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Companion Animal Studies: Slipping Through a Research Oversight Gap

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In human subject research ethics, we appeal to principles of respect for persons, beneficence, and justice. In laboratory animal studies, the three Rs (reduce, refine, replace) are key touchstones, along with an overarching principle of promoting animal welfare—when consistent with the needs of science and within the constraints introduced by the institutional setting. Underlying these different approaches to research oversight are moral status assumptions regarding human and nonhuman animals. Independently of whether appeals to moral status are a specious mechanism to differentiate the two research contexts, there are important structural differences in how the research is typically conducted: in an animal "confinement" facility where conditions are controlled and consent need not be sought, versus with human participants in society whose consent and active compliance is critical.

The featured companion animal longevity study (CALS) falls in a liminal space between these human and nonhuman animal practices and highlights the ethical tensions produced by compartmentalizing these two domains of research oversight. As nonhuman animals in research, dogs are typically regulated by laboratory animal oversight. However, the study's structural features to test the efficacy of rapamycin in increasing dogs' longevity and "health span" more closely reflect those of human clinical trials. While some institutions require additional ethical oversight of companion animal studies (Hampshire 2003), this is a relatively ad hoc solution to the oversight problem. We identify here several particular ethical concerns with CALS that raise important questions about companion animal studies more generally.

In the United States, oversight of animal research is typically conducted by institutional animal care and use committees (IACUCs), which are mandated both by the Animal Welfare Act and by the Public Health Service. Yet, this oversight structure generally contains features that may limit the protections that animals receive (Walker 2006). Most relevant for CALS, IACUC review, unlike in human subject research, does not require a risk–benefit analysis of individual animal research protocols (Carbone 2014). While federal funding mechanisms require assessment of the science value of the research, this is not the same as balancing potential (or actual) harms to animals with proposed benefit to animals and humans. Further, for studies that are funded by private sources—as studies like CALS are likely to be—even an impartial science value assessment may be missing. Similarly, the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) requires evidence of a "rational basis" to undertake companion animal clinical trials (Hampshire 2003, 193) and subsequent reporting of any adverse experiences, but this also does not amount to a risk–benefit analysis. Further, it is unclear from the case description whether CALS falls under CVM oversight, which is applicable when drug sponsors seek approval for a new animal drug application.

An important ethical question for CALS, then, is whether an impartial analysis would determine that the risks to the study dogs are justified by the potential for benefit to these animals, other animals, and/or society generally. Leaving aside larger social questions of the value of longevity research, we may focus on the concrete harms and benefits at issue in this study. Because the dogs proposed for inclusion are healthy, the analogue risk assessment in human trials would set a higher bar for acceptable risks. It would also warrant independent data and safety monitoring to ensure that participants are protected from unnecessary harm and that objective criteria determine rules for the study's discontinuation should harms prove unacceptable. While the CALS case presentation states that there is "no information" available about potential adverse effects of rapamycin in dogs, it is more correct to say that such information is limited. Studies have shown severe adverse effects in dogs, including death, with high dosage (aimed at immune suppression), but rapamycin has been well tolerated at low doses for up to 10 weeks (Urfer et al. 2017; Larson et al. 2016). As CALS is a 3-year intervention, it is all the more crucial within a risk–benefit analysis to consider how and when to withdraw dogs or to stop the entire trial should safety concerns emerge (or, for that matter, clear evidence of drug benefit). Human trials are a much better guide than is

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laboratory animal practice for setting "humane endpoints" to companion animal studies since laboratory practices typically dictate euthanasia as the appropriate endpoint.

On the benefits side of the calculus, CALS's aim of increased health span in particular, while raising the specter of enhancement, potentially offers individual direct benefit (avoiding disability in dogs' older years) alongside a hope of meaningful benefit to other companion animals and, eventually, humans. The animals' guardians (legally "owners"), too, might benefit by facing fewer veterinary costs for and/or gaining more time with their dogs. Yet it is important to recall that although rapamycin is an approved immune-suppressive and anticancer drug in human medicine, it has not been FDA approved either for veterinary use or for the off-label use of increasing longevity and health span in either humans or companion animals.

Although laboratory animal research in the United States could offer risk (or harm)–benefit analysis as a regular part of its oversight (as occurs in the European Union), this would not close the gap in regard to companion animal research. Specifically, there is little room in the framework of conventional animal research oversight to account for other ethical considerations that make companion animal research structurally more like human clinical trials. For example, because biomedical research institutions "own" their laboratory animals, no outside consent to research participation is sought. In any companion animal study, however, there should be a robust consent process involving the guardians of the animals.

As part of a consent process in a study like CALS, many of the ethical complexities typical to human subject research will arise. The potential for both therapeutic misconception and undue inducement are significant, particularly if investigators emphasize that rapamycin is already FDA approved for human use. While the notion of a therapeutic misconception is perhaps odd for healthy dogs, the animals' guardians, despite the lack of evidence, may expect a longevity benefit. Moreover, such a perception may result from the, perhaps unwitting, enthusiasm of the investigators. The potential for undue inducement arises because of the high cost of commercially available rapamycin combined with insufficient attention to the likely risk of harms. Relatedly, borrowing from a human subject framework, CALS might also be said to require a plan for post-trial provision of the study drug. At the conclusion of the 3-year period, if enrolled dogs have benefited from rapamycin, provision of this expensive drug is important to consider, particularly for those dogs randomized to the placebo group.

Important ethical considerations raised in CALS reveal the inadequacy of the system of laboratory animal research oversight to protect companion animals and their guardians. These are significant concerns, particularly when coupled with the science value question of whether CALS's enhancement orientation and healthspan gains should even be perceived as potential medical benefits. Leaving contentious social issues of enhancement aside, CALS illuminates a gap between the oversight of laboratory animal and human subject research. What is the rationale, we might wonder, of two separate oversight systems based on unstated moral status assumptions, rather than a unified system that attends to structural factors in the science and offers respect for all subjects? ■

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