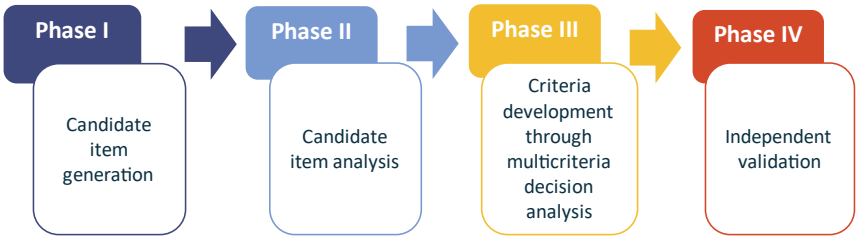
September 27, 2024

Dear Sponsors of the OARSI EsSKOA Initiative & OARSI Board Members,

We are now reaching the end of the second year of funding for this initiative to develop and test classification criteria for early-stage symptomatic knee OA (EsSKOA). As a reminder, we are being guided by the established American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) methodology for classification criteria development, which is comprised of four phases: 1) Generating a list of candidate items (variables) that should be considered for classification. 2) Data acquisition and analyses to examine the ability of the candidate items to discriminate the condition of interest from other conditions (mimickers). 3) Establishing the criteria, weights and provisional classification threshold though an evidence-informed consensus approach, including multi-criteria decision analysis; and 4) Assessing the criteria's performance characteristics in an independent sample.

Phases of EsSKOA classification criteria development



A detailed update was presented by three of our four Early Career Investigators, Armaghan Mahmoudian, Lauren King and Jean Liew, at the OARSI 2024 Congress in Vienna. Progress to date, including publications and presentations, are provided below. Here we provide a summary of progress to date and plans for 2025.

Where are we now?

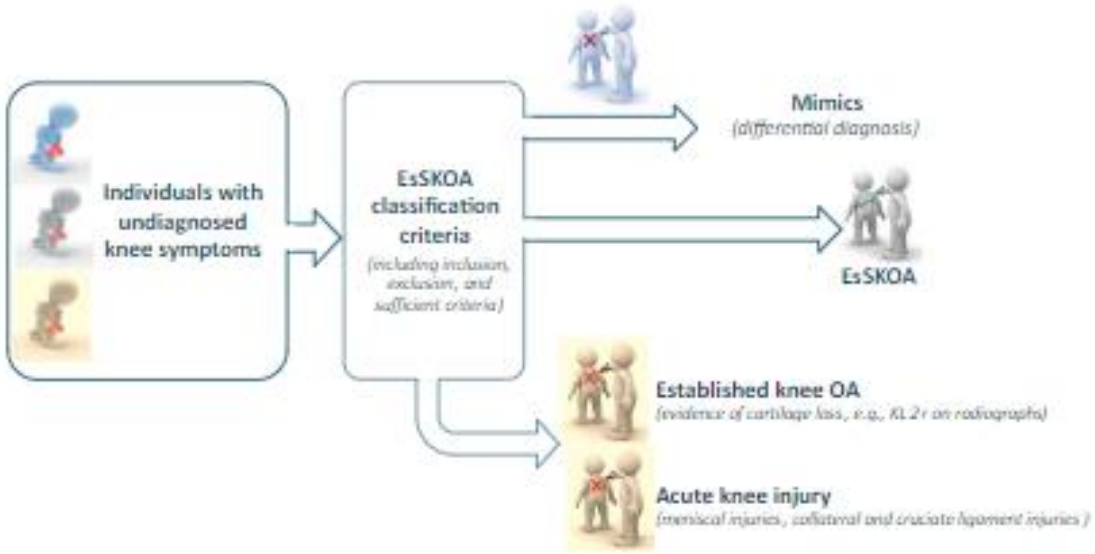
These first two years - completion of **Phase I** - have been incredibly important in laying the foundation for these classification criteria. Through an international Delphi exercise with health professionals[1,2] and a survey of patients[3], we have **identified over 70 candidate items** that our community feels should be considered in classification criteria development. Candidate items include variables across multiple domains, including demographics/clinical history, symptoms, physical exam, laboratory tests, and imaging.

