

# Researchers examine effects of federal recommendations on cartilage repair studies in large animal models

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More than 21 million people in the United States suffer from cartilage damage, and if left untreated, cartilage defects can cause disability and more widespread joint disease. In recent years, scientists have focused on development of new treatments for cartilage repair. But in the past two decades there has been little to no adherence to the recommendations published by U.S. and European regulatory agencies on the manner in which translational research is conducted and reported in large animal models used to study cartilage repair. A team led by researchers from the Perelman School of Medicine at the University of Pennsylvania detailed their findings, and their recommendations for better compliance, in a paper published in this week's *Science Translational Medicine*.

The team analyzed three sets of regulatory guidance documents published by the U.S. Food and Drug Administration, the European Medicines Agency, and the American Society for Testing and Materials, which provide recommendations on how large animal studies should be performed and reported in order to streamline translation to clinical trials. The team evaluated 114 large animal studies - specifically [cartilage repair](#) in horses, sheep, pigs, dogs, and goats - published over the past two decades to determine whether researchers were conducting and reporting on all of the data points recommended in these guidelines. Studies were scored based on adherence to 24 categories extracted from the guidance documents, relating to set up and description of the model -

such as animal age, gender, and weight, as well as study duration and lesion size - and to the methods used for determining successful outcomes - including tissue and immune response, and whether a follow-up MRI or clinical evaluation were performed. Results showed that there was little to no impact of the publication of the guidance documents on the level of adherence of the large animal studies reviewed.

"When we started this project, we assumed that there would be strong positive correlation between the publication of the guidance documents and the level of adherence to these guidelines following publication," said Robert Mauck, PhD, an associate professor of Orthopedic Surgery and Bioengineering and director of Penn's McKay Orthopaedic Research Laboratory. "However when we completed our analysis, we were surprised to find that for the large animal studies we examined, most did not follow the guidelines to any great extent. This got us thinking about the reasons behind the lack of adherence, and the steps that could be taken to help the field more closely align with these recommendations."

Through their analysis, the research team, which also included Christian Pfeifer, MD, of the Regensburg University Medical Center and Matthew Fisher, PhD, of North Carolina State University and the University of North Carolina at Chapel Hill, former postdoctoral fellows in the McKay Orthopaedic Research Laboratory, found that study descriptor categories were met at an adherence rate of approximately 75 percent. However, adherence fell to roughly 40 percent when evaluating study outcomes. The team noted that these measured outcomes—whether they were performed or not—are often influenced by a study's goals. And finances, study duration, and study outcomes often differed greatly depending on whether the study examined was a pilot trial or a larger study.

Researchers note that while the larger, so-called pivotal trials are the most informative for translational studies, pilot trials are equally as important for the development of new treatments. However, this study

suggests that there should be definitive classifications for pilot trials to better differentiate the two approaches, and to highlight those studies that are closer to impacting clinical practice.

"An additional level of adherence to guidance documents will ultimately improve translation from large animal models to human trials," said James L. Carey, MD, MPH, an assistant professor of Orthopaedic Surgery and director of the Penn Center for Advanced Cartilage Repair and Osteochondritis Dissecans Treatment. "With such a considerable focus of developing new treatments for cartilage repair, critical evaluation of pivotal large animal models can often highlight the safety and efficacy of these emerging therapies. For these studies to be most efficacious, we should all focus efforts on outcomes that are most important in predicting success for clinical translation."

The team of researchers included one of their own recent large animal studies in their analysis, and found their results to be in line with the rest of the field: 73 percent adherence for study descriptors, 42 percent for study outcomes, and 56 percent for overall [adherence](#) to recommendations. Based on their data and experiences in translational large animal studies, the team concluded that the field lacks a consensus for measuring and reporting study outcomes, and suggests that additional resources be focused on this field and a standardized reporting structure be implemented and followed, in order to increase the pace of translation of promising new therapies into clinical trials.

**More information:** Impact of guidance documents on translational large animal studies of cartilage repair, [stm.sciencemag.org/lookup/doi/.../scitranslmed.aac7019](http://stm.sciencemag.org/lookup/doi/.../scitranslmed.aac7019)

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