Developing a Preliminary Definition and Domains of Flare in Knee and Hip Osteoarthritis (OA): Consensus Building of the Flare-in-OA OMERACT Group

Francis Guillemin, Camille Ricatte, Annica Barcenilla-Wong, Amandine Schoumacker, Marita Cross, Camille Alleyrat, Thomas Buttel, Michel Cembalo, Hakima Manseur, Hema Urban, Bruno Fautrel, Philip G. Conaghan, Gillian Hawker, Claudia Rutherford, Lyn March, Elisabeth Spitz, and David J. Hunter

ABSTRACT. Flare in knee and hip osteoarthritis (OA) is more than just an exacerbation of pain. Unstructured, semistructured, and focus group interviews followed by Delphi surveys with patients and health professionals (HP) generated candidate domains of an OA flare. Content analysis of interviews with 29 patients and 16 HP extracted 180 statements, which were grouped into 9 clusters. Delphi consensus with 50 patients (Australia, Canada, and France) and 116 HP (17 countries on 4 continents) identified 5 flare domains: pain, swelling, stiffness, psychological aspects, and effect of symptoms. Elements for a preliminary definition of an OA flare are proposed. Registered at clinicaltrials.gov NCT02892058.

Key Indexing Terms:
OMERACT FLARE OSTEOARTHRITIS HIP KNEE DOMAIN

From the INSERM, CIC 1433 Clinical Epidemiology; Université de Lorraine, APEMAC unit, MICS team, Nancy; Université de Lorraine, APEMAC unit, EPSEM team, Metz; Sorbonne Université, GRC 08; AP-HP, Rheumatology Department, Pitié-Salpêtrière Hospital, Paris, France; University of Sydney, Institute of Bone and Joint Research, Kolling Institute; Rheumatology Department, Royal North Shore Hospital; Inner West Psychology; Faculty of Science, School of Psychology, and Faculty of Medicine and Health & Nursing School, University of Sydney, Sydney, Australia; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; UK National Institute for Health Research (NIHR) Leeds Biomedical Research Centre, Leeds, UK; Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

This work was supported by a grant from Association Française de Lutte Anti Rhumatisme – France Rhumatisme (France) and the Kolling Foundation (Australia). This work was endorsed by OMERACT and Osteoarthritis Research Society International and by the STPR Group in Rheumatology in France. PGC is supported in part by the UK NIHR Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the Department of Health. GH receives salary support as the Sir John and Lady Eaton Professor and Chair of Medicine at the University of Toronto.

F. Guillemin, MD, PhD, INSERM, CIC 1433 Clinical Epidemiology, and Université de Lorraine, APEMAC - MICS; C. Ricatte, MSc, Université de Lorraine, APEMAC - EPSEM; A. Barcenilla-Wong, PhD, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; A. Schoumacker, MSc, Université de Lorraine, APEMAC - EPSEM; M. Cross, PhD, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; C. Alleyrat, MSc, INSERM, CIC 1433 Clinical Epidemiology; T. Buttel, MA, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; C. Alleyrat, MSc, INSERM, CIC 1433 Clinical Epidemiology; H. Urban, MBiomed.Sc, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; B. Fautrel, MD, PhD, Sorbonne Université, GRC 08, and AP-HP.

Knee and hip osteoarthritis (KHOA) ranked as the 12th highest contributor to global disability in 2016, with an age-standardized prevalence of 3.8% and 0.85% for knee and hip, respectively. The most common symptoms associated with OA are pain, stiffness, and fatigue, which can flare during the evolution of this chronic condition.

Recent literature has shown that flare in KHOA is more than just an exacerbation of pain. Murphy, et al identified it by quality, timing of symptoms, antecedents, and consequences. Our literature review highlighted the wide variation in the definitions of OA flare and the lack of a valid measurement instrument integrating the patient perspective. Parry, et al, recently extending the review, also identified several flare characteristics beyond pain exacerbation.

