Rise for Animals.

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Office of Science Policy
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RE: Request for Information (RFI): Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research

To whom it may concern:

Rise for Animals supports the abolition of all nonhuman animal experimentation, research, and testing – irrespective of human benefit or utility – and, therefore, supports the NIH's interest in human-relevant new approach technologies ("NAMs") that do not not require or promote the use, exploitation, and harm of nonhuman animals.

The NIH has long known – *and* even admitted – that the use of nonhuman animals for research intended to benefit humans is both misguided and ineffective. Yet, despite publicly acknowledging the "low yield of animal research in benefiting human health" and recommending NAMs as "funding priorities",[1] the NIH has remained the largest funder of nonhuman animal research worldwide. As such – i.e., in facilitating, encouraging, and rendering profitable nonhuman animal research – the NIH continually reinforces the entrenched, dogmatic illusion of such research being both necessary and beneficial to human welfare,[2] *despite* science having proven it to be neither. By way of example only:

- Nonhuman models "have a predictive value below 50%, making them less informative than a coin flip and rendering them of no practical use in predicting human outcomes".[3]

- Up to 89% of preclinical, nonhuman animal research is unreliable.[4]

- Over 95% of potential new drugs fail during clinical trials because of safety or efficacy concerns that were not predicted by preclinical nonhuman animal research.[5]

- The unreliability and irreproducibility of nonhuman animal studies costs the U.S. more than $28 billion per year,[6] with billions of dollars of this funding provided by the NIH.[7]

This submission serves as a call by Rise for Animals for the NIH to align its words and scientific findings with its actions by embracing "scientific antivivisectionism" – "rejection of the idea of the transferability of results from one species to another"[8] – and prioritizing the development, validation, acceptance, and implementation of NAMs. To do so, the NIH must commit to overcoming existing, self-imposed hurdles to the embrace of NAMs by the broader scientific community:

The NIH must shift funding from nonhuman animal research to human-relevant research.

As the world's largest funder of nonhuman animal research, the NIH is a primary driver of the scientific research agenda in the U.S. and abroad. Unfortunately, historically and continuing into the present, the NIH has chosen to squander a vast amount of its research budget by investing in nonhuman animal research *rather than* earmarking these funds for human-relevant research methodologies based on human biology – i.e., rather than investing in the the development, validation, acceptance, and implementation of NAMs.[9] Indeed, "[f]inancial investments in the study of [NAMs] pale in comparison with investments in animal experimentation",[10] and this has had the deleterious effect of both directly encouraging researchers to retain nonhuman animal models (in pursuit of such NIH funding and, thereby, professional self-interest) and indirectly playing to researchers' cognitive bias, which, in overvaluing familiarity and routine, underpins their reliance on nonhuman animal subjects.[11]

Moreover, because progress in the development of NAMs is limited by the availability of funding,[12] the NIH's funding scheme has hobbled and continues to actively hobble NAMs' development, validation, acceptance, and implementation. It follows that, to shift the scientific community away from nonhuman animal research and towards human-relevant NAMs, the NIH must vote with its dollars by prioritizing NAMs research and deprioritizing (if not outright discontinuing) nonhuman animal research funding. It is incumbent upon the NIH to establish a "targeted funding strategy" that includes *and* extends beyond NAMs' development to include "funding for implementing and validating NAMs",[13] as well as the training of researchers about and the access of researchers' to NAMs.[14]

The NIH must dethrone the nonhuman animal model as the "gold standard".

The NIH's treatment of nonhuman animal research methodologies as the preclinical "gold standard"[15] is severely impeding the development, validation, acceptance, and implementation of NAMs.[16] To be sure, before NAMs may be approved for use, they must be "shown to be at least as effective as methods they are designed to replace",[17] *despite* the very real fact that "the methods they are designed to replace" (i.e., nonhuman animal models) have never "been formally validated" in any (much less a similar) way.[18]

The successful realization of NAMs necessarily requires that their data not be assessed via comparison to nonhuman animal model data, which has been found to be neither predictive for humans, nor reliable or reproducible.[19] Instead, NAMs data should, as researchers themselves have concluded, be compared to human-specific data[20]: "Assessment of the biological relevance of the NAM should focus on its alignment with human biology, mechanistic understanding, and ability to provide information that leads to health protective decisions, rather than solely comparing NAM-based chemical testing results with those from traditional animal test methods."[21] This is to say that the NIH must render human data its "gold standard"[22] and establish a regulatory framework specific to the evaluation of NAMs.[23]

The NIH must amend its regulations to further the interests of NAMs.

