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Maximising the output of osteoarthritis research: the ARRIVE guidelines

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Osteoarthritis (OA) is a prevalent multifactorial disease which increases with age and following injury; it is primarily characterised by degeneration of articular cartilage and results in joint stiffness and pain. Animal models have been used to understand the pathophysiology of the disease and identify potential treatment targets. However, not all targets identified with *in vivo* models have proven relevant for treating human disease[1]. Many questions also remain unanswered, with regards for example to cartilage repair, the mechanisms involved in pain or matrix-degrading proteases regulation. A plethora of animal models, which differ in etiopathology and severity have been developed but there is no 'gold standard' that encompasses every aspect of OA. Joint instability can be induced by surgical or chemical techniques in a number of animal species including rats, mice, guinea pigs, rabbits, dogs and sheep. Spontaneous models also exist and more recently genetically modified mouse models have been used[2].

The OA community has been working together to improve the utility of animal models with efforts focused in two directions: harmonisation of experimental methods and outcomes, and critical assessment of the *in vivo* models. The OARSI histopathology initiative, which started a decade ago, aims to standardise the scoring systems used in the evaluation of the OA disease process[3], in order to make results between different studies comparable. Other initiatives have attempted to characterise *in vivo* models of OA and link models to disease mechanisms; two relatively recent initiatives have been led by the Canadian Arthritis Network in collaboration with OsteoArthritis Research Society International (OARSI)[4], and Arthritis Research UK[5].

A common goal of these projects is to improve the efficiency of research in the OA field and their success crucially depends on the transparency in the methods and conduct of animal experiments. Comprehensive reporting is essential to enable models to be characterised and

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Conflict of interest

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experimental outcomes to be standardised. However, as shown in a survey of over 270 studies covering a wide range of experimental fields, carried out by the UK National Centre for the Replacement, Refinement and Reduction of animals in research (NC3Rs), many aspects of an animal experiment are not included in publications[6]. This compromises the peer review process, limits the interpretation that can be drawn from a study, and prevents peers from replicating and building on the findings. To improve the reporting of animal research, the NC3Rs has developed the ARRIVE (Animal Research, Reporting of *In Vivo* Experiments) guidelines[7] (www.nc3rs.org.uk/ARRIVE). The guidelines consist of a 20 items checklist of the key information that should be included in a manuscript to ensure that a study can be reviewed, scrutinised and reproduced.

Specifically, the guidelines recommend including sufficient scientific background to understand the motivation and context for the study and a clear description of the objective. They include a detailed description of the study design including steps taken to minimise subjective bias, such as randomisation of the animals into experimental groups and concealment of treatment while assessing the outcome. Failure to include such steps in a study can compromise the validity of the results, as recently demonstrated in a systematic review looking the effectiveness of potential treatments in animal models of multiple sclerosis. Non-randomised studies were found to report significantly higher efficacy than randomised studies. Similarly, studies which did not blind the assessment of outcome reported higher estimates of efficacy than blinded studies[8].

The ARRIVE guidelines also recommend a comprehensive description of the experimental procedures and animal characteristics and housing. These details are extremely relevant for animal models of OA as disease development or severity often depends on animal characteristics such as gender, age or strain. For example, in a murine model using surgical destabilisation of the medial meniscus to induce the disease, severity has been shown to depend on sex and wild-type strain, as male hormones were shown to exacerbate OA[9] and the 129SvEv strain was associated with a more severe form of the disease[10]. Considering that age is a risk factor for humans, it is perhaps not surprising that 12-month-old mice developed more severe OA lesions and expressed transcriptional differences in their joints compared to 12-week-old mice[11], crucially however this highlights the importance of reporting such animal characteristics to ensure that results are comparable between studies.

Experimental procedures should specify how, when, where the experiment was carried out and why it was carried out that way. Particularly relevant for models using surgical techniques, this includes details about the conduct of the surgery and the anaesthesia and analgesia protocol. Pain is an inherent part of human OA and murine models provide a system to elucidate the mechanisms responsible for OA pain and to identify potential treatments (e.g., Ref. [12]). It is however important to consider that both sex and strain have been identified as confounding factors in the pain response, both in nociception and anti-nociception[13]. Additionally, the type of anaesthetic or post-surgical analgesic used may influence OA-induced pain. All these variables should therefore be available in the publication, as scientific peers will need this information to interpret the results and the implications of the study.

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The ARRIVE guidelines also include reference to describing the housing and husbandry conditions, which may seem like a lot of information to report in a publication, but seemingly irrelevant features such as the number of cage companions, bedding materials, environmental enrichment or food composition have the potential to influence the outcome of OA experiments. For example, group housing has been shown to influence many physiological markers and alkaline phosphatase, a marker of osteoblast activity[14], is lowered in animals that are housed in groups[15]. In Sprague Dawley rats, the type of bedding can modulate levels of antioxidants such as ascorbic acid and glutathione[16], both of which have a role in human OA[17]. In addition, different types of environmental enrichment devices, from plastic tubes to running wheels, have been shown to influence the severity of OA by modifying the activity level of mice[18,19]. Finally, both the type of food and the access to food are important variables to include in publications reporting experiments on OA models as this is linked to obesity, a well recognised risk factor in human OA. High-fat diet has been shown to induce knee OA in mice[19] and there is evidence that providing laboratory rodents with continuous access to food leads to obesity[20].

Finally, the guidelines provide recommendations on how to report experimental results, including adverse effects and details about the statistical analysis. They also include suggestions about what should be reported in the discussion, such as the study limitations, the scientific implications and how the findings of the study are likely to translate to other species and their relevance to humans. These recommendations are not new to Osteoarthritis and Cartilage readers as the journal already advocates such reporting standards, which have been the subject of several recent editorials[21,22]. The journal's decision to endorse the ARRIVE guidelines and republish them in this issue sends a strong signal in terms of the quality of animal research expected in OA. Comprehensive and transparent reporting will in turn facilitate the task of harmonising and mapping the pathogenesis of OA models, to ensure that preclinical research translate into successful treatment strategies in humans.

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