BETTER SCIENCE, FEWER ANIMALS: CATALYZING NIH GRANT MAKING TO IMPROVE BIOMEDICAL RESEARCH AND MEET SOCIETAL GOALS

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Abstract

Animal models are currently the "gold standard" in biomedical research. However, new approaches that do not involve the use of nonhuman animals are evolving to address the public health and medical challenges for which animal models are less well suited. These alternatives represent important advancements and are being recognized as significant advances. There is a clear societal need to encourage such efforts, and there is widespread support to move away from animal-based research by the American public.

The National Institutes of Health (NIH) funds the majority of biomedical research in the United States and should be a key player in developing new methods. There have been numerous bills introduced before the United States Congress that seek to change the way that NIH allocates its resources, with an emphasis on increasing funding for alternatives. To date, none of these bills have advanced in either the House of Representatives or the Senate.

This Article examines how NIH could utilize the policy options available under its current laws and regulations to move toward a research environment that puts greater value on alternatives and, at the same time, moves away from animal models as the gold standard. The major advantages of this approach are that it can be implemented without changing current laws and regulations, is relatively straightforward, and can be executed relatively quickly. If adopted, these policy options have the potential to create a much-needed paradigm shift that will improve scientific research while responding to the societal desire to use fewer animals in the biomedical arena.

I. Introduction

Over the years, animal research has played a vital role in medical and scientific advances.[1] In fact, a substantial portion of scientific research, including biomedical research, relies on animal models as a basis for discovering new knowledge.[2] Within the federal government, data from animal studies are used by different agencies, including the United States Department of Health and Human Services (HHS) which includes NIH and the Food and Drug Administration (FDA).[3] Currently, federal laws, regulations, and policies set out a system acknowledging that research animals should either be treated humanely or used in a way that minimizes, or if possible, eliminates pain and

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[1] Simon Festing & Robin Wilkinson, *The Ethics of Animal Research: Talking Point on the Use of Animals in Scientific Research,* 8 EMBO REPORTS 526, 526 (2007).

[2] *See* Francoise Barré-Sinoussi & Xaiver Montagutelli, *Animal Models are Essential to Biological Research: Issues and Perspectives,* 1 FUTURE SCI. OA FSO63, FSO63 (2015) (noting that the similarities between humans and animals have driven researchers to use animal models for a wide range of studies).

[3] NAT'L RESEARCH COUNCIL OF THE NAT'L ACAD., GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS xiii, xv (8th ed. 2011).

distress, but do not provide any incentives to use technology other than animal models.[4]

For decades, animal models have been seen as the gold standard, but well-known scientists and researchers have begun to challenge that assumption.[5] While animal models have been a staple in biomedical research, these models can be poor predicators due to the underlying molecular, cellular, and physiological mechanisms of animals being distinct from humans.[6] This gap in prediction is the result of several factors, including translation issues between basic scientific findings in a laboratory setting compared to human applications due to the complexity of many human diseases.[7] The complexity of human disease makes the disparities between animal models and humans more significant and can complicate and delay the process of drug development because animal model results are not necessarily predictive of human clinical responses.[8] For example, the rapid and successful development of several vaccines and treatment drugs for COVID-19 developed in less than one year were possible mainly because certain animal studies were skipped, though we do not know in detail how much alternative methods contributed to this achievement.[9] Animal studies have helped science and technology get to the point it is now, but such studies are only one method to find human and environmental health solutions.[10] There is a widening gap in the science needed to understand the underlying biological processes that contribute to human disease, and animal models alone cannot fill it. New technologies and methods that recapitulate human biological functions must be

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[4] Animal Welfare Act, 7 U.S.C. § 2132(g) (2015); Gilly Griffin & Paul Locke, *Comparisons of the Canadian and US Laws, Regulations, Policies, and Systems if Oversight for Animals in Research,* 57 ILAR J. 271, 274, 276–77 (2016); US DEP'T. HEALTH & HUM. SERV. NAT'L INST. HEALTH OFF. LAB'Y ANIMAL WELFARE, *Public Health Service Policy on Humane Care and Use of Laboratory Animals* 2, 4 (2015), https://perma.cc/4M6W-RZL5 (accessed Oct. 2, 2022); Public Health Services Act, 42 U.S.C. §§ 201-291n (2020).

[5] Gail A. Van Norman, *Limitations of Animal Studies for Predicting Toxicity in Clinical Trials: Is it Time to Rethink Our Current Approach,* 4 JACC: BASIC TO TRANSLATIONAL SCI. 845, 850 (2019); Susan Bridgwood Green, *Can animal data translate to innovations necessary for new era of patient-centered and indivdualised healthcare? Bias in preclinical animal research*, 16 BMC MED. ETHICS, 2015 at 1, 6.

[6] Donald E. Ingber, *Is it Time for Reviewer 3 to Request Human Organ Chip Experiments Instead of Animal Validation Studies?,* 7 ADVANCED SCI. 1, 1, 2 (2020), https://perma.cc/6MM7-PMFH (accessed Oct. 3, 2022).

[7] Attila A. Seyhan, *Lost in Translation: The Valley of Death Across Preclinical and Clinical Divide – Identification of Problems and Overcoming Obstacles*, 4 TRANSLATIONAL MED. COMM'N 1, 1–2 (2019); Van Norman, *supra* note 5, at 846, 850; Aysha Akhtar, *The Flaws and Human Harms of Animal Experimentation,* 24 CAMBRIDGE Q. HEALTHCARE ETHICS 407, 407–09, 416 (2015).

[8] Ingber, *supra* note 6, at 2; Seyhan, *supra* note 7, at 5.

[9] Francois Busquet et al., *Harnessing the Power of Novel Animal-Free Test Methods for the Development of COVID-19 Drug and Vaccines,* 94 ARCHIVES TOXICOLOGY 2263, 2267 (2020).

[10] Thomas Hartung, *Opinion Versus Evidence for the Need to Move Away from Animal Testing,* 34 ALTEX 193, 193 (2017).

developed and used to fill this space. NIH is positioned to help foster the development of these technologies through policy change.[11]

NIH is at the forefront of medical research in the United States. Part of NIH's mission is to "seek fundamental knowledge about the nature . . . of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability."[12] The agency identifies goals related to the development of new and alternative research and testing methods, including replacement options to traditional animal models like *in silico* models and organ chips.[13] The funding NIH provides to researchers helps support "fundamental creative discoveries[ ] [and] innovative strategies," as well as the development of scientific resources that can "expand the knowledge base in medical and associated sciences."[14] The acceptance and development of alternatives to animal models can help NIH protect human health by producing the most relevant science for humans. Modern science is now at a point where alternative techniques, such as organoids and organ chips, can provide much needed insight to human systems. The mission and goals put out by NIH make the organization paramount in furthering the shift to alternative methods in research and testing because supporting the use and development of alternative models contributes to fundamental discoveries and innovative strategies for medical science by fostering the entrepreneurial nature of scientists and their participation in the creation of more human-centered methods. Placing alternatives and animal models on an equal playing field

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[11] *See* Andrew Knight, *Animal Experiments Scrutinised: Systematic Reviews Demonstrate Poor Human Clinical and Toxicological Utility,* 24 ALTEX 320, 320, 324–25 (2007) (describing how traditional reliance on animal models has led to a lack of oversight and stalled development of new technologies and improvements to existing models); Daniel G. Hackam & Donald A. Redelmeier, *Translation of Research Evidence From Animals to Humans,* 296 JAMA 1727, 1731–32 (2006) (commenting on the low level of animal-to-human model translation and the opportunity for improvement and supplementation); Ingber, *supra* note 6, at 2; Manuela Cassotta et al., *Rheumatoid Arthritis Research in the 21st Century: Limitations of Traditional Models, New Technologies, and Opportunities for a Human Biology-Based Approach,* 37 ALTEX 223, 223 (2020); Thomas Hartung, *Thoughts on Limitations of Animal Models,* 14 PARKINSONISM & RELATED DISORDERS S81, S82–83 (2008); Xinyu Zhao & Anita Bhattacharyya, *Human Models Are Needed for Studying Human Neurodevelopmental Disorders,* 103 AM. J. HUMAN GENETICS 829, 829 (2018); Lena Smirnova et al., *3S - Systematic, Systemic, and Systems Biology and Toxicology,* 35 ALTEX 139, 151,153 (2018); Thomas Hartung, *Utility of the Adverse Outcome Pathway Concept in Drug Development,* 13 EXPERT OPINION DRUG METABOLISM TOXICOLOGY 1, 3 (2017).

[12] *Mission and Goals*, NIH, https://perma.cc/R3UC-UT57 (accessed Oct. 3, 2022).

[13] *See* Kendall Powell, *Replacing the Replacements: Animal Model Alternatives,* SCI. (Oct. 12, 2018), https://perma.cc/YK7J-6RKX (accessed Oct. 3, 2022) ("New technologies—3D cell culturing, human induced pluripotent stem cells, and gene editing—are leading to new solutions for replacing, refining, and reducing animal models."); T. Arora et al., *Substitute of Animals in Drug Research: An Approach Towards Fulfillment of 4R's,* 73 INDIAN J. PHARMACEUTICAL SCI. 1, 1 (2011) ("[A] number of new *in vitro* techniques have been devised which are called 'Alternatives' or 'Substitutes' for use of animals in research involving drugs.").