We have formalized the **target population** on which the criteria will be applied as follows:

1. Typical knee OA clinical trial enrollment criteria include evidence of **established radiographic knee OA** (Kellgren and Lawrence [KL] grade ≥2) with a certain threshold of knee pain. KL grade 2 indicates "possible joint space narrowing" and reflects advanced

pathobiological joint damage (established KOA). Given our goal is to expand recruitment into trials of individuals with symptomatic knee OA who do not already have structural changes, i.e., KL<2 radiographically, the target population will not include individuals with evidence of cartilage loss on radiographs.

2. Individuals with an **acute knee injury** would not be included in a DMOAD clinical trial. Thus, we will also exclude individuals with a knee injury requiring medical care or knee surgery in prior 6 months.
3. There are many causes of knee symptoms. The EsSKOA criteria must be able discriminate, with accuracy, people who have other causes of knee symptoms (**EsSKOA mimicker conditions**). Through a survey of >100 clinicians that see patients presenting with undiagnosed knee symptoms, we have established that the differential diagnosis of EsSKOA commonly includes non-acute meniscal tear, osteonecrosis, bursitis, ligamentous strain, and immune-mediated inflammatory arthritis. These conditions must therefore be in our target population.



What comes next?

We are now poised to begin **Phase II,** the goal of which is to examine the ability of the candidate items identified in Phase I to discriminate the condition of interest, EsSKOA, from other conditions (the identified mimickers). We also hope to better understand if and how the candidate items differentiate people with EsSKOA from those with established radiographic knee OA.

In the absence of a **'gold standard' for EsSKOA**, we will rely on the opinions of expert clinicians (people who care for patients in the target population) to determine the condition that is *most responsible* for the participant's knee symptoms (EsSKOA, a Mimicker Condition (specify), or Established Radiographic Knee OA) based on their review of the candidate item data available.

Phase II requires robust data to establish the evidence to support or refute the ability of candidate items, alone and in combination, to discriminate people with EsSKOA from those with other conditions. From clinical experience, we believe that *detailed information on patient history and physical examination of the knee* will be critical in discriminating the mimicker conditions from EsSKOA. However, unlike prior ACR/EULAR classification criteria initiatives, we have identified *no existing datasets* with adequate information on the candidate items in the relevant populations to conduct this work. Thus, *primary data collection is required.* It will take longer and require more resources to recruit and assess patients than would secondary data analysis. Thus, we are working hard to identify additional sources of support for this work, including peer-review funding (one grant was submitted in September). The anticipated timeline for Phases II through IV is outlined below; it is ambitious and will very much depend on funding. Still, we remain committed to this work - Phase II provides the evidence base that will inform the multidisciplinary expert panel discussion in Phase III and thus we must get it right.

How will the remaining donor funds be used to achieve our goals?

We are extremely grateful to our two initiative sponsors, Viatris Inc. and Grünenthal, each donating $90,000 USD total in grant funding to support this initiative. We are also grateful of the OARSI Board's ongoing support.

A summary of funds spent to date and proposed use of remaining funds is below. In brief, expenses were $15,768 in 2023 and will be $36,210 in 2024 (expected to December 31). These were for project coordinator support and to cover the costs of knowledge dissemination, including abstract submission, poster printing and manuscript publication. No funds were used to cover costs of ECI travel or accommodation at the annual OARSI Congress. In July of this year, we recruited our Project Coordinator, Ngozi Ekeleme, at the University of Toronto. She is a welcome addition to the team.

Given a total $180,000 USD in donor funds, there are $128,022 remaining. For the upcoming 2025 year, we will focus on data collection to enable Phase II analyses. This will including ongoing funding of our Project Coordinator @ 0.5 FTE = $35,000 USD (salary + benefits + annual cost of living raise), $3,000 to cover costs of knowledge dissemination, and $55,000 to begin data collection. Details regarding the primary data collection are enclosed for your interest. Based on our per case cost estimates, we anticipate recruitment of 65 MRI requiring cases and 65 non-MRI requiring cases with the remaining funds.

As noted above, we have submitted a project grant to cover data collection and travel/accommodation for non-OARSI members to the Expert Panel in Phase 3. We are seeking other such opportunities globally. Should external funding be received to support data collection, this will enable expanded exports to achieve our objectives more swiftly.