From the INSERM, CIC 1433 Clinical Epidemiology; Université de Lorraine, APEMAC unit, MICS team, Nancy; Université de Lorraine, APEMAC unit, EPSEM team, Metz; Sorbonne Université, GRC 08; AP-HP, Rheumatology Department, Pitié-Salpêtrière Hospital, Paris, France; University of Sydney, Institute of Bone and Joint Research, Kolling Institute; Rheumatology Department, Royal North Shore Hospital; Inner West Psychology; Faculty of Science, School of Psychology, and Faculty of Medicine and Health & Nursing School, University of Sydney, Sydney, Australia; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; UK National Institute for Health Research (NIHR) Leeds Biomedical Research Centre, Leeds, UK; Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

This work was supported by a grant from Association Française de Lutte Anti Rhumatisme – France Rhumatisme (France) and the Kolling Foundation (Australia). This work was endorsed by OMERACT and Osteoarthritis Research Society International and by the STPR Group in Rheumatology in France. PGC is supported in part by the UK NIHR Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the Department of Health. GH receives salary support as the Sir John and Lady Eaton Professor and Chair of Medicine at the University of Toronto.

F. Guillemin, MD, PhD, INSERM, CIC 1433 Clinical Epidemiology, and Université de Lorraine, APEMAC - MICS; C. Ricatte, MSc, Université de Lorraine, APEMAC - EPSEM; A. Barcenilla-Wong, PhD, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; A. Schoumacker, MSc, Université de Lorraine, APEMAC - EPSEM; M. Cross, PhD, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; C. Alleyrat, MSc, INSERM, CIC 1433 Clinical Epidemiology; T. Buttel, MA, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; C. Alleyrat, MSc, INSERM, CIC 1433 Clinical Epidemiology; H. Urban, MBiomed.Sc, University of Sydney, Institute of Bone and Joint Research, Kolling Institute, and Rheumatology Department, Royal North Shore Hospital; B. Fautrel, MD, PhD, Sorbonne Université, GRC 08, and AP-HP.
The concept of flare was defined in previous work on rheumatoid arthritis by an Outcome Measures in Rheumatology (OMERACT) group as “a cluster of symptoms of sufficient duration and intensity to require initiation, change or increase in therapy”7. It served as a guide for developing measurement instruments8,9,10.

Although sharing some characteristics such as temporary exacerbation of pain as one of its major components, whether this definition can also serve for defining flare in KHOA has to be examined.

The lack of a clear and agreed upon definition of a flare in OA underlines the need for a conceptual definition before developing a measurement instrument of flare as a patient-reported outcome (PRO) for clinical trials or longitudinal observational studies. Further, to meet the requirement for a valid measure, OMERACT Filter 2.0 mandates the need to first define core outcome domains before developing or choosing an instrument11. The Flare-in-OA Working Group (WG) initiative was endorsed by OMERACT and Osteoarthritis Research Society International (OARSI). Currently, flare is on the research agenda for core domain set of KHOA12.

Our paper reports on the generation and selection of relevant domains and components for flare in KHOA and a proposal for preliminary elements for a definition.

MATERIALS AND METHODS
An inductive approach was used simultaneously in 2 languages, i.e., French and English, with the goal of generating candidate domains labeled with multiple language understanding. Then, consensus building on the selection of the most relevant domains involved participants in 3 continents.

Generation of domains. Unstructured interviews with 10 patients were conducted initially to identify the whole experience of a flare and further generate a semistructured interview guide developed under the guidance of 2 senior health psychologists, and cross-validated across languages. This guide was used by health psychologists and health professionals (HP) fully trained in conducting such interviews in France and Australia to elicit the perception of flare characteristics from HP and patients separately.

People recruited for this investigative step were participants with OA (“patients”) at the Royal North Shore Hospital (Australia), from the KHOA cohort study (Knee and Hip Osteoarthritis Longitudinal Assessment) in France, and HP (nurses, physiotherapists, rheumatologists, general practitioners, orthopedic surgeons) from among OARSI members, and OMERACT working group members. The HP were from the same setting in Australia and from 5 centers in France.

The interviews were recorded, transcribed, and prepared for analysis with Nvivo software in parallel in each country. The content analysis allowed identification of statements obtained verbatim (expressions extracted from interviews) that were meaningful for HP and patients. The French statements were translated into English. Similar statements were grouped in clusters analyzing the same topics. Labels of each cluster were proposed as domain names.

The WG steering group (consisting of clinicians, methodologists, and health psychologists; see Acknowledgment) critically analyzed the clustering of statements and the proposed labeling of clusters based on secondary content examination of the transcripts, taking care to ensure cross-language equivalence.