[14] NIH, *supra* note 12.

when incentivizing research may lead to more solutions for confronting complex human diseases such as cancer, Alzheimer's, and Parkinson's disease.[15]

NIH provides grant and contract opportunities to researchers. These funding opportunities help further NIH's mission and meet its goals by supporting research across disciplines that can and will enhance the health and lives of humans.[16] In the current grant and contract process, there are available pathways to streamline the acceptance and development of alternative research and testing methods. Many scientists are entrepreneurial in nature. By creating incentives such as grant and contract opportunities for these new techniques, NIH will help foster innovation and create more research methods faster by tapping into the natural entrepreneurial spirit of scientists. Although NIH does fund certain endeavors that are focused on alternatives, such as the certain projects at the Wyss Institute, the lack of funding remains a major barrier to the development and use of alternative methods.[17]

NIH has an annual budget of more than $40 billion to fund medical research.[18] Approximately 10% of NIH's budget funds intermural research projects undertaken by NIH scientists, while more than 80% supports extramural research, including more than 50,000 competitive grants across universities, medical schools, and other research institutions.[19] More than 300,000 researchers across 2,500 organizations and universities receive NIH funding.[20]

In 2019, NIH had more than $31 billion for funding across all institutes.[21] The total amount of funding is not only split between the

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[15] *See* Alexandra Sontheimer-Phelps et al., *Modeling Cancer in Microfluidic Human Organs-on-Chips,* 19 NATURE REV. CANCER 65, 65 (2009) ("Organ chips enable experimentalists to vary local cellular, molecular, chemical, and biophysical parameters in a controlled manner, both individually and in precise combinations, while analysing how they contribute to human cancer formation and progression and responses to therapy."); Ingber, *supra* note 6, at 3, 4 (discussing recent advances in human organ-on-a-chip and microfluidic technology which demonstrate their ability to recapitulate human physiology and disease states); Kambez H. Benam et al., *Engineered in Vitro Disease Models,* 10 ANN. REV. PATHOLOGY MECHANISMS DISEASE 195, 196 (2015) ("[E]ngineers. . .have begun to collaborate with biologists to leverage recent advances in tissue engineering and microfabrication to develop novel in vitro models of disease."); Hartung, *supra* note 11, at s81 ("[I]ncreasingly modern methods allow the 3R principle of reducing, refining and replacing animal experiments to be put into practice . . . .").

[16] *What Does NIH Look For?*, NIH, https://perma.cc/ZF93-S9J2 (accessed Oct. 3, 2022).

[17] *FDA/NIH Visit to Wyss Institute Longwood Site Underscores Focus on Regulatory Science,* WYSS INST. (Oct. 11, 2011), https://perma.cc/64TU-U367 (accessed Oct. 9, 2022); Katy Taylor, *Recent Developments in Alternatives to Animal Testing*, *in* ANIMAL EXPERIMENTATION: WORKING TOWARDS A PARADIGM CHANGE 585 (Kathrin Herrmann & Kimberley Jayne eds., 2019).

[18] *Budget*, NIH, https://perma.cc/Q59G-3W5X (accessed Oct. 3, 2023).

[19] *Id*.

[20] *Our Knowledge*, NIH, https://perma.cc/S7F6-JW6D (accessed Oct. 3, 2022).

[21] *National Institutes of Health (NIH) Funding: FY1996-FY2023*, CONG. RSCH. SERV. (May 20, 2022), https://perma.cc/PP5R-U9TQ (accessed Oct. 1, 2022); NATIONAL INSTI-

different institutes, but also between research grants, research and development contracts, fellowships, training grants, construction, and other awards.[22] Nearly all of the funding budget was allocated for the 49,092 research grants awarded.[23] There are several ways that the NIH process could be altered to turn toward increased funding of replacement alternatives and test methods that substitute animal models with non-animal models such as cell-based or computer models. These ways will be evaluated in the following Sections.

Although animal testing has been seen as the gold standard for years, technological advances suggest that methods should be updated to ensure that human health problems are being efficiently and fully studied.[24] There is a scientifically recognized need to expand the methodologies in research toward these techniques that better recapitulate human biological response.[25] Animal experimentation is not the only available option currently available for research, and alternative models can be used where animal models fail or are not predictive. Barriers such as the differences between how human and animal systems address disease and species differences in genetics and physiology can be avoided by using alternatives.[26] For example, while mice and humans have a significant amount of DNA in common, the gene sequences are not a perfect match and disparities will exist that impact translation and predictivity.[27] Even higher order animals that are more closely related to humans, such as chimpanzees, have significant genetic differences.[28] As a result, moving up the phylogenic scale does not address this problem. Additionally, the predictive value of animal models, or lack thereof for certain problems such as inflammatory diseases, shows the importance of supporting the development of models

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TUTES HEALTH, FINANCIAL MANAGEMENT REPORT 8 (2019) [hereinafter NIH MANAGEMENT REPORT].

[22] *Activity Codes Search Results*, NIH, https://perma.cc/W2S4-KJ8Z (accessed Oct. 1, 2022); NIH MANAGEMENT REPORT, *supra* note 21, at 8–9.

[23] NIH MANAGEMENT REPORT, *supra* note 21, at 8–9. Across all institutes, $28,143,252,479 was awarded. NCI received the most funding of all the institutes, with $5,747,125,000.

[24] *See* Niall Shanks et al., *Are Animal Models Predictive for Humans*?, 4 Phil., Ethics, & Humans. Medicine 1, 1, 18 (2009) (discussing how animal models are insufficient to predict human responses to drugs and chemicals); Robert A.J. Matthews, *Medical Progress Depends on Animal Models – Doesn't It?*, 101 J. ROYAL SOC'Y MED. 95, 95, 97 (2008) (critiquing the notion that "virtually every medical achievement in the past century has relied on animal models in some way").

[25] Ingber, *supra* note 6, at 12.

[26] Akhtar, *supra* note 7, at 407–08.

[27] *See* Harry Olson et al., *Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals*, 32 REGUL. TOXICOLOGY & PHARMACOLOGY 56, 56–57 (2000); Junhee Seok et al., *Genomic Responses in Mouse Models Poorly Mimic Human Inflammatory Diseases,* 110 PNAS 3507, 3507 (2013); Michael G. Palfreyman et al., *The Importance of Using Human-Based Models in Gene and Drug Discovery*, DRUG DISCOVERY WORLD (Oct. 3, 2002), https://perma.cc/FW4P-QPM7 (accessed Oct. 3, 2022).

[28] Palfreyman, *supra* note 27.

that can work where animal models have not or cannot.[29] NIH should not only be funding alternatives, but should be maintaining its high standards for those who develop and use these methods, because the new technologies being developed can flourish where animal models may not be as useful anymore.

Not only has NIH already shown an interest in supporting alternative research and testing methods, but other federal agencies including the EPA and FDA have also begun to show their support for alternatives to animal models.[30] The EPA has published a strategic plan on New Approach Methodologies (NAMs).[31] NAMs include innovative technologies and procedures which can be used to test chemical hazards and their risks without the need for animal testing.[32]

In 2018, EPA issued its "Strategic Plan to Promote the Development and Implementation of Alternative Test Methods" within the Toxic Substances Control Act (TSCA) program.[33] The Frank R. Lautenberg Chemical Safety for the 21st Century Act amended the TSCA and directed the EPA to reduce and replace testing on vertebrate animals ("to the extent practicable[ ] [and] scientifically justified"), and to "promote the development and timely incorporation of alternative test methods."[34] The FDA has also published a number of documents discussing the importance of alternatives to animal models, including the "FDA Predictive Toxicology Roadmap," and the "2021 Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science Report."[35] These reports outline the FDA's commitment to promoting the development and use of new technologies to better predict human responses to substances relevant to its mission, and to identifying the need for continued investment into the development of innovative products and methods to inform regulatory decision-making.[36] If the Humane Research and Testing Act (now included as part of the HEARTS Act of 2022) is passed, NIH may be in a position to support alternatives as a result of federal legislation. But NIH has the power to implement policy changes more easily, without relying on legislative and regulatory changes. The policy suggestions in this Article do not

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[29] Seok, *supra* note 27, at 3507.

[30] David Grimm, *U.S. EPA to Eliminate All Mammal Testing by 2035*, SCI. (Sept. 10, 2019), https://perma.cc/5J6L-L53W (accessed Oct. 12, 2022); *Animal Testing & Cosmetics*, FOOD & DRUG ADMIN. (Mar. 4, 2022), https://perma.cc/349Q-BW3T (accessed Oct. 12, 2022).

[31] FOOD & DRUG ADMIN., *supra* note 30.

[32] *Id*.

[33] *Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program*, EPA 6 (June 22, 2018), https://perma.cc/BS3D-Y73L (accessed Oct. 10, 2022).

[34] *Id*. at 6, 9.

[35] *2021 Advancing Regulatory Science at FDA: Focus Areas of Regulatory Science (FARS)*, FOOD & DRUG ADMIN., https://perma.cc/9EWW-W7VZ (accessed Oct. 10, 2022); *FDA's Predictive Toxicology Roadmap,* FOOD & DRUG ADMIN. (2018), HTTPS://PERMA.CC/A8DE-VMD8 (accessed Oct. 10, 2022).

[36] *Id.*

require engaging in the lengthy and difficult process needed to change a federal law.

Despite NIH's interest in alternative models, 71% of the grant applications submitted to NIH between FY2008 and FY2015 involved mouse models.[37] Significant work has already been made on non-animal models, and these models should be taken into more consideration when it comes to funding, granting, and publications.[38] Making changes to NIH's grants and contract process to encourage increased development and use of alternatives would show NIH's intent to support new developments and help researchers think more about human-relevant testing methods. These changes would also further the development, use, and reporting of new technologies. Small policy changes by NIH could effectively lead to an influx of applications containing new technologies and help move forward human health and biomedical research.

This Article advances a roadmap for NIH funding that would raise the profile of alternatives to animal models and testing and support current—and spark further—development, use and validation of such models, therefore, creating a more level playing field for researchers and investigators who want to pursue these technologies. Section I of this Article provided an overview and framed the issues that the remainder of the Article examines. Section II examines the NIH with a focus on the granting process. Section III goes into greater depth about the granting and contracting processes at NIH. Section IV offers a series of changes that could be made in the granting and contracting processes to level the playing field for alternatives. Section V contains conclusions and suggestions about how to move forward and implement the strategies outlined in this Article. The policy changes proposed in this Article do not require sweeping changes such as new laws or regulations, but merely make the grant process more easily navigable and encouraging by offering the same opportunities to projects focused on alternatives as those available to projects using animal models.

II. The National Institutes of Health

In 1930, the Ransdell Act established the National Institutes of Health and authorized the government to accept donations for the "study, investigation, and research in the fundamental problems of the diseases of man."[39] When it began, NIH was authorized only $750,000

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[37] Mike Lauer, *A Look at NIH Support for Model Organisms, Part Two*, NIH OFF. EXTRAMURAL RSCH. (Aug. 3, 2016), https://perma.cc/E9YH-QN5X (accessed Oct. 10, 2022).

