Q5: What is the role of studies in veterinary populations with clinical osteoarthritis, such as pet dogs or horses, or equine athletes?

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RESPONSE/RECOMMENDATION:
Spontaneous painful osteoarthritis (OA) in companion pet dogs and companion or athletic horses offers translational research potential. Such naturally occurring 'models' are readily available and may better reflect the complex genetic, environmental, temporal, psychological, and physiological influences present in humans. Valid outcome measures relevant to the human pain experience have been developed, and current data suggest the predictive validity of the models is good when assessing putative therapeutics. Given the similarities to human OA and the relative availability of tissue, the opportunity for target discovery exists, but is, as yet, unproven.

LEVEL OF EVIDENCE: Strong

RATIONALE:
Given how prevalent musculoskeletal pain associated with joints, bones and muscles is, it is surprising, that existing pharmacological therapies for chronic, persistent OA pain are rather limited. The current practice of translational biomedical research is not producing novel therapeutics to address this unmet need. [1-3] The failure of translational pain research has been discussed with emphasis on the models and outcome measures in pre-clinical research. [4-9] The majority of preclinical models are induced (i.e., created) to model or mimic the target clinical conditions. While these have increased our mechanistic understanding of disease, they do not appear to have worked as well for selecting new analgesic drug candidates. [3,10] This has led to suggestions to utilize spontaneous disease models in non-rodent animals to help inform pain therapeutic development. [7,11-16]

Clinical OA is common in pet dogs, with recent data indicating at ~40% of the dogs have clinically detectable OA-pain. [17,18] In horses, OA is among the most common causes of lameness, with ~60% of equine lameness related to OA. [19,20] Biomechanically, structurally, histologically, genetically, and molecularly, human, equine and canine OA are similar. [21-29] The burden of disease is remarkably similar between humans and dogs – for example, recent data show that in 'age-equivalent' cohorts, the prevalence of multi-joint OA was almost identical. [30] Equine OA affects horses of all ages and use; in one study, over 80% of geriatric horses had reduced joint range of motion attributed to OA, [31] which is a similar burden to that seen in older people. [32,33]

OA pain occurring naturally in dogs and horses may offer a more accurate representation of the complex interplay between genetic, environmental, psychological, temporal and physiological factors seen in humans than traditional laboratory models, [16] and better represent the human pain experience, which is complex. [34,35] The course of joint disease in companion animals and animal athletes is similar to the course of joint disease in humans. Additionally, the accelerated progression of OA in dogs and horses allows for a more efficient evaluation of long-term effects of interventions compared to work in humans. While the variability and complexity of naturally occurring OA in dogs and horses may be seen as a challenge, the fact that this mirrors the complexity and variability of human OA is also a strength of these models.

For spontaneous models of OA-pain to be useful in translational research, the outcome measures need to have been developed, validated, and should ideally be relevant to the human condition. In pet dogs and horses, outcome measures across multiple domains relevant to humans have been developed and validated: function based on proxy assessments by owners (mirroring validated parent assessments of children); [36-42] objective measures of limb use and gait; [37,43-54] objective measures of activity; [55-59] measures of sensitivity (quantitative sensory testing); [60-66] and, in dogs, measures of cognitive function and affect. [67,68]

Randomized clinical trials (RCTs) in dogs and horses can be designed and conducted with rigor comparable with human RCTs. [69] This strategy can be considered bridging, in contrast to a direct jump from induced animal pain studies to clinical trials in humans, and such work can help inform the go-no-

go (GNG) decision making that is critical in therapeutic development. While companion pets and animal athletes develop OA spontaneously, and therefore represent an ethical, non-induced model, these are privately owned companion animals, and ethical oversight is required. Veterinarians should always be involved with and oversee the care of the individual animals participating in any study. There are a variety of well-equipped veterinary sites (e.g. University Colleges of Veterinary Medicine, Veterinary Referral Centers) with the expertise to participate in well-controlled companion animal studies. Multicentric research is most often necessary to optimize timelines, and homogenizing data collection and analysis across multiple centers is very challenging but facilitated by established networks of institutions (e.g. Clinical and Translational Science Award One Health Alliance (COHA: https://www.ctsaonehealthalliance.org/) that research naturally occurring diseases that affect animals and humans. While the costs per animal associated with running these pre-clinical clinical trials are higher than the per-animal costs associated with rodents, they are very much less than the overall costs associated with human clinical trials – especially when a trial fails.

If the ultimate problem is the failure of rodent research to predict clinical utility, then the question of predictability is critical. Efficacy evaluation(s) in pet dogs with persistent pain may be more predictive of how a drug will perform in Phase II and III human clinical trials, [15] Across many classes of compounds in which there have been studies of chronic pain conditions in companion animals and the same conditions in humans, the analogous results have been seen in the dog [70-75] and horse, [76-79] with the equine model having distinct advantages for the evaluation of intra-articular therapies.

Recent studies of human dorsal root ganglia (DRG) tissues clearly show significant neurobiological differences from rodents, [80] suggesting that assumptions about target validity based on rodent neurobiology should be made cautiously. Tissue is not always easily obtained from humans, however peripheral tissue can be readily obtained from the millions of joint surgeries performed each year on pet dogs, [81] and athletic horses commonly undergoing arthroscopy. [82-84] Furthermore, euthanasia of veterinary species can allow for collection of central nervous system tissues, including DRG tissues.[37,38] Horses donated to research programs for humane euthanasia provide unique advantages, allowing for the collection of articular cartilage and synovial membrane. [85-87] The outcome measures described above are used to phenotype pain in companion and athletic animals, and, when coupled with information garnered from articular and CNS tissues, may point to novel relevant pathways. [84,88-93]

In addition to their translational value, studies conducted in veterinary patients with naturally occurring OA offer important and often under-recognized animal welfare benefits. Unlike traditional laboratory animal models, pet dogs and horses enrolled in veterinary clinical trials already suffer from spontaneous, clinically relevant OA pain that requires medical intervention. They also form social relationships with humans, making their interactions during studies generally positive rather than stressful. Participation in well-designed clinical trials, therefore, aligns scientific objectives with the animal welfare objectives both to reduce overall use of laboratory animals, as well as improve animal health and welfare.

By serving as an intermediate translational step between induced laboratory models and human trials, veterinary studies can inform go/no-go decisions and reduce reliance on additional induced animal experiments, consistent with the principles of Replacement, Reduction, and Refinement (3Rs). From a welfare perspective, enrolled animals receive structured diagnostic evaluations, protocolized monitoring, and potential access to novel or optimized therapeutic interventions under veterinary oversight, frequently exceeding the standard of care available outside the research setting. For owners, participation can reduce financial barriers to advanced diagnostics or management, enabling treatment of painful disease that might otherwise be inadequately addressed. This bidirectional benefit inherent in One Health–oriented research reframes some aspects of veterinary clinical research not as an expansion of animal use, but as a strategic reallocation toward studies that simultaneously advance science and alleviate existing suffering.

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