

# **OARSI FDA OA INITIATIVE**

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## **Claim of Symptomatic Relief Working Group**

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## Claim of Symptomatic Relief Working Group Members

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### 1. What are the key domains that are critical to measure improvement in OA clinical trials?

- **Pain**
- **Physical functioning**
- **Stiffness**
- **Social participation**
- **Emotional functioning**
- **Sleep**
- **Fatigue**
- **Patient ratings of global improvement and satisfaction**
- **[ Health-related quality of life ]**

**2. Of these key domains, which should be required for approval of a treatment for OA?**

- **Pain should be the primary efficacy endpoint for approval of a treatment for “pain relief in patients with OA.”**
- **Physical functioning should be the primary efficacy endpoint for approval of a treatment for “improvement of physical functioning in patients with OA.”**
- **Pain, physical functioning, and patient global improvement could be required for approval of a treatment for “improvement of signs and symptoms of OA.”**
  - **in a gatekeeper analysis that would allow a claim for “pain relief in patients with OA” if the other endpoints were not significant.**
- **Remaining domains would be secondary or exploratory outcomes that are not essential for approval.**

**3. Are there important domains that have not been considered in the past, such as fatigue or sleep disturbance?**

- **Fatigue, sleep, and stiffness are all considered important.**
- **However, at the present time there are limited data validating these outcomes in OA and inadequate understanding of the clinical importance of change in measures of these domains.**
- **Thus, these outcomes should be considered secondary at the present time.**

**4. What functional assessments would be useful, if any? What is the value of observed functional performance vs. self-report of functional limitation?**

- **In selecting a patient-reported outcome (PRO) measure of physical function, the WOMAC function scale, the Knee Injury and Osteoarthritis Outcome Score (KOOS), and the Hip Disability and Osteoarthritis Outcome Score (HOOS) can all be considered.**
- **There are physical therapy measures that have been developed to assess function that are typically observed performance measures. If validated, these could be considered secondary outcomes that would complement but not substitute for PROs.**
- **By using both “subjective” and “observed” measures, there may be increased information regarding baseline ability to perform activities as well as treatment response.**

**5. Is WOMAC pain equivalent to a VAS or NRS measure of pain? What about other pain measures: BPI, McGill, CAT, and Lequesne Algofunctional Index?**

- **For assessing pain intensity, in most circumstances a 0-10 numerical scale is best; a 0-10 cm visual analogue scale is a very close second choice. Pain scales with fewer response options (verbal rating scales) have somewhat less responsiveness to change and to discriminating active treatments from placebo.**
- **The validity of these general measures of pain intensity is generally comparable to OA-specific measures such as the WOMAC.**
- **The target joint must be specified.**
- **Other pain characteristics (e.g., pain quality, distress, interference) are generally secondary outcomes.**

**6. Should there be an effort to design a per-patient responder index?**

- **The OMERACT-OARSI responder index includes pain, physical functioning, and patient global ratings in one validated measure of patient response. With such a composite, multiplicity issues are not relevant.**
- **The relative contributions of the three components of OMERACT-OARSI responder index to determining responder status should be determined. This could provide a basis for considering the index as support for a claim of “improvement of signs and symptoms of OA.”**
- **The WOMAC total score should not generally be used because it does not provide domain-specific information.**

**7. Flare design trials—what is their utility/necessity? New trial designs (e.g., randomized withdrawal trials)**

- **Parallel group, flare, randomized withdrawal, and adaptive designs are all a focus of current interest.**
- **The flare design became popular in studying the effects of NSAIDs in patients who flared on withdrawal of their clinically used NSAID.**
- **This design may provide results that overemphasize the observed or potential benefits of drugs. In addition, the risk-benefit question is not fully addressed with a standard flare design.**
- **For these reasons, an enriched randomized withdrawal design could be an improvement over the flare design. This design provides efficacy and safety data, although the control group is biased by including patients who originally tolerated the active therapy.**

## 8. Inclusion/exclusion criteria.

- **Separate trials should be done in knee and hip (or another joint) OA until it has been determined across different treatments whether efficacy varies depending on the specific joint investigated.**
- **The key pain-related inclusion criteria should include pain for  $\geq 3$  months and baseline pain intensity  $\geq 4/10$ .**
- **Trials of symptomatic treatments will typically be three months in duration.**
- **A major consideration is whether and what rescue and concomitant analgesic treatments should be allowed.**