[38] *See* Ingber, *supra* note 6, at 22 (discussing advances in human organ-on-a-chip technology, "which demonstrate their ability to recapitulate human physiology and disease states, as well as human patient responses to clinically relevant drug pharmacokinetic exposures, with higher fidelity than other in vitro models or animal studies").

[39] The Ransdell Act of 1930, Pub. L. No. 71-251, 46 Stat. 379.

to build additional buildings and permitted to use donations to create a system of fellowships.[40] Now, NIH is the largest public funder of biomedical research in the world.[41] To meet its mission, NIH contributes to human health and biomedical knowledge through its support of "cutting-edge research and cultivating the biomedical workforce of today and tomorrow."[42] NIH has followed through with this support by funding innovative research and experiments since its inception. For example, a NIH grantee performed the first human liver transplant, and NIH researchers held the first large clinical trials of lithium as a mood stabilizer.[43] A considerable number of NIH achievements have been based on knowledge gained partially from animal models.[44] Despite these notable successes the NIH has had through funding animal model research, not all of its supported research projects lead to beneficial knowledge or solutions to human health problems, and advocacy groups have brought litigation against NIH based on such alleged shortcomings.

In September 2021, People for the Ethical Treatment of Animals (PETA) sued NIH, alleging that the continued funding of sepsis experiments on animals for decades despite no new breakthroughs, wastes taxpayer money.[45] PETA's brief argued that NIH admitted mice are not good models for humans.[46] According to PETA, NIH is abusing "the agencies' discretion" and violating "[its] obligation to fund research to improve human health and minimize the number of animals used in experiments."[47] PETA has noted that funding the new wave of biomedical research, including organ chips and organoids, could and should move research away from "slow, expensive" animal experiments.[48] This technology can be used by NIH to develop successful methods in sepsis research and hold NIH to its obligation to improve human health.

More than 95% of the NIH budget is allocated for research, including research and development contracts.[49] Additionally, NIH helps fa-

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[40] *Id*.

[41] *Grants & Funding*, NIH, https://perma.cc/9TX5-9UK2 (accessed Oct. 10, 2022).

[42] *Impact of NIH Research*, NIH, https://perma.cc/HR84-G3T5 (accessed Oct. 10, 2022).

[43] *Our Health*, NIH, https://perma.cc/FSS5-HKTY (accessed Oct. 10, 2022).

[44] *See e.g.*, *Protecting At-Risk Children From a Severe Respiratory Disease,* NAT'L INSTS. HEALTH INTRAMURAL RSCH. PROGRAM (Jan. 14, 2022), https://perma.cc/8JC7-M63K (accessed Oct. 10, 2022).

[45] Press Release, PETA, *PETA Files Groundbreaking Lawsuit Against NIH, HHS Over Sepsis Animal Experiments*, (Sept. 21, 2011) (on file with Animal Law Review).

[46] *Id*.

[47] *Id*.; Seok, *supra* note 27, at 3507–12; Francis Collins, *Of Mice, Men, and Medicine,* NIH DIRECTOR'S BLOG (Feb. 19, 2013), https://perma.cc/ML75-TQ7S (accessed Nov. 3, 2021).

[48] *See, e.g.*, Lindsay Pollard-Post, *Students' Organ-on-a-Chip Technology Could Save Countless Lives*, PETA (July 29, 2015), https://perma.cc/JW7Q-7KUH (accessed Oct. 10, 2022) (discussing funding of "placentas-on-a-chip" studies).

[49] *Total NIH Budget Authority: FY 2021 Operating Plan*, NIH, https://perma.cc/ZJG2-L2N6 (accessed Oct. 10, 2022).

cilitate shared knowledge across the biomedical field because grantees publish their research findings.[50] These publications are available in the NIH-supported repository through the National Library of Medicine (NLM).[51] NIH-funded research and access to these publications help spur biomedical development in both the public and private sectors.[52] This research includes advancements in drug development and relevant patents.[53]

Five percent of NIH grants over twenty-seven years led to publications cited in patents awarded during development of FDA-approved drugs.[54] A 2018 study found that the fundamental basic research of 210 FDA-approved drugs between 2010 and 2016 was assisted by NIH funding.[55] It has also been documented that for every $100 million of NIH funding through grants and contracts, approximately six new patents are created.[56] The contributions of NIH to human health and biomedical research have lasting impacts and these contributions should continue to expand as technology evolves.

NIH is composed of six centers and twenty-seven institutes.[57] Each center and institute has a certain role and its own research agenda that may focus on specific body systems—such as the National Eye Institute (NEI) and the National Heart, Lung and Blood Institute (NHLBI)—or on particular diseases, such as the National Cancer Institute (NCI).[58] Each separate institute and center contribute to NIH's overall mission to seek fundamental knowledge about living systems and use that knowledge to benefit public health.[59] While most of the centers and institutes within NIH could play a role in the development and use of alternatives, the Center for Scientific Review (CSR), a center within NIH that acts as a gateway for NIH grant applications,

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[50] *8.2.3 Sharing Research Resources*, NIH, https://perma.cc/6VPR-BEUK (accessed Oct. 10, 2022).

[51] *PubMed Central*, NAT'L LIBR. MED., https://perma.cc/V2HG-3SHJ (accessed Oct. 10, 2022).

[52] *Measuring the Impacts of Federal Investments in Research: A Workshop Summary*, THE NAT'L ACADS. (US) COM. MEASURING ECONOMIC & OTHER RETURNS FED. RSCH. INV. (2011), https://perma.cc/7MUP-SFB3 (accessed Oct. 10, 2022) (noting that "public research tends to spur private research").

[53] *Id*. (noting that the drug industry relies more on public sector research than do other industries, and that these drugs result in patents).

[54] NIH, *supra* note 45; Danielle Li et al., *The Applied Value of Public Investments in Biomedical Research*, 356 SCI. 78, 80 (2017).

[55] *See* Ekaterina Galkina Cleary et al., *Contribution of NIH Funding to New Drug Approvals 2010-2016,* 115 PNAS 2329, 2330 (2018) ("Overall, NIH-supported publications were identified in 198 of the 210 drug searches and in all 151 target searches. Thus, NIH funding was directly or indirectly associated with every one of the 210 NMEs approved from 2010–2016.").

[56] NIH, *supra* note 42.

[57] *Institutes, Centers, and Offices*, NIH (June 14, 2018), https://perma.cc/SLW6-F2UR (accessed Sept. 29, 2022).

[58] *Id.*; *Institutes at NIH*, NIH, https://perma.cc/NRZ7-U36M (accessed Sept. 29, 2022).

[59] NIH, *supra* note 58.

is a central hub for all grants.[60] However, CSR is not in charge of creating grant opportunities.[61] CSR acts as a portal for the review of grant applications and their scientific merit. In order to carry out its mission of ensuring fair review of grant applications, CSR oversees the organization of peer review groups tasked with evaluating research applications.[62] CSR states that it collaborates with the scientific community, including NIH institutes, to "identify critical problems and develop solutions for supporting the best science."[63] Adjusting the grant process, including the peer review process, to be more inclusive of alternatives will help CSR contribute to supporting the best science, and help NIH as a whole meet its mission to better human health and continue being a leader in biomedical research.

III. General Grants and Contracts Regulations and the NIH Process

The Public Health Services Act provides that the HHS "may allocate funds for the national research institutes and national centers to make grants for the purpose of improving the public health through demonstration projects for biomedical research" through the actions of NIH.[64] HHS helps maintain and develop the grants process regulations for the NIH.[65] HHS regulations covered under Titles 41, 42, and 45 of the Code of Federal Regulations apply to NIH and the NIH biomedical research community as a whole.[66] The regulations are split between grants applicable to State, local, Indian tribes (2 C.F.R 215), higher education, hospitals, and other non-profit organizations (45 C.F.R 75), and for-profit organizations.[67]

The regulations are further divided between pre-federal award requirements and post-federal award requirements.[68] Using the federal regulations, both HHS and NIH developed their own grants policy statements.[69] Since 1998, NIH has adhered to its own grants policy statement and no longer follows the HHS grants policy statement, al-

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60 Ctr. for Sci. Rev., *About CSR*, NIH (Sept. 14, 2022) https://perma.cc/5E2M-QJBS (accessed Sept. 29, 2022).

61 Ctr. for Sci. Rev., *For Applicants,* NIH, (Oct. 16, 2020) https://perma.cc/AX6T-EJVB (accessed Oct. 3, 2022).

62 NIH, *supra* note 60.

63 Ctr. for Sci. Research, *Power of NIH Peer Review,* NIH (Apr. 14, 2018) https://perma.cc/V2UZ-7WQZ (accessed Oct. 3, 2022).

64 Public Health Services Act, 42 U.S.C § 284n (2007).

65 US Dep't Health & Human Servs., Nat'l Instit. Health, NIH Grants Policy Statement, 1–45 (2021) [hereinafter NIH Grants Policy Statement].

66 NIH, *1111 – Laws and Regulations* (2009).

67 U.S. Dep't Health & Human Services Off. Assistant Sec'y for Res. & Tech. Off. Grants, HHS Grants Policy Statement I-14 (2007) (hereinafter HHS Grants Policy Statement).

68 45 C.F.R. §§ 75.200–75.218; 45 C.F.R. §§ 75.300–75.391.

69 HHS Grants Policy Statement, *supra* note 67, at ii; *see generally* NIH Grants Policy Statement, *supra* note 65 (explaining NIH and HHS grant statement policies).

though the policy statements are strikingly similar.[70] Each institute within NIH functions under the same grants requirements expressed in the grants policy statement, but because of their distinct missions and purposes, there may be differences in their individual grants requirements.[71] Recipients of NIH funding must comply with all applicable federal statutes, regulations, and policies, as well as the specific institutional policies that may be in place.[72]

Within NIH, the Office of Extramural Research is tasked with guiding research institutes on their grant, cooperative agreements, and contract programs.[73] This office manages the funding process at all stages.[74] Part of the Office of Extramural Research's duties include overseeing the funding opportunity announcements for each of the institutes.[75]

NIH uses different types of financial assistance instruments, including grants and cooperative agreements.[76] Out of the $41.6 billion that NIH received in FY2020, more than $30 billion went to extramural grants and cooperative agreements, excluding contracts.[77] Cooperative agreements and grants differ by NIH's involvement in the project they are used to fund.[78] NIH is more involved with projects under cooperative agreements, acting as a support mechanism in high-priority research areas.[79] While cooperative agreements typically are not from investigator-initiated applications, grants are.[80] Grants are more frequently used to fund target research projects since most applications are investigator-initiated.[81] The most common investigator-initiated submission is for research and research training.[82]

In addition to grants, contracts are available for researchers seeking funding opportunities. Contracts differ from grants in that contracts are a legal agreement binding parties with defined requirements, specific deliverables, and a defined schedule.[83] Funding for contracts are typically not included in the total amount of funding for extramural research.[84] In the terms of NIH, a contract is "a legally

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[70] HHS GRANTS POLICY STATEMENT, *supra* note 67, at i n. 1.