Selection of domains. Delphi surveys were conducted in 2 rounds among patients from national settings from the SPARK study (Study of Risk Factors for Pain Exacerbation in Osteoarthritis of the Knee) and Arthritis Alliance, Australia, from STPR group centers in France, and from HP as well as scientists, as per OARSI membership. OMERACT rules for Delphi consensus building were applied at each round, i.e., a threshold of 70% agreement should be reached to make a decision13.

In the first round, 165 HP participated and rejected 2 domains: pain, swelling, stiffness, triggers, consequences of the symptoms, psychological aspects, and protective factors. Two domains were rejected: buckling and other symptoms (Table 1).

In the second round, 50 patients retained 7 domains: pain, swelling, stiffness, triggers, consequences of the symptoms, psychological aspects, and protective factors. Two domains were rejected: buckling and other symptoms (Table 2).

Finally, the consensus reached by the OMERACT 2018 meeting participants was that:

1. Pain, swelling, and stiffness domains were fully supported by both HP and patients;
2. Buckling and other symptoms domains were removed by both HP and patients;
3. The psychological aspects domain showed slightly discrepant results between patients (72%) and HP (67.2%) rating somewhat below the prespecified threshold. In keeping with new OMERACT guidance for reaching consensus13 that recommends a 70% threshold in either patient or combined other stakeholder groups, this domain was retained. Because flare is a patient perception that conditions healthcare use, it was considered relevant to weigh patients’ opinions higher than those of others and retain this domain.

RESULTS
Generating domains. Individual semistructured interviews with 29 patients and 16 HP generated 180 statements specific to an OA flare. Content analysis involved grouping the statements into 9 clusters, which were labeled by names reflecting the covered topic (Supplementary Table 1 and Supplementary Table 2, available with the online version of this article). The WG steering group approved clustering and labeling of these topics.

Selecting domains. Participants in the Delphi survey were HP (researchers, rheumatologists, physiotherapists, orthopedic surgeons, nurses) from 17 countries on 4 continents, and patients were from Australia, Canada, and France.

During the first Delphi round, 91 patients rejected the domain “buckling.”

In the second round, 50 patients retained 7 domains: pain, swelling, stiffness, triggers, consequences of the symptoms, psychological aspects, and protective factors. Two domains were rejected: buckling and other symptoms (Table 1).

In the first round, 165 HP participated and rejected 2 domains: buckling and other symptoms. In the second round, 116 HP participated and retained 7 domains: pain, swelling, stiffness, triggers, consequences of the symptoms, psychological aspects, protective factors; and rejected 2 domains: buckling and other symptoms (Table 2).

Finally, the consensus reached by the OMERACT 2018 meeting participants was that:

1. Pain, swelling, and stiffness domains were fully supported by both HP and patients;
2. Buckling and other symptoms domains were removed by both HP and patients;
3. The psychological aspects domain showed slightly discrepant results between patients (72%) and HP (67.2%) rating somewhat below the prespecified threshold. In keeping with new OMERACT guidance for reaching consensus13 that recommends a 70% threshold in either patient or combined other stakeholder groups, this domain was retained. Because flare is a patient perception that conditions healthcare use, it was considered relevant to weigh patients’ opinions higher than those of others and retain this domain.
causes of the flare rather than the flare itself; in the Delphi survey, was finally removed because further was considered to be a behavioral protection adopted when called impact of the symptoms, because “protective factors” the flare occurred as an attempt to limit its effect (such as resting, changing activity).

From the discussion at OMERACT 2018, several elements emerged from this framework for setting a preliminary definition of a flare in KHOA: it is a transient state, different from the usual state of the condition, with a duration of a few days, characterized by onset, worsening of pain, swelling, stiffness, impact on sleep, activity, functioning, and psychological aspects that can resolve spontaneously or lead to a need to adjust therapy.

DISCUSSION
From a large number of statements, 5 core domains characterizing a flare in KHOA were selected based on consensus by patients, HP, and OA researchers. Their final selection took care to avoid missing important but rare manifestations and accounted for health providers having a comprehensive view of the disease combined with patients’ statements of their actual experience.

The advantage of conducting domain definition and choice using an inductive approach was that domain labeling was informed by patients’ statements extracted verbatim from qualitative research. Such a bottom-up approach gives accuracy and relevance to the domain labeling, which is usually the first way people approach a questionnaire to assess content (face validity). This helped the generation of candidate domains in developing a conceptual framework through an inductive approach.

Our proposed preliminary definition has several points in common with previous attempts to define OA flare in the...

---

Table 1. Selection of domains by patients in first (n = 91) and second (n = 50) Delphi rounds. Values are %.

