Q14. Can/should we define a minimum level/size for each pain-dependent behavioral outcome that is relevant/clinically meaningful? This would be both the size of change from baseline to be considered bona fide "OA-pain" and change with any treatment to be considered a meaningful therapeutic effect (similar to clinically meaningful effect size in clinical trials).

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Response/Recommendation: Given persistent concerns regarding the translational validity of studies employing preclinical *in vivo* models,[1-12] and the scarcity of reviews summarising a clear transition from preclinical data into clinical outcomes[13], defining a minimum clinically meaningful threshold for each pain-dependent behavioural outcome would seem not only justified, but necessary. At present, defining a minimum change that constitutes osteoarthritis (OA) pain and/or a successful response to intervention risks oversimplifying the often-phasic and heterogeneous nature of OA-pain and responses to intervention that are observed in both animals and humans. Meaningful threshold definition will require: (1) determining the magnitude of change that translates to a clinically meaningful effect; and (2) comprehensive and standardized characterization of behavioural outcomes across ages, sexes, species, models, disease stages, and disease pheno-/endo-types including pain states. In the absence of such data, ***priority should be given to the continued evaluation and improvement of bidirectional preclinical-clinical study alignment.***[2, 8, 10, 14-16] This means ensuring that the selected preclinical models reflect the intended target clinical population (including relevant pain phenotypes); and that the pain-dependent behavioural outcome/s and study time points correspond with, or have a known translational relationship with, the intended clinical measure/s of pain.

Level of Evidence: The current evidentiary basis supporting the feasibility of, and justification for, defining minimum relevant/clinically meaningful thresholds to improve the translational efficacy of OA-pain preclinical research is low. However, the importance of improved alignment of preclinical and clinical trial outcomes remains.

Delegate Vote: Agree: Disagree: Abstain:

Rationale: Clinical definitions of OA-pain and meaningful effects. It is important to first acknowledge that OA is a clinically heterogeneous disorder,[17-19] and that "OA-pain" itself represents a multifaceted experience encompassing diverse symptomatic presentations, trajectories and underlying mechanisms.[20-29] Accordingly, a range of clinical assessment tools have been developed and employed, including patient- or observer-reported outcome measures (PROMs/OROMs; e.g. WOMAC, KOOS, HOOS, ICOAP, AUSCAN), performance-based functional tests (e.g. strength, endurance, speed, mobility/range of motion), and quantitative sensory testing paradigms (e.g. pressure pain thresholds, temporal summation and conditioned pain modulation).[23, 30-38] Notably, these instruments are primarily designed to characterise the severity and impact of an individual's pain experience over time or relative to comparator groups, rather than to establish a definitive diagnosis of "OA-pain" based on a single predefined threshold.[26] One could argue that clinically meaningful "OA-pain" is simply the level at which an individual seeks medical treatment which may be captured by global measures of pain intensity. Currently, no equivalent assessment tool has been developed for species commonly used in preclinical OA studies. Furthermore, pain thresholds would vary substantially according to individual pain sensitivity, psychosocial influences, access to care and other contextual factors that affect health-seeking behaviours.[20, 21, 39-46] Taken together, the absence of a universally accepted clinical definition of "OA-pain" inevitably complicates efforts to define translationally equivalent thresholds in preclinical studies that could be considered diagnostic measures of "bonafide OA-pain".

More decisive progress has been made in defining clinically meaningful changes in response to treatment. Approaches include: (1) estimation of the minimum clinically important difference or change (MCID/MCIC), which seeks to identify the smallest change perceived as being beneficial; (2) responder classifications based on predefined magnitudes of improvement (e.g. OMERACT-OARSI responder criteria); and (3) the Patient Acceptable Symptom State (PASS), which reflects whether patients consider their current symptom state to be satisfactory, irrespective of the magnitude of change, and is often anchored to external measures (e.g. pain intensity or WOMAC scores) to define a cut-off value that is indicative of a "good" symptomatic state.[47-51] These approaches aim to establish thresholds that indicate the efficacy of a treatment intervention. However, the magnitude of change is often influenced by temporal changes (including regression to the mean), psychosocial influences, and expectation-driven placebo or nocebo responses, all of which can modify perceived changes in pain and functional outcomes.[52-58] Moreover, baseline symptom severity strongly shapes the magnitude of measurable improvement, and the clinical relevance of a given change may ultimately depend on trade-offs between treatment benefits, financial costs, accessibility, and the practical burdens associated with treatment adherence.[59-61] Importantly, clinical improvements in OA trials are typically measured using PROMs,[51] and observed changes often reflect composite treatment effects, underlying symptom variability and contextual influences. These complexities are rarely replicated within controlled, preclinical experimental settings.