[71] NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-45.

[72] *Id*.

[73] *About the Office of Extramural Research,* NIH, https://perma.cc/F783-AAMV (accessed Oct. 3, 2022).

[74] *Id*.

[75] *Id*.

[76] NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-45.

[77] Mike Lauer, *FY 2020 by the Numbers: Extramural Investments in Research,* NIH OFF. EXTRAMURAL RSCH. (Apr. 21, 2021), https://perma.cc/4VV4-72LL (accessed Oct. 4, 2022).

[78] NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-51.

[79] *Cooperative Agreements (U)*, NAT'L INST. ALLERGY & INFECTIOUS DISEASE, https://perma.cc/Q6RB-PSJM (accessed Oct. 4, 2022).

[80] NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-51.

[81] *Id*. at I-51–52

[82] *Id*. at I-52.

[83] *Contracts*, NIH, https://perma.cc/79FZ-8FKG (accessed Oct. 4, 2022).

[84] Lauer, *supra* note 77.

binding agreement to acquire goods or services for the direct use or benefit of the Government," while a grant is an "assistance mechanism to support research for the public good."[85] Grants can be based on a peer review of broad criteria, while a contract award is based on stated evaluation factors.[86] Grants have less government oversight than contracts or cooperative agreements and require reports rather than deliverables to be submitted.[87] The contract regulations for funding bodies are codified in the Federal Acquisition Regulations (FAR).[88]

Under the FAR, contracts used for research and development with the primary purpose to advance scientific and technical knowledge should only be used "when the principal purpose is the acquisition of supplies or services for the direct benefit or use of the Federal Government" rather than for public or private benefits.[89] If the primary purpose of the research is for another public purpose, then grants or cooperative agreements should be used.[90]

The current grants and contracts regulations do not deter researchers from using or developing alternative methods, so there is no regulatory bar to their deployment in research. If replacement alternatives are to be encouraged, NIH would need to change its policies and granting process so that researchers who are pursuing projects such as using or developing alternatives are not downgraded because they are not applying traditional project applications. The policy changes proposed in this Article do not require sweeping changes such as new laws or regulations, but merely make the grant process more easily navigable and encouraging by offering the same opportunities to projects focused on alternatives as those to projects using animal models. A brief published by the Stanford Institute for Economic Policy Research evaluating the projects funded by NIH recently revealed that there may be a traditional bias that harms novel and new science.[91] The institute determined that this bias may be a result of pressure to produce "visible results" which are easier to be achieved by working on already established science.[92] Deviating from the standardized format of grant

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[85] NIH, *supra* note 83.

[86] *Id*.

[87] *Id*.

[88] 48 C.F.R. § 35.001 (2022). The Federal Acquisition Regulations discuss research and development contracting in Section 35. Research within this section is specific to "applied research," meaning research that "(a) normally follows basic research, but may not be severable from the related basic research; (b) attempts to determine and exploit the potential of scientific discoveries or improvements in technology, materials, processes, methods, devices, or techniques; and (c) attempts to advance the state of the art." "Development" is defined as the "systematic use of scientific and technical knowledge in the design, development, testing, or evaluation of a potential new product or service to meet specific performance requirements or objectives . . . ."

[89] 48 C.F.R. § 35.003.

[90] *Id*.

[91] Jay Bhattacharya & Mikko Packalen, *Encouraging Edge Science Through NIH Funding Practices*, STAN. INST. ECON. POL'Y RSCH. 1, 1–3 (2018).

[92] *Id*. The policy brief is supported by a study conducted in 2020. *See* Mikko Packalen & Jay Bhattacharya, *NIH Funding and the Pursuit of Edge Science*, 117 PROC.

applications may make projects focused on alternatives less likely to be chosen for funding because they do not fall into the traditional bias and go beyond the requirements of the criteria already established.[93] Having a process that actively encourages the use of alternatives will not put applicants looking to use or develop alternatives at a disadvantage merely because they took a different approach from the traditional applicants.

To meet its mission, NIH should not limit research opportunities for methods that can lead to advancements for human health. Researchers should have the same funding opportunities regardless of which models they are working with since they are the most equipped to determine what will work best for their purposes. Providing equal opportunities for different models through funding will encourage the development of better alternative models in areas where animal models have faced barriers.

Although animal models to date have played a paramount role in biomedical development, these models face barriers.[94] Some of these barriers—including biological distinctions between humans and nonhuman animals—could be addressed by focusing on models that accurately reflect human biology. The perceived reliability and support of animal models over decades of medical advancements have cemented the idea that they are the gold standard. This traditional view contributes to potential bias of reviewers who may be unaware of alternative models when reviewing grants. Barriers such as distinct underlying molecular, cellular, and physiological mechanisms between humans and animals present an opportunity for NIH to support new research and development to overcome these barriers and continue making strides for human health.[95] Changing the funding process will not only support new methods that can be used in place of older methods that have not always been accurate predictors of human health but will also help alleviate the favorable bias shown toward the gold standard animal models by providing opportunities specifically for alternatives. These policy changes will allow the grants system and NIH research to continue running as smooth as possible while the new technology, such as organ chips and organoids, are being supported and change is occurring.

NAT'L ACAD. SCI. 12011, 12011 (2020) (measuring whether NIH succeeds in funding novel work or "edge science").

93 *See* OTTO O. YANG, GUIDE TO EFFECTIVE GRANT WRITING: HOW TO WRITE A SUCCESSFUL NIH GRANT APPLICATION 15, 15 (2005) (describing how the current NIH process is rigid and unforgiving toward applications that deviate from the standardized format).

94 *See* Javier Mestas & Christopher C. W. Hughes, *Of Mice and Not Men: Differences Between Mouse and Human Immunology*, 172 J. IMMUNOLOGY 2731, 2731 (2004) (describing how mouse biology, though widely used to extrapolate information about humans, differs in many significant respects from human biology).

95 Ingber, *supra* note 6, at 2.

IV. Toward a More Comprehensive Scientific Approach to Funding Research

The NIH funding process for grants and contracts has several stages. The first involves notification of grant and contract options.[96] The publication of grant and contract options helps applicants locate opportunities that meet their research and for which they can apply. Within this first step, NIH could implement multiple changes that would make the application process more open to alternatives by both providing new opportunities, as well as making the opportunities easier to locate. These changes will help alternatives be on a level playing field with other techniques such as animal models.

After applicants apply for opportunities that suit their research, they undergo the peer review process.[97] Within the peer review process, there are additional opportunities to minimize bias and build a procedure that would open the door to new innovative research. The projects that are selected to go through the peer review process can then be tasked with making research more publicly available to help further other research into alternatives and help start building a reliable and informative database of information upon which scientists can continue to build.

There are opportunities throughout the entire funding process that NIH can implement to support alternatives. These changes are possible together or individually and would work alongside legislative initiatives such as the creation of a new center within NIH. The Humane Research and Testing Act of 2021 (now part of the HEARTS Act of 2022) would create a center focused on alternative models within NIH.[98] This center could help direct applicants to certain opportunities, as well as use their own resources to implement other suggestions to help further the development and use of alternative models.

A. Notification of Grant and Contract Availability

The initial stage of the funding process within NIH is the notification of grant or contract availability.[99] For both competitive and cooperative grants, NIH (or any awarding agency under HHS) is required to provide specific information in the public announcement.[100] Although there are specific requirements of what must be included in each announcement, there are no limiting requirements for the notice of funding opportunities within the federal administrative requirements.[101]

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96 45 C.F.R. § 75.203.

97 *Grants Process Overview*, NIH (Mar. 20, 2017), https://perma.cc/897U-895D (accessed Sept. 29, 2022).

98 Humane Research and Testing Act, H.R. 1744, 117th Cong. (2021).

99 45 C.F.R. § 75.203.

100 45 C.F.R. § 75.203(a).

101 45 C.F.R. § 75.203(c).

There are five frequently used types of applications for the NIH grants process.[102] Four of the five types of applications qualify as "competing" because applicants must compete for funding.[103] The competitive application process requires going through a peer review.[104] The four types of competing applications include a new application or a first time request for funding on a project not currently receiving financial support from NIH.[105] Other types of competing applications include renewals, revisions, and resubmissions.[106]

NIH, as well as other federal agencies, use Funding Opportunity Announcements (FOA) to advertise the availability of grants or cooperative agreements. There are different types of FOAs, but NIH primarily uses Request for Applications (RFAs) and Program Announcements. Currently there are no specific requirements across all FOAs that specifically mention alternative testing and research methods.

NIH has an opportunity to direct researchers to focus on developing alternatives by addressing alternatives to animal research within each announcement or mandating that a certain percentage of total announcements focus on the use and development of alternatives. Beyond NIH, specific centers and institutes within NIH can make requests for applications. If the HRTA is passed into law, the new center for alternatives to animal testing would have the ability to make their own requests for applications. But until that point, NIH can still make the funding process more favorable toward alternatives during the application solicitation process.

1. Request for Applications

RFAs are used to meet specific goals such as goals of a specific institute. RFAs can solicit both grants and cooperative agreements but are limited to "well-defined scientific area[s] to accomplish specific program objectives."[107] RFAs provide information to interested candidates about the amount of funds and submission dates.[108] In addition to the above information, RFAs for cooperative agreements also indicate the responsibilities of both the award recipients and NIH.[109]

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102 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-51.

103 *Id*.

104 *Id*.

105 *Id*.

