

OARSI Initiative to Develop Classification Criteria for Symptomatic Knee OA at an Early Structural Stage (EsSKOA)

The FACTs
(May 2026)

Goal of the Initiative



To expand the construct of symptomatic knee OA to include those earlier in the course of disease who have not yet developed established radiographic structural abnormalities



To do so, we are developing classification criteria for Symptomatic Knee OA at an Early Structural Stage (EsSKOA)



The criteria need to have high specificity (no false positives at the expense of false negatives) to identify 'early-stage' knee OA cases & exclude people with other conditions causing knee symptoms

Rationale

In the early stages of OA, people may have knee symptoms with little or no OA structural abnormalities on radiographs

People with symptoms deserve symptomatic treatment irrespective of whether they progress radiographically

People with symptoms who are at high risk of radiographic progression deserve care that may reduce this risk

Enrollment of people with symptomatic knee OA earlier in the disease course into DMOAD clinical trials may enhance the likelihood of trial success.

Well-established precedents in other diseases

Non-radiographic axial spondyloarthritis (nr-axSpA)

- A form of axial inflammatory arthritis that *has not caused* substantial erosive damage to the sacroiliac joints on x-ray
- Nr-axSpA ~ reduced QoL &, in *some* patients, can evolve into ankylosing spondylitis (AS, also termed *radiographic axSpA*)
- Background:
 - 1985: Recognized that there is often a period where classic signs & symptoms of axial inflammatory disease are present *in the absence of radiographic changes in the SIJs* fulfilling the modified New York criteria
 - Subsequently named *non-radiographic* axial SpA to recognize that *not all cases proceed to radiographic axSpA/AS*

This effort *is not* about pre-clinical OA



By pre-clinical, we mean ‘*pre-symptoms*’.



Regulatory approval of disease-modifying therapies requires evidence of improvement in *patient-relevant outcomes*.



Thus, the effort to develop classification criteria currently focuses on those *with symptoms* rather than asymptomatic pre-clinical OA.

Once the EsSKOA criteria are developed & validated, studies must...

- Identify risk factors for “progression” (symptomatic, structural) among people with EsSKOA
- Pre-clinical studies may then be conducted to identify risk factors for ‘incident EsSKOA’