<table>
<thead>
<tr>
<th>Domain</th>
<th>First Delphi Round</th>
<th>Second Delphi Round</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Must Be Kept</td>
<td>Could Be Kept</td>
</tr>
<tr>
<td>Pain (duration, severity, frequency)</td>
<td>67.0</td>
<td>26.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>47.3</td>
<td>36.3</td>
</tr>
<tr>
<td>Stiffness</td>
<td>59.3</td>
<td>33.0</td>
</tr>
<tr>
<td>Buckling</td>
<td>28.6</td>
<td>36.3</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>24.2</td>
<td>47.3</td>
</tr>
<tr>
<td>Triggers (tiredness, activity, movement)</td>
<td>62.6</td>
<td>29.7</td>
</tr>
<tr>
<td>Consequences of the symptoms (sleep, concentration, activity, need help, walking)</td>
<td>60.4</td>
<td>33.0</td>
</tr>
<tr>
<td>Psychological aspects (mood, annoyance, frustration)</td>
<td>40.7</td>
<td>42.9</td>
</tr>
<tr>
<td>Protective factors (rest, change of activity)</td>
<td>56.0</td>
<td>35.2</td>
</tr>
</tbody>
</table>

Table 2. Selection of domains by health professionals in first (n = 165) and second (n = 116) Delphi rounds. Values are %.

<table>
<thead>
<tr>
<th>Domain</th>
<th>First Delphi Round</th>
<th>Second Delphi Round</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Must Be Kept</td>
<td>Could Be Kept</td>
</tr>
<tr>
<td>Pain (duration, severity, frequency)</td>
<td>96.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Swelling</td>
<td>69.1</td>
<td>25.5</td>
</tr>
<tr>
<td>Stiffness</td>
<td>58.2</td>
<td>32.7</td>
</tr>
<tr>
<td>Buckling</td>
<td>18.2</td>
<td>46.1</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>13.9</td>
<td>47.9</td>
</tr>
<tr>
<td>Triggers (tiredness, activity, movement)</td>
<td>51.5</td>
<td>35.2</td>
</tr>
<tr>
<td>Consequences of the symptoms (sleep, concentration, activity, need help, walking)</td>
<td>57.6</td>
<td>35.8</td>
</tr>
<tr>
<td>Psychological aspects (mood, annoyance, frustration)</td>
<td>38.2</td>
<td>46.1</td>
</tr>
<tr>
<td>Protective factors (rest, change of activity)</td>
<td>47.3</td>
<td>39.4</td>
</tr>
</tbody>
</table>
literature. Several experts on the committee participated in previous qualitative work conducted to understand the pain experience in OA. Flare was characterized as a state different from the patient’s usual condition. Parry, et al. proposed focusing on onset/worsening of symptoms and signs, attainment of a minimum symptom threshold during flare, speed of onset/worsening, and duration of elevated symptoms/signs, while Murphy, et al. reported pain flares were common, fleeting, and often experienced in the context of activity engagement. These definitions and ours are convergent, with some differences, e.g., about onset mode, and require further refinement before a final definition is accepted.

Only 2 languages were used to generate domains, which might leave the meaning of domain labels uncertain for further translation. Such initiative at the very beginning of a data-driven approach is not common, leading to careful examination of the meaning of the domain labels and their correct correspondence with statements generated from patients, which could be helpful for translation into other languages. Another limitation was that the Delphi process missed some relevant stakeholders (i.e., regulators, industry).

This work provides a framework for defining a flare in KHOA and identified domains that form the basis for developing items for a patient-reported outcome instrument that incorporates components relevant to OA flare.

ACKNOWLEDGMENT
Working Group (WG) Steering Group: Annica Barcenilla-Wong, Marita Cross, Francis Guillemin, David J. Hunter, Lyn March, Camille Ricatte, Claudia Rutherford, Amandine Schoumacker, Elisabeth Spitz. WG Chair: Francis Guillemin, Gillian Hawker, David J. Hunter, Lyn March (OMERACT mentor). Collaborator: Joanna Makovey, Sydney, Australia. We thank the Osteoarthritis Research Society International (OARSI) members, health professionals, and people who participated in the various stages of this work, and Joanna Makovey, Sydney, for facilitating communication regarding the project.

ONLINE SUPPLEMENT
Supplementary material accompanies the online version of this article.

REFERENCES