Shifting funding to NAMS and officially acknowledging, both theoretically and practically, that nonhuman animal models shall no longer serve as the scientific "gold standard" must be the NIH's first steps *only*. Indeed, many reasons exist for the persistence of nonhuman animal research even when superior NAMs

exist, including "bureaucracy, political malaise, and entrenchment in the scientific establishment".[24] To overcome these impediments to NAMS development, validation, acceptance, and implementation, the NIH must:

- **Expunge any actual or perceived regulatory requirement that research be performed on nonhuman animals when "new animal-free, human-relevant methods" are available, *and* require that available NAMs be utilized instead of nonhuman animal methods**.[25] Taken together, these measures would allow the NIH to overcome "major barriers to achieving change", as the animal research industry will remain "reluctant to invest in NAMs if [] results are unlikely to be accepted."[26]

- **Pilot a binding clarification of the 3Rs that meaningfully and unequivocally identifies "replacement" as the top priority**.[27] Researchers should be neither encouraged nor permitted to give "refinement" and "reduction" priority over "replacement"[28]; to this end, researchers' interests in studying "entire, functioning bodily systems"[29] should not be permitted to overshadow the irrefutable recognition that nonhuman animals' systems do not model human systems (that researchers are using "the wrong living system") – i.e., researchers may not be permitted to choose complexity over relevance.[30]

- **Avow and direct that not all nonhuman animal models must be replaced** – that the use of many such models be discontinued immediately[31] *regardless* of the availability of a substitute NAM[32] – **and prohibit the ongoing use of nonhuman animal models that have failed to demonstrate "satisfactory predictive value for humans"**.[33]

- **Establish, and require inter-laboratory sharing via, a preclinical database**. Recipients of grant funding should be required to share their research data and findings with peers via an open-access database, such a database having the potential "to revolutionize the evaluation of both old and new technologies through statistical comparisons with a gold mine of millions of data points."[34]

Through the adoption of scientific antivivisectionism and the use of its considerable authority and resources to facilitate (and, concomitantly, mandate) the development, validation, acceptance, and implementation of NAMs, the NIH has the opportunity to act in the interests of both humans and nonhumans. It is Rise for Animals' fervent hope that it does so.

For the animals,

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Endnotes

1. Keen, J. (2019). Wasted Money in United States Biomedical and Agricultural Animal Research. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 244-272). essay, Brill (quoting Francis Collins and Elias Zerhouni, the latter stating that "[w]e need to refocus and adapt new methodologies for use in humans to understand disease biology in humans").

2. Ram, Rebecca. (2019). Extrapolation of Animal Research Data to Humans: An Analysis of the Evidence. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 341-375). essay, Brill (stating that the use of nonhuman animals "is the only area of scientific research where the same dated techniques are still being used 60-70 years later, despite their limitations being well known. No other area of science continues to use such a dogmatic approach.").

3. Greek, R., & Kramer, L. (2019). How to Evaluate the Science of Non-human Animal Use in Biomedical Research and Testing: A Proposed Format for Debate. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 65-87). essay, Brill (stating that, "[w]hen human health is involved low predictive value means anything below 90-95%" and that "[b]ased on evolved complex systems, evolution, and empirical data, animal models, overall, do not and cannot have a numeric predictive value above about 50%; and, hence, for all practical purposes, they have no predictive value."); *id.* ("The paradigm of animal modeling is not scientifically viable for predicting human response to drugs and diseases, and, thus, animal models should not be used to predict human responses to drugs and disease."); *id.* (noting that no species "regardless of genetic similarity, will ever be similar enough to another to serve as a valid predictive model. That is, according to science, the observation of a drug response in one species is uninformative about the drug response in another species.").