Timeline:

We estimate that full recruitment of the 650 study subjects required for Phases 2 and 3 will require two to two and a half years, depending on the number of sites that are willing and able to participate and of course procurement of the necessary funds. We are optimistic that our OARSI community will be keen to participate.

We will use the first 325 recruits' data for the purposes of Phase 2 candidate item data analyses. Thus, data analyses can begin well before the final sample is recruited. While we are aiming for the Expert Panel discussion to be held in conjunction with the 2026 OARSI Congress, this may be overly optimistic – 2027 is more likely.

Proposal for Primary Data Collection:

Purpose: To identify which candidate variables for EsSKOA classification best distinguish EsSKOA from Mimicker Conditions and Established Radiographic Knee OA.

Design: Prospective cohort study conducted across continents.

Participants: *Inclusion criteria:* 1) Adult (≥18 years); 2) Knee symptoms (pain, aching, discomfort and/or stiffness in one or both knees) first noticed ≥3 months earlier. Recruitment must ensure adequate representation of people in our three groups: EsSKOA, mimicker conditions, and established radiographic OA. *Exclusion criteria:* 1) Knee injury requiring medical care or knee surgery in past 6 months; and 2) Unable to provide consent.

Assessments: *Ascertainment of the Candidate Items*

Standardized online questionnaire to collect information on demographics, clinical history, and knee symptoms (both knees).

Standardized physical exam of the knees & measurement of height and weight to calculate BMI. Findings recorded on an electronic data collection form.

Laboratory investigations: serum rheumatoid factor, anti-CCP antibody, c-reactive protein, and urate.

Imaging: *Bilateral knee radiographs* (weightbearing anteroposterior view in full extension, a standing lateral view in 30-degree flexion, and a skyline view in 45-degree flexion). Radiographs will be scored for KL grade by a trained reader. Participants without established radiographic OA changes in any knee compartment (medial/lateral tibiofemoral or patellofemoral), i.e., those with KL score of 0 or 1, will be scheduled to undergo *3T MRI of the most symptomatic knee* within 4 weeks using routine clinical MRI sequences (standardized across sites). MRIs will be read by a trained radiologist, evaluating OA-related joint changes and features of Mimicker Conditions using a standardized reporting form.

Follow-up: Reassessment of knee symptoms at 3 and 6 months via standardized online questionnaire.

Outcome of interest (gold standard case status): Clinician's opinion regarding the most likely diagnosis for the participant's knee symptoms, assessed at the level of the knee: EsSKOA, Mimicker Condition, or Established Radiographic Knee OA.

Analysis: Using one-half of the sample, we will assess the ability of each of the candidate variables, alone and in combination, to discriminate EsSKOA from Established Radiographic Knee OA or Mimicker Conditions. The remaining half of the cohort will be reserved to assess the test characteristics of the final criteria set in an independent, unanalyzed sample.

Sample size: The ACR classification criteria development checklist (ref) recommends at least 100 cases and 100 controls in each of the derivation and validation datasets. To provide at least 100 individuals with EsSKOA, Mimicker Conditions, and Established Radiographic Knee OA in each of the two datasets, we will aim to recruit 650 participants. Of these, one-half (325) will be used

for classification criteria development (derivation dataset), and one-half (325) will be used for external validation (validation dataset). Of individuals recruited, MRI will not be required for those with established radiographic knee OA, but will be collected for the remaining two-thirds of individuals (n=430 individuals).

Budget per case in $ USD*

- **Baseline Assessment – Questionnaire + Physical Examination** (RA or clinician, as required) **= $100**
- **Participant Reimbursement** (travel/parking & honorarium gift voucher) **= $25**
- **X-Ray = $100** (not including costs for reading)
- **Laboratory Testing = $85**
- **MRI = $175** (not including costs for reading)

TOTAL PER CASE: $485 with MRI / $310 without MRI

Based on the above estimates, we will require $208,550 for MRI cases and $68,200 for non-MRI cases = $276,750 in total.

*Costs may vary by country/institution

Timeline:

We estimate that full recruitment of the 650 study subjects will recruit two years, depending on the number of sites that agree to help with recruitment. We are optimistic that our OARSI community will be keen to participate. We will use the first 325 recruits' data for the purposes of Phase 2 data analysis of the candidate variables. Thus, data analyses can begin well before the final sample is recruited. While we are aiming for the Expert Panel discussion to be held in conjunction with the 2026 OARSI Congress, this may be overly optimistic.