106 Renewals are requests for additional funding after a project has already started. Renewal applicants compete with the other competitive applications including first time applicants. Revision is an application that can include budgetary changes or expansion of research scope—these applications are for projects in a current budget period. Resubmissions are applications that were unfunded after their initial application and are now being resubmitted with changes. Non-competing progress reports are required for projects to receive continued support from a grant beyond the initial budget period. *Id*. at I-51–52.

107 *Id*. at I-53.

108 *Id*.

109 *Id*.

NIH has the authority to "develop areas of high priority or special research interest" to direct researchers to seek funding for projects in those areas.[110] There are currently no limitations to the types of projects that NIH may deem high priority or of special interest.[111]

2. *Program Announcements, Parent Announcements, and Notices of Special Interest*

Program Announcements are advertisements covering new and ongoing programs generally.[112] These announcements can include changes in current programs or act as notices for available grant funding.[113] Parent Announcements are similar to Program Announcements, but rather than focusing on programs, they allow applicants to submit investigator-initiated applications under specific activity codes.[114] Parent Announcements only remain open for three years.[115] Certain Program Announcements and Parent Announcements are connected to Notices of Special Interest (NOSI). NOSIs highlight specific research areas and inform potential grant applicants of FOAs in those research areas.[116] The current NOSIs are available online, but as of the end of the calendar year 2021, none relate to the development and use of alternative methods.[117]

In 2019, NIH issued a notice indicating that it intended to expand the use of NOSIs to cover specific scientific research topics.[118] NOSIs are now implemented as a way for NIH to direct applicants to FOAs that are directly related to a special interest.[119] NIH could create a NOSI for the development of alternatives generally across all institutes, or even specify for individual institutes within the NIH such as development of alternatives for cancer research, development of alternatives for environmental health, and more.

Although NIH does not have NOSIs for alternative models, they do have NOSIs for animal models. There are two active NOSIs as of the end of the calendar year 2021 that would provide funding for the development of new animal models.[120] One of the NOSIs directs appli-

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110 *Id*. at I-53–54.

111 *Id*.

112 *Id*. at I-53.

113 *Id*.

114 *See Parent Announcements (For Unsolicited or Investigator-Initiated Applications)*, NIH, https://perma.cc/245R-RAKK (explaining generally parent announcements).

115 *Id*.

116 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-53.

117 *See Find Grant Funding*, NIH, https://perma.cc/8N2A-FNF9 (accessed Oct. 3, 2022) (from "drop down" menu choose NIH, all, NOSI, date range to apply the search criteria to look at Notices of Special Interest, which shows 244 results).

118 *See NIH Expanding Usage of Notices of Special Interest*, NIH (June 14, 2019), https://perma.cc/4CPV-VX96 (accessed Oct. 3, 2022).

119 *Id*.

120 *See Notice of Special Interest: Notice of Availability of Funds for Administrative Supplements for Pediatric Radiation/Nuclear Animal Models, MCM, Biodosimetry De-*

cants to an exploratory/developmental research grant for the development of animal models.[121] The National Institute for Allergy and Infectious Diseases (NIAID) NOSI does not provide a detailed rationale for requesting animal models beyond stating that the models are "necessary." The second NOSI, which is not limited to a specific institute, states that NIH is looking for animal models in relation to multiple organ systems.[122] This NOSI also mentions that NIH is interested in other models, such as animal-tissue-on-chip models to complement the use of animals, but there is no mention of human-organ-chip models or other human-based alternative models.[123]

The second NOSI seeking animal models is connected to a Parent Announcement for the development of animal models.[124] This Parent Announcement was initially posted in 2019 but was reissued on March 17, 2021.[125] The purpose of this FOA is to "encourage[ ] innovative research to develop, characterize, and improve animal models, biological materials, and novel technologies to better understand human health and disease."[126] This FOA seeks proposals that can be applied to multiple body systems and will be relevant to more than one NIH institute or center.[127] While this FOA is not exclusive to animal models, and briefly mentions alternatives such as cell/tissue culture systems and integrative informatics models, the title and promotion of the FOA emphasizes animal models above alternative models.[128] Additionally, these alternative models are only mentioned as a project option if they will improve animal models—the alternative models would only be considered and evaluated by how they could refine or impact already existing animal models.[129] This FOA acknowledges that current animal models have flaws that interfere with biomedical research by recognizing that certain diseases that impact animal models may inhibit other diseases from being studied at the same time on those mod-

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velopment, NIH NIAID (Jul. 14, 2020), https://perma.cc/NB78-TK4J (accessed Oct. 3, 2022) (describing NIAID's Radiation and Nuclear Counter measures Program's need to develop animal models to study radiation effects on children); *Notice of Special Interest (NOSI): Development of Animal Models of Down Syndrome and Related Biological Materials as Part of the INCLUDE (Investigation of Co-occurring Conditions Across the Lifespan to Understand Down Syndrome) Project*, NIH (Dec. 18, 2019), HTTPS://PERMA.CC/7HXK-FJUZ (accessed Oct. 3, 2022) (describing this NOSI's goal of developing animals models to study health conditions related to Downs Syndrome).

121 *See Development of Animal Models and Related Biological Materials for Research (R21)*, NIH (Sept. 9, 2019), https://perma.cc/2S4M-64XJ (accessed Oct. 3, 2022) (providing an overview of a FOA for the development of new animal models for multiple body systems disease studies).

122 *NOSI: Development of Animal Models*, *supra* note 120.

123 *Id*.

124 NIH, *supra* note 121.

125 *Id*.

126 *Id*.

127 *Id*.

128 *NOSI*, *supra* note 120.

129 *Id*.

els.[130] Given that improving human health is central to NIH's mission, in cases where NIH acknowledges that animal models fall short, it should consider whether seeking additional animal models is prudent and in line with its ultimate goal. Alternative models that are based directly on human-biology would not face some of the confounders that limit animal models such as the risk of contracting animal diseases and would work similarly to other options that are mentioned in the FOA, such as animal-tissue-on-chip models.[131]

According to NIH, the March 17, 2021, FOA looks at the development of animal models to "encourage innovative research to develop, characterize, and improve animal models . . . to better understand human health and disease."[132] Studies have shown that animal models have limitations in predicting certain human health issues and diseases such cancer.[133] For example, a study looking at animal models and clinical trials for cancer noted that the rate of successful translation from animal models to clinical trials for cancer is less than eight percent.[134] The same study suggested that this failure rate is likely related to the animal models not accurately mimicking the human disease conditions.[135] Rather than direct applicants to funding opportunities for the development of new animal models, NIH should both create opportunities for funding and direct applicants to these new FOAs for alternative models.

NIH can use the same authority it used to create the NOSIs for the development of animal models and specific FOAs to initiate focused funding opportunities for non-animal models. By promoting the availability of funding for alterative models, researchers will be incentivized to explore the use of alternative methods already available or to develop new models. These funding opportunities could be specific to individual institutes within NIH or could be for general research applicable to all NIH institutes. NIH has a duty to support alternatives in research and development to achieve its mission of enhancing human health. NIH should be advertising funding opportunities in that realm of alternatives instead of, or in addition to, the development of more

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130 NIH, *supra* note 121.

131 *See* Akhtar, *supra* note 7 (describing technological innovations in non-animal models).

132 NIH, *supra* note 121.

133 *See* Shanks, *supra* note 24, at 2 (explaining that "[t]here is a serious scientific controversy concerning the predictive power of animal models" for human health issues such as cancer); Pandora Pound & Merel Ritskes-Hoitinga, *Is It Possible to Overcome Issues of External Validity in Preclinical Animal Research? Why Most Animal Models are Bound to Fail,* 16 J. TRANSLATIONAL MED. 1 (2018) ("[P]reclinical animal models can never be fully valid due to the uncertainties introduced by species differences. . . . This is because species differences would continue to make extrapolation from animals to humans unreliable.").

134 Isabella WY Mak et al., *Lost in Translation: Animal Models and Clinical Trials in Cancer Treatment,* 6 AM. J. TRANSLATIONAL RSCH. 114, 114 (2014).

135 *Id*.

animal models—especially since NIH has already acknowledged the failure of animal models in certain cases.[136]

B. Peer Review Process for Grant Awards

Under the Public Health Services Act, applications for NIH grants and cooperative agreements are required to undergo a peer review process.[137] The review process is required to evaluate the scientific merit of each application, although in some cases for solicited contracts the peer review process is not necessary.[138] Federal requirements of the peer review process are outlined broadly and placed in the hands of the Director of NIH.[139] Research needs to undergo a peer review process and, as of the enactment of the National Institutes of Health Reform Act of 2006, also a review under an advisory council composed of members from all relevant scientific disciplines.[140] The two-step review process used by NIH is sometimes referred to as the "dual review system."[141]

During the initial peer review process, a panel of non-federal scientists review the application and provide a score.[142] The members of a peer review committee are referred to by NIH as a Scientific Review Group (SRG).[143] The members of SRGs have training and experience that qualifies them to "assess[ ]. . . the likelihood for [a] project to exert a sustained, powerful influence on the research field(s) involved."[144] After considering specific criteria, the SRG generates an "overall impact score" for the application.[145] A large amount of the review consideration focuses on the "scientific merit" of a proposal.[146]

The second stage of the review process involves a review by a council made up of senior scientists with broader experience and members of the public with knowledge and interest in the mission of the specific institute that would provide the funding.[147] This part of the process focuses more on the connection the proposed project has to the funding NIH's specific priorities including the NHLBI, National Institute of General Medical Sciences (NIGMS), and National Institute of

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136 *See* Collins, *supra* note 47 (explaining that for "molecules designed to target a sepsis-like condition, 150 drugs that successfully treated this condition in mice later failed in human clinical trials."); 42 U.S.C. § 284n(3) (2007).

137 42 U.S.C. § 284n(3) (2007).

138 Peer review may not be required if the "solicitation is to re-complete or extend a project that is within the scope of a current project that has been peer reviewed, or there is a Congressional authorization or mandate to conduct specific contract projects." 42 C.F.R. § 52h(10)(c) (2004).

139 42 U.S.C § 289a (2007); 42 U.S.C. § 289(b)(1) (2007).

140 National Institutes of Health Reform Act of 2006, 42 U.S.C. § 284a (2018).

141 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-72.