4. Keen, J. (2019).

5. *See, e.g.,* Archibald, K., Coleman, R., & Drake, T. (2019). Replacing Animal Tests to Improve Safety for Humans. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 341-375). essay, Brill.

6. Herrmann, K. (2019). Refinement on the Way Towards Replacement: Are We Doing What We Can? In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 3–64). essay, Brill.

7. Greek, R., & Kramer, L. (2019); *see* Keen, J. (2019) (estimated that $5-9 billion dollars of taxpayer money are spent on biomedical and agricultural nonhuman animal research each year).

8. Ferrari, A. (2019). Contesting Animal Experimentation through Ethics and Epistemology: In Defense of a Political Critique of Animal Experimentation. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 194-206). essay, Brill (explaining further that, according to this rationale, "modern animal models are of limited use and can even be dangerous because the data produced are not easily translatable to humans").

9. *See* Keen, J. (2019). ("Animal research squanders precious public and private monies directly, indirectly, by opportunity cost, and by unintended negative consequences."); *see also* Archibald, K., Coleman, R., & Drake, T. (2019) ("When the costs of withdrawn and restricted drugs, as well as the failures during development, are factored into the total cost of developing a successful new drug, this results in an estimated average of $4 billion and could reach as high as $12 billion.").

10. Akhtar, A. (2012). *Animals and Public Health: Why Treating Animals Better is Critical to Human Welfare*. Palgrave Macmillan, at 162 (noting further than "the US Government's agencies have spent less than $10 million over a ten-year period on validating alternatives for regulatory use, and validating alternative methods is rarely a priority for government funding. The development of human-based alternatives to animal research is an underdeveloped field largely because so few resources are devoted to its development as a result of our commitment to animal-based methods.").

11. Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022). Identifying Key Factors for Accelerating the Transition to Animal-Testing-Free Medical Science through Co-creative, Interdisciplinary Learning between Students and Teachers. *Animals*, 12(20), 2757. https://doi.org/10.3390/ani12202757 (" . . . increased funding and investments in animal models could serve as lock-in mechanism" that hinders transition to NAMs); Keen, J. (2019) (defining the "law of the hammer" as "a cognitive bias involving over-reliance on a familiar tool" and describing it to be "invoked by the overwhelming preclinical tendency to use animal models in spite of their near universal transition failure").

12. Herrmann, K. (2019) (noting further that "replacement" research "has to compete with refinement research for limited funds").

13. Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) (specifying the need for "comprehensive validation of models before commercialisation").

14. *See* Herrmann, K. (2019); von Aulock, S. (2022). Engagement of scientists with the public and policymakers to promote alternative methods. *ALTEX*, 543–559. https://doi.org/10.14573/altex.2209261 (asserting that scientists working on "animal-free, human-biology-based methods" need to "present and defend their world . . . to inspire and inform peers of the technological opportunities offered by these methods and approaches . . . Such communication with peers will be most effective when based on strong scientific arguments addressed to fellow scientists from unrelated fields, who may not yet realize that their work could find application in the replacement of animal use.").

15. Akhtar, A. (2012), at 162 (acknowledging that nonhuman animal experimentation is accepted as the "'gold standard' .. . based on tradition, rather than proven efficacy"); Blattner, C. (2019). Rethinking the 3Rs: From Whitewashing to Rights.In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 168-193). essay, Brill; *see* Ferrari, A. (2019) (acknowledging that biomedical researchers consider nonhuman animal research as the "best scientific standard"); Kramer, K. (2023). When Is Something an Alternative? A General Account Applied to Animal-Free Alternatives to Animal Research. *Cambridge Quarterly of Healthcare Ethics*, 1–13. https://doi.org/10.1017/s0963180123000300.