Measuring pain-related outcomes in animals: In preclinical animal studies, pain cannot be directly or verbally reported and therefore, must be inferred through behavioural and functional measures that serve as indirect indicators of pain-associated states. Similar to clinical research, these measures span multiple domains, including observer-reported outcome measures (e.g. validated owner-reported tools in canine and feline populations), quantitative sensory tests (e.g. mechanical allodynia, thermal allodynia, and mechanical hyperalgesia), and functional assessments (e.g. weight-bearing, gait analysis, grip strength, or voluntary activity).[8, 10, 36, 38, 62-69] Historically, animal studies have relied heavily on evoked or reflexive pain measures; however, there is increasing recognition that non-evoked or spontaneous behavioural changes and functional outcomes may provide information that more closely reflects the multidimensional nature of pain observed and measured in clinical OA populations[63].

Defining “OA-pain” in animals: Reflecting the clinical landscape, there are currently no universally accepted definitions or thresholds for preclinical “OA-pain” or specific pain states (e.g. specific cut-offs for mechanical allodynia, hyperalgesia, or reductions in activity). Establishing a fixed, clinically meaningful threshold for each behavioural outcome is further complicated by both species-level differences, and within-species variability arising from biological, psychological, environmental and social influences on pain-related behaviours. Both clinical and preclinical research demonstrate that measurable pain-associated outcomes are shaped by interacting intrinsic and extrinsic factors.[70-77] In animal models, these factors include model-specific variables (e.g. species, strain, age, sex, induction method, comorbidities); assessment methods (e.g. incremental vs continuous, electronic filaments for mechanical allodynia; static vs dynamic measures of limb weight-bearing); environmental influences (e.g. acclimatization; stress-induced hyperalgesia or analgesia; assessor experience); social interactions including the social transfer of pain behaviours; and also temporal variability (e.g. disease stage, test duration, acute vs chronic pain states).[10, 63-66, 74, 75, 78-93] Critically, behavioural outcomes may also vary because of individual or overlapping contributions of different underlying pain mechanisms, i.e. nociceptive, neuropathic, or nociplastic processes.[94] Accordingly, the establishment of robust thresholds requires greater methodological harmonization, and development of mechanistic phenotyping frameworks that account for the diversity of species, models, and clinically relevant disease contexts.

Translational implications and opportunities: Defining clinically meaningful thresholds requires consideration of translational effect sizes and study design alignment of (prophylactic vs established disease) between preclinical and clinical research.[16, 95-97] In highly controlled rodent experiments utilising supra-therapeutic doses, relatively large treatment effects are expected but have been proposed as a pragmatic buffer against model limitations and the substantial placebo effects observed in human trials, which may account for more than 35% of the measured response.[16, 52] However, the generalisability of standardised minimum effect sizes across models, interventions, administration routes, and OA joints remains uncertain. In more heterogeneous veterinary populations, smaller effect sizes may be more indicative of human efficacy although quantitative benchmarks remain undefined.[2, 8, 98] A balanced approach which considers both absolute and proportional changes, may facilitate more meaningful cross-study comparisons[99] but there is little evidence that such approaches would improve translation. The interpretation of a meaningful effect should also consider the therapeutic objective and baseline pain severity. For example, interventions targeting severe symptomatic pain may prioritize improvements in function or stimulus evoked hypersensitivity and accept smaller changes as meaningful improvement. In contrast, strategies aimed at earlier disease stages may focus on preventing symptomatic progression or eliminating low grade but persistent symptoms.

Despite the focus on clinically meaningful change, the limited translation of preclinical OA-pain research may partly reflect the disconnect between commonly used experimental models and the human populations they inform.[10, 100] Mechanistic and interventional studies are frequently conducted in young, male rodents under controlled laboratory conditions. In contrast, OA patients are more heterogenous, older and females often report worse pain outcomes.[17-19, 101, 102] Improving model alignment with the intended clinical scenario should be a key consideration and may be complemented by evaluating multiple models/contexts.[103] Naturally occurring OA in veterinary populations offers a useful bridge, capturing biological and environmental variability that better mirrors human disease.[2, 8, 9] Additionally, the diversity of animal models and experimental contexts available (including differences between species, strains, epigenetic influences and experimental conditions) should not necessarily be viewed solely as confounders but may instead provide opportunities to identify distinct components and mediators of OA-pain.[10, 104-106]

Summary: Although the classification of specific pain states can be informative, establishing behavioural thresholds that define “OA-pain”, or a clinically meaningful change in response to intervention, remains inherently challenging. As pain is a multidimensional experience, multimodal assessments are essential to capture the interacting behavioural, functional, and sensory components that contribute to the overall pain phenotype. Rigid thresholds may risk oversimplifying this complexity and, in some cases, could even hinder translation if potentially effective therapies are discarded prematurely before reaching early-phase clinical testing. Overall, it remains critical to interpret the magnitude of change observed in any given study within the clinical context to which its design and outcomes are intended to translate.

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