142 *Id.*

143 *Id.* at I-41.

144 *Id*.

145 *Peer Review*, NIH, https://perma.cc/E25T-PHPZ (accessed Sept. 27, 2022).

146 NIH GRANTS POLICY STATEMENT, *supra* note 65, at IIB-62.

147 *Id*. at I-76.

Biomedical Imaging and Bioengineering (NIBIB).[148] It is highly unlikely that an application that has not been reviewed and approved by both the SRG and the advisory council will receive funding.[149]

There are at least three ways that NIH can make the peer review process inclusive of alternative methods. One change that NIH can make is to add a specific requirement of consideration for the development and usage of alternative methods in the overall review process. A second change could be to include an evaluation of alternative method consideration within the previously existing criteria. A third method is that NIH could advertise which institutes or centers are already encouraging alternatives or interested in pursuing research of alternatives so applicants can direct their applications toward those centers and institutes.

1. Alternatives in Currently Required Criteria

The peer review panel is required to evaluate the following criteria: (1) significance, (2) investigator(s), (3) innovation, (4) approach, and (5) environment.[150] Three of the above criteria have the potential to directly take into consideration the use and development of alternative methods: significance, innovation, and approach. This Part will focus on those three criteria. When reviewers consider the significance criterium, they are evaluating whether the project can "address an important problem or critical barrier to progress" in the relevant field of study and whether a successful outcome from the project will change the characteristics of the field such as its current concepts, methods, and technologies.[151] The innovation evaluation pertains to the inclusion of alternative methods similar to the significance criterium. The innovation criterium requires reviewers to take into consideration whether the proposed project "challenge[s] and seek[s] to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or intervention," as well as whether these novel methods are a "refinement, improvement, or new application" over previously used methodologies.[152]

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148 The mission of the NHLBI is to "provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives[,] . . . stimulate basic discoveries into clinical practice, foster[ ] training and mentoring of emerging scientists and physicians, and communicate[ ] research advances to the public." The mission of NIGMS is to "support basic research that increases understanding of biological processes and lays the foundation for advances in disease diagnosis, treatment and prevention . . . ." The mission of NIBIB is to "improve health by leading the development and accelerating the application of the life sciences to advance basic research and medical care." *List of NIH Institutes, Centers, and Offices*, NIH, https://perma.cc/Y4NW-RXQG (accessed Sept. 29, 2022).

149 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-76.

150 42 C.F.R § 52h(8) (2004); NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-73.

151 *Find Grant Funding*, *supra* note 117.

152 *Id*.

Both the innovation and significance criteria present ample opportunity for NIH to include specifics to alert peer reviewers to pay close attention to the development and usage of alternative methods. In certain circumstances, alternative methods can be more predictive than animal models because findings in some animal experiments show "poor concordance with human clinical outcomes."[153] Alternative models are innovative and can be used to improve the predictability between animal models and human clinical data.[154] The significance and innovation criteria already require reviewers to consider the reviewed method's relationship to the future of the field and whether it improves current methodologies.[155]

Research shows that alternative methods are important to the future of biomedical research as well as are an innovative supplement to problems within the current techniques.[156] The approach criterium could be modified to include consideration of alternative methods, but not in the same way that the significance and innovation criteria can. The approach criterium looks at whether the "overall strategy, methodology, and analyses" are the best option to achieve the goals of the proposed project.[157] One of the specific questions for the approach criterium already addresses the use of nonhuman animals by questioning whether the investigators have considered how the biological variables of the animals may impact the project.[158] While there is no general criteria requirement within this criterium for the evaluation of alternative methods versus animal-testing methods, projects that plan to use live vertebrate animals must meet additional requirements.[159]

2. Additional Review Criteria for Alternatives

There are several review criteria for applications that are not appropriate for all applications or responses to proposal requests and an-

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153 EUROPEAN COMM'N, REPORT ON A EUROPEAN COMM'N SCIENTIFIC CONFERENCE: NON-ANIMAL APPROACHES THE WAY FORWARD 5 (2016).

154 *See* Michael Bracken, *Why Animal Studies are Often Poor Predictors of Human Reactions to Exposure*, 102 J. ROYAL SOC'Y MED. 120, 121 (2009) (concluding that new animal research, "if they are used to inform the design of clinical trials, particularly with respect to appropriate drug dose, timing, and other crucial aspects of the drug regimen, will further improve the predictability of animal research in human clinical trials"); *Limitations of the Animal Model*, NAT'L ANTI-VIVISECTION SOC'Y, https://perma.cc/5TUA-8C4E (accessed Sept. 27, 2022) (arguing that instead of focusing on whether animals can be predictive of humans, "the better question to ask is to which humans the data could be applied, considering the genetic variability among our own species [as well as environmental differences such as diet and lifestyle, which may further complicate extrapolation].").

155 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-73.

156 Powell, *supra* note 13.

157 *Definitions of Criteria and Considerations for Research Project Grant (RPG/R01/R03/R15/R21/R34) Critiques*, NIH (Mar. 21, 2016), https://perma.cc/XDG6-MARQ (accessed Nov. 16, 2022).

158 *Id*.

159 *See* OLAW, *Worksheet for Applications Involving Animals*, NIH (June 22, 2017) https://perma.cc/4Y67-Z2JB (accessed Oct. 1, 2022).

nouncements.[160] Criteria such as those concerning vertebrate animals are only included for certain proposed projects.[161] Vertebrate animals are currently taken into account for applications submitted for NIH funding that involve the care and use of animals to help determine the "scientific and technical merit" of a project, and subsequently the project's overall score.[162] One of the criteria that NIH takes into consideration for projects that plan on using live vertebrate animals is the applicants' justification for using the live animal as opposed alternative models.[163] NIH can expand the justification section for projects using live animals to include any project that will use any species of animals whether or not they are alive.

Additionally, NIH could take a modified 3Rs approach. The 3Rs—replacement, reduction, and refinement—is a framework for ethical and humane animal research.[164] Currently, NIH considers the welfare of animals used in research, which falls into the refinement section.[165] Rather than focusing on the refinement of current animal tests, NIH could start moving toward reduction and replacement, where reduction minimizes the number of animals used and replacement replaces animal models with other techniques. Changing focus to replacement can help avoid the barriers of animal models by accelerating the development and use of alternative models to address human health issues unable to be addressed by animal models.

3. Requests for Specific Centers, Institutes, and Scientific Review Groups

Applicants may submit an Assignment Request Form when completing an application.[166] Though optional, NIH encourages applicants to submit an Assignment Request Form to help direct an application to a specific study section (or SRG) or awarding component (NIH institute or center).[167] This form allows applicants to request a specific awarding institute or center.[168] Additionally, this form also allows applicants to make NIH aware of potential conflicts some reviewers may

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160 *Grants & Funding, Write Your Application*, NIH, https://perma.cc/9W2L-T9ZU (accessed Oct. 12, 2022).

161 *Id*.

162 *Id*.

163 *Id*.; Animal Welfare Act, 7 U.S.C. § 2143(3) (2008); Health Research Extension Act of 1985, Pub. L. No. 99-158 § 495 (1985).

164 *See The 3Rs*, NAT'L CTR. FOR REPLACEMENT REFINEMENT & REDUCTION ANIMALS IN RSCH., https://perma.cc/XQ8X-JV2C (accessed Oct. 1, 2022) (defining the 3Rs approach to improving animal welfare for animals used in research studies).

165 *Id*.

166 *Request a Scientific Review Group*, NAT'L INST. HEALTH CTR. SCI. REV., https://perma.cc/3EUP-R98S (accessed Oct. 1, 2022).

167 *Id*.

168 *General Application Guide for NIH and Other PHS Agencies, G.600 - PHS Assignment Request Form*, NIH (Dec. 17, 2018), https://perma.cc/6LT6-62NL (accessed Oct. 1, 2022).

have with an application or whether certain expertise is needed to review the application.[169]

The information that applicants provide on this form is not actually part of their application, so it would not impact the evaluation of the proposed research or project. An NIH institute, such as that proposed in the HRTA or the HEARTS Act that is dedicated to funding and developing alternatives to animal testing, would be an easy way to direct applications to a specific part of the NIH that would be interested in projects using alternatives or developing alternatives. Researchers could request to have their applications put in front of expert peer reviewers who would have the appropriate expertise to evaluate their research or project. Even without such a dedicated institute, NIH could establish an alternatives study section or scientific review group for this purpose.

i. Scientific Review Groups and Alternatives

Applications are reviewed in study sections or scientific review groups.[170] Integrated Review Groups (IRG) are made up of multiple study sections grouped by discipline.[171] Applications typically get assigned first to an IRG and then to a more specific SRG within the larger IRG.[172] NIH could create an IRG that looks at alternatives and then have specific SRGs within that IRG. Additionally, NIH could provide an easily accessible list for prospective applicants to view that shows which IRGs or SRGs have evaluated proposals using or focused on alternatives and the outcomes of those evaluations.

An IRG that is focused on alternatives would allow the additional implementation of SRGs such as Alternatives in Cancer Research or Alternatives in Kidney Systems. The implementation of a new IRG would make it easy for applicants to identify the best study section for alternatives. A specific project intending to use or develop alternatives could then be placed into an SRG based on the specific discipline of the project.

Additionally, within the already existing IRGs, there could be SRGs that focus on alternatives for that scientific discipline. Since the IRGs already encompass a broad spectrum of disciplines and crossover between the different centers and institutes within the NIH, there is room for NIH to develop alternatives related SRGs for each of those disciplines as a way to direct applicants and resources.

There are currently no study sections dedicated to alternatives or indicate that NIH may be open to alternative methods.[173] Without the

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[169] *Id*.

[170] *Application Assigned to a Review Group*, NIH (Jun. 10, 2022), https://perma.cc/36QY-Z9V8 (accessed Nov. 16, 2022).

[171] *Id.*

[172] *The Assignment Process*, NIH (July 2, 2018, 10:35 AM), https://perma.cc/UN9V-W8BF (accessed Oct. 25, 2022).