16. *See* Gluck, G. (2019) *Afterword: Evidence Over Interests*. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 389-691). essay, Brill ("The tendency of scientists to confer authority to 'established' theories and methods have been the central factor in the delay of medical progress, and so it is now with much of the work in animal research."); Hartung, T. (2019), *Research and Testing Without Animals: Where Are We Now and Where Are We Heading?* In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 673-687). essay, Brill ("The major obstacle for the development of new non-animal methods is the prevailing over-reliance on the value of animal-based procedures as an information source....").

17. Archibald, K., Coleman, R., & Drake, T. (2019) (stating also: "The formal process of test-method validation is so slow, expensive, and demanding in its current format that it represents an effective block to testing existing methods and a significant barrier to testing new methods. This situation is further complicated by the fact that the 'gold standard' with which new data must be compared is usually animal data that is of unknown value."); *see* Kramer, K. (2023) (noting that "it is unreasonable to expect an alternative to Y to have a high chance of success if Y is not a very effective solution either. It deserves note here that animal research has proven not to be highly reliable, in many areas of biomedical research....").

18. Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) (stating that "animal studies have never been validated according to the newly formulated strict requirements for NAMs"); Akhtar, A. (2012) (""Another major hurdle to the development and use of non-animal testing methods is that government regulations tend to require far more validation than was ever required, if at all, for the animal experimental methods they are intended to replace. Ironically, these new methods are often required to be validated against existing animal experimental methods, most of which have never been validated themselves. This creates a double-standard that allows the acceptance of most animal experimental methods as the 'gold standard' (based on tradition, rather than proven efficacy), providing a disincentive to the development of alternative methods."); Archibald, K., Coleman, R., & Drake, T. (2019) (stating also: "The formal process of test-method validation is so slow, expensive, and demanding in its current format that it represents an effective block to testing existing methods and a significant barrier to testing new methods. This situation is further

complicated by the fact that the 'gold standard' with which new data must be compared is usually animal data that is of unknown value."); *see id.* (stating that it can no longer be justified to use "testing methods that have never been validated, while novel methods must demonstrate a level of performance that current methods not only have never been asked to perform but are clearly unable to perform").

19. Blattner, C. (2019) (stating that "we are waiting to abandon a test that does not work until we can find one that does"); *see id.* (further noting that NAMs must be validated against existing nonhuman animal models); *see* Akhtar, A. (2012), at 163 ("An even bigger problem with policies requiring the validating of human-based tests against animal experiments is that the latter are unlikely to predict human responses consistently, and may not even be consistent in general. Thus a human-based model might actually be consistent and predict human responses but would fail validation, while it is the animal test that is in fact inferior."); Archibald, K., Coleman, R., & Drake, T. (2019) (stating that new technologies are "assessed on how well they can predict" animal data, "thus ensuring that they cannot succeed if the drug affects animals differently from humans, which we now know is very often the case."); Greek, C. R., Greek, J. S., & Goodall, J. (2003). *Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals*. Continuum, at 57 ("Even an FDA official confessed that 'most of the animal tests we accept have never been validated . . . the FDA is comfortable with them.'").

20. Archibald, K., Coleman, R., & Drake, T. (2019) (asserting that new methods must "be evaluated using historical 'legacy' data", by "studying the safety profiles of drugs that have been extensively used in human subjects....").

21. van der Zalm, A. J., Barroso, J., Browne, P., Casey, W., Gordon, J., Henry, T. R., Kleinstreuer, N. C., Lowit, A. B., Perron, M., & Clippinger, A. J. (2022). A framework for establishing scientific confidence in new approach methodologies. *Archives of Toxicology*, *96*(11), 2865–2879. https://doi.org/10.1007/s00204-022-03365-4 (noting also that, " . . . the predictive capacity has usually been determined through comparison to results from traditional animal test methods, for which reproducibility and human biological relevance were often assumed rather than empirically demonstrated.").

22. *See, e.g.,* Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) (identifying "in vivo human data" as the "'gold standard' reference"); van der Zalm, A. J., Barroso, J., Browne, P., Casey, W., Gordon, J., Henry, T. R., Kleinstreuer, N. C., Lowit, A. B., Perron, M., & Clippinger, A. J. (2022) (referring to "human [] data" as "the gold standard").