## 9. What is the research agenda required to inform each of the above questions?

- **Measures of the following outcomes should be developed and validated in accord with the new FDA guidance for PROs:**
  - **Fatigue**
  - **Sleep**
  - **Stiffness**
  - **Physical performance**
  - **Prevention of symptomatic progression**
  - **Characteristics and frequency of flares**
- **Continued research on the validity and responsiveness of the Patient Acceptable Symptom State and Minimal Clinically Important Improvement responder indices is strongly encouraged.**

**9. What is the research agenda required to inform each of the above questions (continued)?**

- **The relative advantages and disadvantages of analyses of mean changes, responders, area under the curve, and landmark endpoints must be examined. The statistical power of such analyses is an especially important consideration.**
- **Research designs should be developed for clinical trials of intermittent treatment, efficacy and safety of long-term treatment, and community effectiveness and comparative effectiveness (pragmatic trials).**
- **The extent to which efficacy in knee or hip OA can be extrapolated to other joints should be evaluated in completed and ongoing trials.**



Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials

**Resource for Evaluating Procedures and Outcomes of Randomized Trials (REPORT)**

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## Osteoarthritis database

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### 171 placebo-controlled clinical trials

- oral, transdermal, and topical treatments
- blinded, randomized trials of knee, hip, and/or hand OA
  - ✓ 119 placebo-controlled
  - ✓ 52 placebo-controlled with active comparator
  - ✓ 61% knee only, 7% hip only, 27% knee or hip
- 235 active treatment arms
  - ✓ 74% medications (e.g., APAP, NSAID, opioid)
  - ✓ 20% nutraceutical or medicinal herbs
- research design
  - ✓ 89% parallel, 11% crossover
  - ✓ 28% required flare in some or all patients

Outcome measure	All trials N = 171		Positive trials N = 140	
	# arms	% +	# arms	% +
Pain: spontaneous	113	72.6	93	88.2
Pain: activity, wght bearing	51	72.5	43	86.0
WOMAC Pain total	120	75.0	106	84.0
WOMAC Pain walking (A1)	22	86.4	22	86.4
WOMAC Physical function	123	69.1	107	77.6
WOMAC Stiffness	106	65.1	92	72.8
WOMAC Total score	81	71.6	71	78.9
Lequesne index	43	62.8	36	69.4
Patient global ratings	100	74.0	92	79.3
Clinician global ratings	77	79.2	73	83.4
Discontinue lack efficacy	52	96.2	52	96.2
Rescue medication dosage	72	45.8	63	52.4

## Responder indices

Outcome measure	All trials N=171		Positive primary analysis only N=140	
	# arms	% +	# arms	% +
Patient reported	66	81.8	58	89.7
Clinician rated	45	77.8	35	91.4
≥ 30-50% response in pain or function	25	64.0	23	65.2
OMERACT/OARSI (all versions)	19	78.9	17	88.2

Characteristic	171 trials placebo-controlled OA trials			
	n	Outcome		p
		Positive (141)	Negative (30)	
Placebo response (0-100)	115	12.9	9.6	.06
Active response (0-100)	105	25.7	11.6	.001
Active-placebo	105	12.8	2.0	.001
Baseline pain/function (0-100)	122	60.6	46.9	.001
Sample size (n)	158	382.2	145.9	.002
Treatment duration, days	150	93.0	213.4	.006
Year of publication	171	2000.4	1999.3	.53
Discontinuation rate, %				
placebo group	102	25.1	22.7	.61
active group	102	20.1	27.6	.15

		171 trials placebo-controlled OA trials			
		n	Outcome		p
Characteristic			Positive (%)	Negative (%)	
Design	Parallel	153	83.7	16.3	.32
	Crossover	18	72.2	27.8	
Flare	No	124	76.6	23.4	.001
	Yes	47	97.9	2.1	
Instrument scale	<10	41	80.5	19.5	.70
	≥10	130	83.1	16.9	
Instrument category	Pain/ function	59	86.4	13.6	>.99
	WOMAC or Lequesne	13	92.3	7.7	
Joint	Knee	106	79.3	20.8	.20
	Knee or hip	49	87.8	12.2	

## Future activities

- The preceding analyses, which are preliminary, will be confirmed and extended, and two articles will be prepared for publication.
- In addition to the analyses of positive vs. negative study outcomes presented in the preceding slides, the following analyses are being conducted:
  - analyses of outcome measures and of study outcomes using standardized effect sizes.
  - multivariate analyses of relationships between clinical trial methodological characteristics and study outcomes.
  - sensitivity analyses in which only trials of first-, second-, and third-line medications are included.