[173] *See Review Branches*, NIH CTR. FOR SCI. REV. (May 13, 2022), https://perma.cc/RL6Y-4XKZ (accessed Oct. 1, 2022) (listing the specific topic areas under the Review

creation of an IRG or SRG that focus on alternatives, there are still a few already organized IRGs that could be more favorable for alternatives. For example, the Bioengineering Sciences and Technologies IRG considers grant applications on the "fundamental aspects of bioengineering and technology development" in areas like modeling of biological systems, chips and microarrays, and gene and drug delivery systems.[174]

Within the Bioengineering Sciences and Technologies IRG, there is an SRG that reviews applications about modeling technologies for biological systems that could be a good match for many projects using alternative models, and another SRG that looks at lab-on-a-chip technology.[175]

NIH should make information relating to alternatives and different IRGs and SRGs more readily available to help applicants locate the appropriate study sections for their projects. The NIH Center for Scientific Review has developed the Assisted Referral Tool to recommend appropriate study sections to applicants depending on the grant application supplied by the user.[176] This program is a good example of how NIH is already making the grant process more friendly toward alternatives because the user is able to select whether or not their research involves animals.[177] Although the user is able to select whether their research will use animals, it only narrows down the study sections for projects that will be using animals by omitting study sections with less than five percent animal research.[178] This interface does not necessarily make the application process more accessible to applicants using or researching alternatives. In conjunction with other changes NIH could make to their study sections, this tool could allow applicants to search within sections that have connections to alternatives or have already had experience with applications related to alternatives.

SRGs already have some overlap, but applicants may want to request a specific group because the members of that group have greater experience with evaluating alternatives to animal testing. NIH should provide easily accessible information about the members and past applications. This information would make it clearer for applicants to determine which SRGs to request or even which reviewers to exclude

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Branches of the CSR); *Regular Standing Study Sections and Continuing SEPs*, NIH CTR. FOR SCI. REV. (June 28, 2018), HTTPS://PERMA.CC/K4HH-LPLS (accessed Oct. 1, 2022) (listing the regular standing study sections and continuing SEPs).

174 *Bioengineering Sciences and Technologies IRR-BST*, NIH CTR. FOR SCI. REV. (Aug. 11, 2022), https://perma.cc/8LUF-9SKL (accessed Oct. 1, 2022).

175 *Modeling and Analysis of Biological Systems Study Section - MABS,* NIH CTR. FOR SCI. REV., https://perma.cc/3JMZ-F67T (accessed Sept. 26, 2022); *Instrumentation and Systems Development Study Section - ISD*, NIH CTR. FOR SCI. REV., https://perma.cc/AUP8-C9KG (accessed Sept. 26, 2022).

176 *ART User Guide*, NIH CTR. FOR SCI. REV., https://perma.cc/DFT6-PY6F (accessed Sept. 26, 2022).

177 *Id*.

178 *Id*.

from the evaluation process of their application.[179] SRGs are made up of different reviewers, some of whom may not have experience with alternative models and may be ill-equipped to evaluate projects using or developing these models. An available list of projects using or developing alternatives that SRGs and reviewers have evaluated will help applicants determine how to make certain requests pertaining to their applications.

An additional strategy includes providing training to each study group and peer reviewer on the importance of alternatives. Specific training on evaluating alternative models may also increase applicant confidence in the reviewers' ability to accurately make decisions regarding projects focused on the development of new alternative models. Improving the existing model by equipping study groups and peer reviewers to better evaluate these projects would greatly impact the process without requiring major changes, such as the development of an entirely new SRG by NIH.

ii. National Center for Alternatives to Animals in Research and Testing

The Humane Research and Testing Act would establish a National Center for Alternatives to Animals in Research and Testing as part of NIH.[180] An institute within NIH dedicated to alternatives would make it clearer for applicants to direct their applications to reviewers who will be better prepared to understand and evaluate the applicant's proposed project or methods. Applicants would not need to identify the new center unless they choose to but having the option to select an institute that is committed to alternative methods could be advantageous since projects would not be competing against other projects that use traditional animal testing methods and the alternative projects.

The current NIH grants process includes several potential methods for encouraging innovation and alternative methods. Re-evaluating and changing the criteria that already exist in the process can help applicants who intend to use or develop alternative methods to be considered in a light that values their intended purpose. Peer reviewers who are already versed in alternative methods or are aware that alternatives to animal models are an innovative solution to human health issues could be more inclined to select these proposals over other more traditional research models. Constructing the guidelines in a way that

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[179] *See Request a Scientific Review Group,* NIH CTR. FOR SCI. REV., https://perma.cc/4H9G-QYYF (accessed Sept. 26, 2022) (allowing applicants to specify preferences for reviewing groups as well as concerns regarding reviewers that might have conflicts of interests).

[180] *Let's Pass the Humane Research and Test Act of 2021*, CITIZENS FOR ALT. TO ANIMAL RSCH. & EXPERIMENTATION, https://perma.cc/4LJ4-KVBS (accessed Sept. 26, 2022).

represents the positives of alternative models will help streamline the process for research projects dedicated to alternatives to earn funding.

C. Notice of Award and Compliance

The Notice of Award (NoA) is a legal document that notifies a recipient that they have received an award.[181] The NoA contains information relevant to the grant including the budget, the project description, and any restrictions on the use of funds.[182] NIH or any of its Institutes awarding the grant can include additional terms and conditions to the NoA.[183] These terms and conditions can be program or award specific.[184] NIH could increase accountability of award recipients and ensure alternatives are used to the highest extent possible by including additional restrictions or terms within their NoAs for projects focused on alternatives. These additional terms could be used to make sure projects not dedicated to development and usage of alternatives try to minimize their use of animal models by requiring a report on why they are unable to use alternatives.

1. Alternatives Focused Terms

NIH is permitted to include additional terms and conditions to their awards that are not required under federal law.[185] The grants policy statement contains specific additional terms for certain grants including those for for-profit organizations, Federal entities, and for construction of research facilities.[186] These additional terms could include a commitment to using alternative methods to the fullest extent possible or requiring publication updates related specifically to their alternative processes. These additional terms could be included in the award notification as well as available in the NIH Grants Policy Statement.

Including additional terms about a project's commitment to using alternatives will show NIH's clear intentions of supporting the development and use of alternative methods. These terms could be used singularly or in conjunction with other changes in the grants process to promote alternatives. A singular way that this change could promote alternative would be to include a requirement to publish reports on the considerations and usage of alternatives.

2. Accountability for Using Alternatives

For projects that receive funding on the basis of using or developing alternative methods, NIH should be prepared to hold funding recipients accountable if after being awarded NIH determines that the

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181 NIH GRANTS POLICY STATEMENT, *supra* note 65, at IIA-57.
182 *Id*. at IIA-57–58.
183 *Id*. at IIA-61.
184 *Id*.
185 *Id*. at IIB-1.
186 *Id*.

project cannot be fulfilled without the use of animals. Federal regulations permit HHS awarding agencies, including NIH, to take action if a recipient does not meet the terms and conditions of their award.[187]

NIH is permitted to withhold payments, disallow funding of the non-compliant activity (e.g., the animal tests), suspend or terminate the award, or withhold future federal awards for the project or program.[188] These actions could be taken to ensure that applicants who apply for grants under terms of using alternative models rather than animal models are held accountable if they use animal models in their research. Compliance may become more relevant if NIH begins offering grants specifically reserved for researchers using alternative methods.

Placing additional terms in an NoA can highlight NIH's dedication to the use to alternatives. These terms can act as enforcement mechanisms to protect research interests in the development and use of alternatives. NIH already uses additional special terms to protect the interests of special grant projects award,[189] and grants focused on the development and use of alternatives would be no different.

D. Results and Publications

Once a project has received funding from the NIH, there are a number of policies that the recipient must follow.[190] These policies do not explicitly relate to the development and usage of alternative methods but could be changed to promote alternatives. Every recipient of funding needs to acknowledge that they have received federal funding when describing the project in press releases, statements, and other documents.[191] Results of projects funded by the NIH are required to be publicly available.[192] Additionally, if a publication comes out of a federally funded research project the publication needs to be included in either the annual or final progress report to the funding Institute.[193] NIH could add a requirement that it must be noted the project was selected and funded with consideration of the alternative methods (if that project is using or developing alternatives). A discussion on alternatives could also be required to be included in published results and data for federally supported projects.

Results of projects funded by NIH are required to be made available to the public and research community.[194] Depending on the form that results and outcomes from funded research take, the regulations regarding publication, availability, and use of results differ. While

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[187] Uniform Administrative Requirements, Cost Principles, and Audit Requirements for HHS Awards, 45 C.F.R. § 75.371 (2022).

[188] *Id*.

[189] NIH GRANTS POLICY STATEMENT, *supra* note 65, at IIA-61.

[190] *Id*. at IIA-3.

[191] *See* Steven's Amendment, Act of Nov. 21, 1989, Pub. L. No. 101-166 § 511 (1989).

[192] NIH GRANTS POLICY STATEMENT, *supra* note 65, at IIA-119.

[193] *Id*. at IIA-120.

[194] *Id*. at IIA-119.

NIH encourages recipients of funds to share knowledge through scientific journals, it is not a requirement under NIH policy.[195] The public is only required to have access to results if the results have been published.[196]

Federal law requires NIH funded investigators to provide a final, peer-reviewed, manuscript to be published in PubMed Central (PMC).[197] PMC is an archive of biomedical literature at NIH's National Library of Medicine.[198] Investigators do not need to submit their manuscript to be made available on PMC until it has been accepted for publication elsewhere, but once it is accepted elsewhere it must be made available to the public within one year of the date of publication.[199] NIH could help promote alternative models by requiring publications for projects that both use or develop alternatives and do not use or develop alternatives.

Requiring NIH funded projects that are developing or using alternatives to make results available to the public may help further the acceptance of non-animal models. Requiring publication of results through NIH whether a manuscript has been accepted elsewhere removes any bias that alternative models may face due to the traditionality of animal models. The more information available about alternative methods, the more accepted they may become by animal model proponents.[200]

NIH-funded research using animal models should publish their justifications for not using alternative models. Currently under federal law, any "applicant for a grant, contract, or cooperative agreement involving research on animals" administered by NIH needs to include "a statement of the reasons for the use of animals in the research to be conducted with funds provided under such grant or contract," as well as require each principal investigator to consider alternatives to any procedure likely to cause pain or distress.[201] While this requirement may help researchers think about their reasoning for using animals, it is more of an afterthought than an incentive to use alternatives, making it ineffective. Publishing reasons for choosing not to use alternative models provides more information to researchers who want to work on alternatives for research that is previously unable to use al-

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195 *Id*. at IIA-120.