23. *See* Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) ("Opportunities to promote further innovation and validation of NAMs lie in the funding of these models, as well as the formulation of a list for clear transition objectives for different fields of research that aim towards phasing out animal testing."); van der Zalm, A. J., Barroso, J., Browne, P., Casey, W., Gordon, J., Henry, T. R., Kleinstreuer, N. C., Lowit, A. B., Perron, M., & Clippinger, A. J. (2022) (" . . . many regulatory data requirements were written to be fulfilled by test methods available at the time (i.e., traditional animal test methods). These statutes have complicated gaining regulatory acceptance of NAMs that may not provide identical information to the traditional animal test methods, even if the information provided by the NAMs may in fact be more human relevant and health protective. Such practical limitations must be addressed to establish scientific confidence in, and maximize the use of, NAMS in human health assessments."); *see id*. ("An updated framework, designed specifically for establishing scientific confidence in NAMs, should ensure that NAMs are fit for purpose (i.e., fulfill the intended purpose) and provide technically reliable information that is relevant to the understanding of human biology and health protective for the endpoint of concern . . . The process should recognize that the results of the NAM need not directly align with the results of the traditional animal test. Additionally, the NAM need not produce the same information generated by the traditional test method...."); *id.* (laying out a "framework for evaluating NAMs" that "is expected to increase scientific confidence in, and thus the adoption and uptake of, NAMs across regulatory jurisdictions and chemical sectors.").

24. Taylor, K. (2019). Recent Developments in Alternatives to Animal Testing. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 583-609). essay, Brill.

25. Akhtar, A. (2012), at 163 (" . . . a final hurdle is that regulatory agencies do not usually mandate the use of alternative testing methods, where they exist and have been proven valid, in place of the traditional animal experiments. Thus, there is little incentive for pharmaceutical companies and others to switch gears and use alternative methods in research and drug development if they are already wedded to an animal model. Arguably,

there has been a net loss of ground because alternative human-based methods, which would have likely gotten us further scientifically, have been neglected in favor of animal experimentation . . . It is incumbent upon investigators and research-supporting institutions to prioritize the replacement of animals in experiments."); *id* (suggesting also that "a serious and primary dedication to development of nonanimal testing methods" be demanded); Archibald, K., Coleman, R., & Drake, T. (2019) (citing evidence that "shows that animal methods are often still used . . . even when superior validated methods are available"); *see* Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) (" . . . in the current regime, the lack of implementation of animal-free models is associated with the collective belief in the translational value of animal studies, which are still seen as the best comparator, despite the fact that there is abundant evidence for the reproducibility and translatability issues, such as the reproducibility crisis." (internal citation omitted)).

26. Ram, Rebecca. (2019); Archibald, K., Coleman, R., & Drake, T. (2019) ("Pharmaceutical companies would make much greater use of new methods if governments encouraged it, but inflexible requirements for animal tests are a major deterrent. Reliance on animals is so entrenched and institutionalized that the system is 'locked in', and intervention is necessary to overcome the many factors contributing to entrenchment against change."); *see* Akhtar, A. (2012) (stating that the treatment of "animal experimental methods as the 'gold standard'" has provided a "disincentive to the development of alternative methods").

27. *See* Blattner, C. (2019); Redmond, C. (2019). *When Is an Alternative Not an Alternative? Supporting Progress for Absolute Replacement of Animals in Science.* In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 654-672). essay, Brill ("There needs to be honesty among regulators and the research community that the use of any animal product is not a complete replacement or an alternative, only then can there be encouragement to fully replace animal testing with ethical and reliable human-relevant models."); Kramer, K. (2023) ("The first of the famous '3Rs' from animal research ethics essentially stipulates that experiments on animals, where possible, should be replaced by tests on entities that cannot suffer from being experimented on–reducing the number of animals used and refining experiments becomes relevant only when animal experiments are indicated at all. Although the original formulation of the 3Rs . . . avoided using the world 'alternative,' this first R has come to be interpreted as prescribing the substitution of animal experiments by animal-free alternatives.").