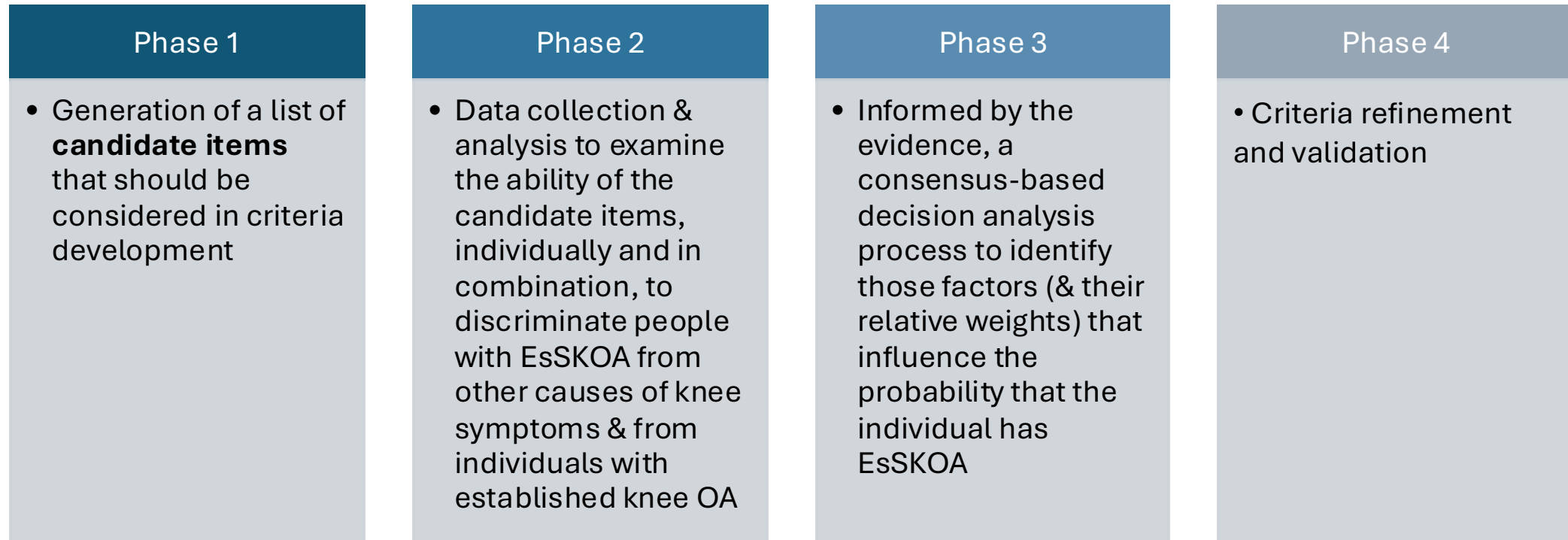
Future Clinical Trials in KOA

- Assuming regulatory approval of EsSKOA as an indication, trial inclusion would be based on EsSKOA + *additional criteria*, as for any clinical trial
- For example:
 - DMOAD trial: EsSKOA with risk factors for progression (TBD) or a specific mechanistic phenotype, e.g., certain clinical characteristics or endotype
 - Symptom treatment trial: EsSKOA with a threshold level of symptom severity

What is our methodological approach?

We're following the ACR–EULAR framework for classification criteria development

The goal is to find the most concise combination of factors that, when applied to individuals with undiagnosed knee symptoms, can accurately identify those with EsSKOA



What have we done thus far?

May 2026

Phase 1 – Framing the Work



Thinking about the target population in which the criteria might be applied*

- Adults (18+) **with** knee symptoms (pain, aching, stiffness, discomfort) **but not with...**
 - Established KOA in tibiofemoral OR patellofemoral joints on weight-bearing fixed flexion OR skyline knee radiographs
 - Previous joint replacement or osteotomy
 - Acute injury requiring medical care or knee surgery in past 6 months
 - Another condition more likely to explain the knee symptoms, e.g., pre-existing inflammatory arthritis

* The target population will be finalized in Phase 3.

Justification for exclusions

Prior surgery or an
“acute knee injury”:

- Would not be enrolled in a clinical trial of a DMOAD therapy

Another condition
more likely to explain
symptoms:

- While people may have more than one condition (e.g., OA with gout / RA), these individuals would not generally be entered into clinical trials as it would be difficult to interpret response to therapy

Established
radiographic OA:

- Already included in trials

How will we define structural stage?



We refer to radiographic stage to define structure.

Radiography is simple, widely accepted, and available in most countries.



Radiography has many limitations, but it is still a proxy for structural OA stage.

MRI?

- To be feasible for use in all settings, the classification criteria should not rely on tests that are not readily available everywhere, e.g., advanced imaging, non-commercial biomarkers
- If MRI features prove discriminatory for EsSKOA, they may be incorporated as **optional criteria**

Phase 1 – Elaboration of Candidate Items

- Multiple strategies were used to identify POTENTIAL candidate items for consideration in criteria development to differentiate EsSKOA from other conditions that cause knee symptoms
- **86 candidate items** being considered:
 - Patient history
 - Knee symptoms
 - Knee examination
 - Knee radiographs
 - Knee MRI
 - Laboratory tests (RF, anti-CCP, urate, others)

King et al, 2025

Phase 1: What conditions cause knee symptoms?

- Based on Expert Clinician Delphi Survey, most common conditions are:
 - Knee OA
 - Traumatic collateral ligament strain
 - Patellofemoral pain syndrome
 - Patellar tendonitis
 - Meniscal tear
 - Bursitis
 - Undiagnosed immune-mediated inflammatory arthritis
 - Undiagnosed crystal-induced inflammatory arthritis
 - Baker's cyst

Hawker et al, 2025

Phase 2: Candidate Item Analyses



Candidate item analysis

- Requires data (information) about the candidate items on large numbers of people/knees
- An environmental scan for existing datasets identified 19 cohorts
 - A review of the eligibility criteria and variables available determined that there is unlikely to be sufficient data available for candidate items AND on individuals without established radiographic knee OA or mimic conditions
 - A pilot study is being developed to test this assumption in the NIH-funded OsteoArthritis Initiative, OAI, dataset

