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Care Res 2004;51:738–45.
17. Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomised controlled, 6-week trial [ISRCTN53366886]. BMC Musculoskelet Disord 2005;6:44.
18. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. Ann Rheum Dis 2007;66:1178–83.
19. Boswell DJ, Ostergaard K, Philipson RS, Hodge RA, Blum D, Brown JC, et al. Evaluation of GW406381 for treatment of osteoarthritis of the knee: two randomized, controlled studies. Medscape J Med 2008;10:259.
20. Hochberg MC, Fort JG, Svensson O, Hwang C, Sostek M. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials. Curr Med Res Opin 2011;27:1243-53.
21. Essex MN, O'Connell M, Bhadra Brown P. Response to

nonsteroidal anti-inflammatory drugs in African Americans with osteoarthritis of the knee. J Int Med Res 2012;40:2251-66.
22. Sands GH, Brown PB, Essex MN. The efficacy of continuous versus intermittent celecoxib treatment in osteoarthritis patients with body mass index ≥30 and <30 kg/m(2.). Open Rheumatol J 2013;7:32-7.
23. Strand V, Simon LS, Dougados M, Sands GH, Bhadra P, Breazna A, et al. Treatment of osteoarthritis with continuous versus intermittent celecoxib. J Rheumatol 2011;38:2625-34.
24. Gibofsky A, Hochberg MC, Jaros MJ, Young CL. Efficacy and safety of low-dose submicron diclofenac for the treatment of osteoarthritis pain: a 12 week, phase 3 study. Curr Med Res Opin 2014;30:1883-93.
25. Liu A, Kendzerska T, Stanaitis I, Hawker G. The relationship between knee pain characteristics and symptom state acceptability in people with knee osteoarthritis. Osteoarthritis Cartilage 2014;22:178-83.
26. Bartholdy C, Klokker L, Bandak E, Bliddal H, Henriksen M. A standardized "rescue" exercise program for symptomatic flare-up of knee osteoarthritis: Description and safety considerations. J Orthop Sports Phys Ther 2016;46:942-6.
27. Altman R, Hochberg M, Gibofsky A, Jaros M, Young C. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. Curr Med Res Opin 2015;31:2331-43.
28. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
29. Berthelot JM, De Bandt M, Morel J, Benatig F, Constantin A, Gaudin P, et al; STPR group of French Society of Rheumatology. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE' instrument. Ann Rheum Dis 2012;71:1110-6.