Budget Status: *all values are in USD*

$15,768 in expenses were incurred in 2023. The budget proposed for 2024, actuals for 2024, and proposed budget for 2025 are provided below, with commentary regarding variances.

	2024 Proposed	**2024 Actual** (to December 31)	**Explanation for variance**	**2025 Proposed**
Staff Project Coordinator 0.5 FTE	30,000	33,400	PC recruited (July 22, 2024); prior to recruitment, a senior RA was covering the role, who is paid at a higher rate	0.5 FTE = 35,000 (salary + benefits + annual cost of living raise)
Travel 4 ECIs to OARSI 2024 Meeting costs for Expert Panel	 8,000 3,000		No funding was allocated to travel as per the advice of OARSI Board	---
Phase III Expert Panel Consultation services, travel, accommodation	30,000		This step requires data analyses of the candidate items; it will likely occur in late 2026 or 2027	---
Honorarium Focus groups $100 x ~ 30 clinicians/researchers	3,000	-	Work was completed by online survey (Identification of Mimicker Conditions)	
Publication Costs OAC & OAC Open, Abstracts	10,000	2,810	We will continue to incur costs over time	3,000
Phase II Primary Data Collection (to enable Candidate Item Analyses) *				53,000
Total	84,000	36,210		91,000

*Peer-reviewed operating grant has been submitted to garner additional support for this aspect of the project and additional grants will be submitted over the ensuring months as opportunities arise. However, this work is required irrespective of the success of these grants. If the grants are successful, this will expand funding available.

Progress to September 2024

In brief, we have accomplished the following:

Scoping review of the literature[4]: identified that definitions of "early knee OA" varied widely. Most included individuals with KL grade 2 or greater. This is consistent with existing knee OA classification criteria, which largely identify those with Established Radiographic Knee OA. Many studies also required participants to have "knee pain on most days of the prior month/3 months", yet we have learned from our qualitative research[5] that knee OA symptoms are frequently insidious and intermittent at the start, progressing slowly over what may be years. This review supported the need for classification criteria for early-stage symptomatic knee OA, which will enable expansion of the patient population admitted to OA trials and, in turn, hopefully greater success of novel OA disease-modifying therapies.

We have **identified potential candidate items (Phase I)** through an international Delphi exercise with health professionals[1,2] and a survey of patients[3]. Candidate items include variables across multiple domains, including demographics/clinical history, symptoms, physical exam, laboratory tests, and imaging. Based on the candidate item list, detailed information on patient history and physical examination of the knee will be critical in discriminating other conditions from EsSKOA.

A survey of clinicians across a range of disciplines (including primary care, sports medicine, chiropractic, physiotherapy, physiatry, rheumatology and orthopaedics) (publication in progress) has **identified the conditions that should be included in the differential diagnosis of EsSKOA (Mimicker Conditions):** meniscal tear, osteonecrosis, bursitis, ligamentous strain, and immune-mediated inflammatory arthritis. The survey also confirmed that no key variables were missing from our list of candidate items.

An environmental scan of the international OA research community is about to be launched to **identify existing datasets with sufficient information** on the potential candidate items – in particular, including detailed knee examination, and including individuals with possible EsSKOA and some or all of the potential Mimicker Conditions. We do not anticipate funding sufficient data to conduct our candidate item analyses and are therefore preparing for primary data collection.

An **operating grant has been submitted** to the Canadian Institutes of Health Research (CIHR) in September 2024 to garner funding to support primary data collection; additional funding will be sought from other funding agencies by EsSKOA team members. Included in the request for funding to CIHR is a qualitative study to elucidate the perspectives of people living with intermittent knee symptoms, and minimal, if any, structural change on x-ray regarding the threshold at which they would accept the potential risks of medical therapy to avoid progression to established OA. This will be central to the development of classification criteria for EsSKOA since the point at which we define "early" symptomatic knee OA must correspond to a state of illness at which the patient is willing to consider seeking medical attention, initiating therapy, or participating in a clinical trial of an investigational therapy.

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