Primary Data Collection of Candidate Items in Symptomatic Knees



Adults with 1-2 eligible knees

Eligible knees:

- Symptoms at any time in the past 3 months
- No surgery/injury in the past 6 months
- No joint replacement ever
- No other established diagnosis, e.g., dx RA



We will recruit ~ 200 each with EsSKOA, other conditions causing knee symptoms or established radiographic knee OA (rKOA)

Recruitment status based on expert clinician assessment and radiographs (KL 2+)



Assessments:

Standardized patient questionnaire
Standardized expert clinician physical examination
Laboratory testing
Radiographs – TF/PF
MRI – those without KL 2+ on radiographs
Additional biospecimens will be collected to enable future consideration of novel biomarkers in EsSKOA classification



Blinded adjudication process to assign 'gold standard case status' (EsSKOA or another condition)



Analyses will assess the association of candidate items (independent variables) to case status (EsSKOA – yes/no)

Recruitment of Expert Clinicians

(to serve as Phase 2 Adjudicators & Phase 3 Expert Panel Members)

Adjudicators & expert panel members must represent a breadth of clinical expertise in “knee” diagnoses

We will recruit approximately equal numbers of rheumatologists, physiotherapists, sports medicine / primary care physicians, and orthopaedic surgeons.

The differential diagnosis for symptomatic knees is broad & discernment of the most likely cause of the symptoms challenging

We will recruit individuals with at least 10 years’ clinical experience who have seen ≥ 5 patients per month, on average, presenting with undiagnosed knee symptoms.

OARSI is an international community that values inclusion & diversity

We will recruit individuals to ensure broad geographic representation (continents) and both men and women.

Phase 3: Criteria Development



Criteria Development

- Assemble the Expert Clinical Panel
 - 16-20 clinical experts from the four clinical disciplines, with representation across continents & men and women
- Expert Panel activities pre-meeting
 - Review Phase 2 candidate item analysis findings
 - Review a spectrum of “paper” cases representing people presenting with undiagnosed knee symptoms & provide perceived probability that the patient has EsSKOA (Likert scale)

Expert Panel Meeting

1. Discussion of cases for which there was lack of consensus on EsSKOA probability
 - What features were important in ruling in / ruling out EsSKOA?
 - Identifies the domains / categories within domains for the classification criteria
2. Discrete choice experiment using 1000 Minds® software
 - Derives the weights for domains/ categories within domains (sum of the weights is the estimated probability that a patient has EsSKOA)
 - Determine threshold 'score' to optimize specificity for identifying EsSKOA & excluding mimics
3. Finalize 'target population' for application of the criteria

Phase 4: Criteria validation



Criteria validation



We will recruit an additional 200 participants in Phase 2 to serve as the independent 'validation' sample



In those subjects, we will calculate the sensitivity, specificity, and predictive values for discriminating people with EsSKOA from those with other conditions



Revisions may be required, e.g., shift in score threshold for classification, based on results

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Who is leading this initiative?





Advisory Committee

Stefan Lohmander (Chair)

Francis Berenbaum, Marc Hochberg, Muneaki Ishijima, Nancy Lane, Margreet Kloppenburg, Siddharth Das, Ali Mobasher, Elena Losina, Changhai Ding, Carolyn Emery, Stephanie Filbay



Steering Committee

Ida Haugen (Chair)

Martin Englund, Gillian Hawker, Tuhina Neogi, Stefan Lohmander, Armaghan Mahmoudian, Tom Appleton, Jos Runhaar



Methodology Working Group

Gillian Hawker and Tuhina Neogi (Co-chairs)

Aleksandra Turkiewicz, Martin Englund, Jos Runhaar, Armaghan Mahmoudian, Lauren King, Jean Liew, Qiuke Wang



Expert Clinical Panel
(TBD)

Patient Research
Partners (appointed)

Case Status
Adjudicators (TBD)

Ad hoc
topic
expertise

Statistics

Biomarkers

Imaging

Clinical
trials

Project Manager:
Arin Deveci

Funding received to date for this initiative



Got questions?

Please contact our Project Coordinator
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