28. Blattner, C. (2019) (noting further that the "political and legal preoccupation with refinement and reduction shifts the focus away from where it should be" (i.e., on replacement)).

29. Carvalho, C., Alves, D., Knight, A., & Vincente, L. (2019). Is Animal-based Biomedical Research Being Used in Its Original Context. In K. Hermann & K. Jayne (Eds.), *Animal Experimentation: Working towards a paradigm change* (pp. 377-390). essay, Brill.

30. Ram, Rebecca. (2019) (identifying the desire to study entire, functioning bodily systems" as one of the "main obstacle[s] to the total replacement of animal use in biomedical research"); *see* Greek, R., & Kramer, L. (2019) (discussing the Trans-Species Modeling Theory and complexity science, which posits that a complex system is nonsimulable, and noting that "it is outside the realm of science to use one complex system in expectation of its having predictive value for another, when the perturbation affects higher levels of organization"); *see also* Hartung, T. (2019) ("Ultimately, all alternative approaches come with limitations, too; but, compared to animal models, these limitations can be surmounted by combining these new advanced animal-free methods.").

31. Ram, Rebecca. (2019); *see* Greek, R., & Kramer, L. (2019) ("Given that non-human animal models have unacceptably low predictive value for human responses to drugs and disease, the use of animal models in drug development and disease research could be abandoned immediately for the same reasons that society has abandoned wrong or harmful practices such as phrenology, bloodletting, and trephination–they were simply ineffective."); Taylor, K. (2019) (asserting that "reduction" in nonhuman animal testing will not always rely on "replacement": "If we change the goal to one of improving the humanity and quality of medical knowledge, rather than replacing like for like, then a significant proportion of animal research could end today."); *see* Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) ("It is essential to realise [sic] that one-to-one replacement (replacing one animal test with one alternative test) may not be the only way forward and that an entirely new approach should be adopted....").

32. *See* Akhtar, A. (2012), at 163 (" . . . many experiments currently being conducted could be eliminated today...."); von Aulock, S. (2022).

33. Herrmann, K. (2019) (asserting that the absence of funding for nonpredictive nonhuman animal models would likely result in a "significant reduction of animal use and, thus, [] an increased effort to find more animal-free, robust, human biology based methods."); *see* Akhtar, A. (2012) (arguing for the "identification and immediate replacement of animal experiments agreed to be highly irrelevant to human health"); Greek, R., & Kramer, L. (2019) ("Since animal models do not have predictive value for human outcomes, their use should be abandoned . . . Animal models do not have predictive value in determining human responses to drugs, and their use must be halted independent of whether an alternative exists."); *see also* Kramer, K. (2023) (noting the criticism that NAMs "in practice, are often applied as *an addition to* rather than as a *replacement of* animal experiments....").

34. Archibald, K., Coleman, R., & Drake, T. (2019); *see* Abarkan, F. Z., Wijen, A. M., van Eijden, R. M., Struijs, F., Dennis, P., Ritskes-Hoitinga, M., & Visseren-Hamakers, I. (2022) (identifying the "lack of communication" within the scientific community as an impediment to the shift away from nonhuman animal models, and connecting the performance of systematic reviews by researchers with "an increased awareness of the limitations of animal studies"); *id*. (" . . . focus group attendees noted the inconvenience for individual researchers to set up and finance systems to enhance open data, and the hesitancy to share data publicly by companies due to competitive environments."); Svenson, K. L., Krasinski, S. D., Ellis, M., Rosenthal, N., Liu, E. T., & Fasman, K. H. (2022) ("Because the best validation of a model is recapitulation of the published phenotype by another laboratory, delayed submission to a repository is an impediment to enforcing reproducibility. Further, if a model cannot be validated, these negative results are not published or recorded, resulting in a significant waste of time and resources as others can benefit from the knowledge of such negative results. We recommend that the Resource Sharing Plan in a grant application includes a commitment to timely deposition . . . into a suitable public repository."); *see also* Akhtar, A. (2012)(suggesting that "transparency and registration of all animal experiments conducted by public and private institutions" be supported through the establishment of a register "similar to clinical trial registries.").