196 *Id.* at IIA-20; 45 C.F.R. § 75.365 (2014). No HHS awarding agency can restrict public access to records of the recipient that are related to the federal award except for personally identifiable information or other information that would not be available as a result of a FOIA request.

197 42 U.S.C. § 282c (2009).

198 *PubMed Central*, *supra* note 51.

199 42 U.S.C. § 282c.

200 *See* Juan Carlos Marvizon, *Computer Models are Not Replacing Animal Research, and Probably Never Will*, SPEAKING RSCH. (Jan. 7, 2020), https://perma.cc/JFF6-ZJ82 (finding that computer models are not replacing animal models because there are less publications on computer models on PubMed).

201 Health Research Extension Act of 1985, Pub. L. No. 99-158, § 495(c)(2), 99 Stat. 820, 876; Animal Welfare Act, 7 U.S.C. § 2143(a)(3)(B).

ternatives. Enlarging the availability of information related to the development and use of alternative models can help encourage further research into the development and use of alternatives. Additionally, publishing justifications for not using alternatives may require researchers to put more thought into their decision, as opposition to animals in research testing is growing among the American public.[202]

Currently, most grant-related information submitted by applicants is public information.[203] Once NIH grants an award, the information submitted by an applicant may be available to individuals or organizations other than the NIH.[204] Right now, the public is able to see information on NIH-funded projects such as project descriptions on Research Portfolio Online Reporting Tools (RePORT), or request them from the National Technical Information Service (NTIS).[205] Additional information is only made available on a case by case basis, such as through a Freedom of Information Act (FOIA) request.[206]

Under FOIA, NIH must provide grant documents that the public requests and are covered under the FOIA statute.[207] The information that NIH will make available in response to a FOIA request are funded applications, funded progress reports, award data, and final reports after they have already been sent to another organization for an audit, survey, review, or performance evaluation.[208] There is additional information that NIH will not make available to the public even in response to a FOIA request including pending competing grant applications.[209]

While some information is available on RePORT, an interested party would need to know specifics about a project to find information. NIH could make a webpage available that includes information specifically related to federally funded research projects using or developing alternative models to animal testing. When researchers and members of the public are more aware of the projects working on or using alternatives, these models will be more accepted, understood, and hopefully used.

Rather than require members of the public to go through the timely process of making a FOIA request,[210] which does not even include information such as applicants competing for a grant that has not yet been awarded, NIH can publish the information on their web-

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202 Mark Strauss, *Americans are Divided Over the Use of Animals in Scientific Research,* PEW RSCH. CTR. (Aug. 16, 2018), https://perma.cc/UK45-P4LN (accessed Oct. 1, 2022); Ike Swetlitz, *Americans' Opposition to Animal Testing at Record High, Survey Finds*, STAT NEWS (May 12, 2017), https://perma.cc/6H3K-6PJF (accessed Oct. 1, 2022).

203 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-68.

204 *Id*.

205 *Id*. at I-68–69.

206 *Id*. at I-69–70.

207 Freedom of Information Act, 5 U.S.C. § 552 (2016).

208 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-70.

209 *Id*.

210 *See How Long Will it Take to Process My Freedom of Information Act (FOIA) Request?*, U.S. GEOLOGICAL SURV., https://perma.cc/N7ZK-MJTY (accessed Oct. 1, 2022).

site for easier access—possibly as an alternatives "scorecard" or report. Additionally, NIH could include information regarding competing grant applications for the public to evaluate how many projects using animal tests compared to how many projects using alternatives are selected out of the applicants. Making information about competing applications that have not yet been selected could help researchers evaluate potential bias from study sections and institutes regarding alternatives. Furthermore, NIH could make finding published information regarding alternatives easier by adding an easier search mechanism for alternatives in the NIH grant databases.

NIH has a duty to help inform other researchers and the public about federally funded methods to advance science even if results of projects are not published elsewhere.[211] NIH's data sharing policy states that NIH "believes that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health."[212] Under this belief, NIH should support the required publication of all NIH funded research related to alternatives whether it be by research using or developing alternative methods or by research using animal models.

E. NIH Initiatives—Raising the Profile of Alternatives in RFPs and Other Funding Mechanisms

Prior to being evaluated through the peer review process, each applicant must fill out application forms.[213] Funding opportunity announcements provide application forms for the applicants to use.[214] Prospective applicants must respond to a funding opportunity in order to submit an application, and therefore applicants need to locate opportunities that fit their project.[215] NIH can make the funding process more supportive of alternative models through two different methods. First, NIH can create a specific type of grant denoted by a new activity code that directs funds only to researchers working on alternatives or using alternatives. Second, NIH can allow prospective applicants to include search criteria for funding opportunity announcements that narrow the options to only those for the development and use of alternative methods.

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211 *See* NIH GRANTS POLICY STATEMENT, *supra* note 65, at IIA-121 ("NIH considers the sharing of such unique research resources . . . an important means to enhance the value of NIH-sponsored research. Restricting the availability of unique resources can impede the advancement of further research.").

212 Id. at IIA-122.

213 *See id*. at I-72 ("Competing applications for NIH grants and cooperative agreements . . . are subject to peer review . . . .").

214 *Types of Applications*, NAT'L INST. HEALTH GRANTS & FUNDING, https://perma.cc/S87F-Y6MP (accessed Oct. 1, 2022).

215 NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-52.

1. New Activity Code and Research Criteria for Alternatives

NIH advertises the funding opportunities online, and prospective applicants can either respond to a generic parent announcement or search for specific subject areas within the funding opportunity announcements.[216] Grants are published using activity codes that differentiate the types of research programs available to receive funding.[217] Research grants have their own activity codes for prospective applicants to search through including Small Business Innovative Research and Exploratory/Developmental Research awards.[218] Small Business Innovative Research grants are for the purpose of supporting research in the private sector for ideas that can be commercialized.[219] Exploratory/Developmental Research grants are awarded to support and encourage new projects in their early stages of development that may result in novel methodologies or models that will impact biomedical or clinical research.[220]

Both the Small Business Innovative Research grant and Exploratory/Developmental Research awards are types of "R Series" research grants.[221] R Series grants are not limited to a certain size, type, or award amount.[222] Other types of grants include Program Project/Center Grants or "P series," which are typically larger than R Series grants due to including diverse research activities.[223] NIH could develop a specific grant type that falls under either of the above categories to help encourage applicants dedicated to the use and development of alternative methods.

NIH has already created grants with specific goals related to animal testing.[224] There are 246 different types of grants including one specifically to help develop and support animal models (P40).[225] This grant falls under the research program, projects, and centers type, with an identical grant under the cooperate agreement type (U42).[226] Additionally, there are funding opportunities for researchers

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[216] *See Funding*, NIH CENT. RES. FOR GRANTS & FUNDING INFO., https://perma.cc/QE4Y-KRVL (accessed Sept. 27, 2022) (providing links to "View all Parent Announcements" and "Find Grant Funding").

[217] *Types of Grant Programs,* NIH CENT. RES. FOR GRANTS & FUNDING INFO., https://perma.cc/86BT-6YG6 (accessed Sept. 27, 2022).

[218] *Id*.

[219] *Id*.

[220] *NIH Exploratory/Developmental Research Grant Award (R21)*, NIH CENT. RES. FOR GRANTS & FUNDING INFO., https://perma.cc/XL2C-32AU (accessed Sept. 27, 2022).

[221] NIH CENT. RES. FOR GRANTS & FUNDING INFO., *supra* note 217.

[222] *See id*. (listing a variety of R Series grants of various sizes, types, and award amounts).

[223] *Id*.

[224] *See Activity Code Search Results*, NIH Cent. Res. for Grants and Funding Info., https://perma.cc/N3QL-96HG (accessed Sept. 27, 2022) (listing three grant types which specifically reference animal research).

[225] *Id*.

[226] *Id*.

and centers working on primate research.[227] NIH can create new grant options for alternatives in the manner it has for projects working on animal models or on nonhuman primates.

Certain types of grants require specific supporting material and criteria for the application.[228] These grants can be identified by specific types of characteristics including purpose—the development and use of alternatives can be used as a distinguishing measure for grants.[229] NIH and individual institutes within NIH have the ability to apply "specialized eligibility criteria" for different characteristics of grants.[230] The creation of specialized criteria could help start a granting mechanism for projects dedicated to the use and development of alternatives.

Both the development of a new activity code for research dedicated to developing and using alternative methods and the addition of a specific category of criteria would show researchers that the NIH supports a transition to alternative models. Not only will creating a new activity code and criteria for alternatives show the researchers they have the support of NIH, but doing so would also create funding opportunities specific to new models. Giving alternatives their own funding opportunities separate from grants that may consider projects using animal models would drive competition in alternative methods and potentially spark more interest in the new techniques.

2. Alternatives Oriented Search Mechanisms for Prospective Applicants

By adjusting the way to locate specific research opportunities available and the convenience of funding the opportunities for prospective applicants, researchers interested in alternatives will be able to locate the options available more easily. These researchers may have been previously prevented from forwarding their research efforts due to funding. By minimizing the time needed to do so, these researchers, who previously would have been unable to fund funding, may have a chance to locate funding opportunities. Changing the search mechanisms would save researchers time, as well as allow them to more easily identify opportunities that are a better fit for their research into alternatives.

The current available funding opportunities can be found in multiple locations.[231] The NIH website offers a search bar to narrow down

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[227] *Id*.

[228] NIH GRANTS POLICY STATEMENT, *supra* note 65, at I-59.

[229] *See id.* (listing additional materials required for training-related and individual career development grants).

[230] *Id*. at I-50–51.

[231] *See, e.g.*, *Parent Announcements (For Unsolicited or Investigator-Initiated Applications),* NIH CENT. RES. FOR GRANTS & FUNDING INFO., HTTPS://PERMA.CC/57HR-S5EJ (accessed Sept. 27, 2022) (listing various broad funding opportunity announcements); U.S. Gen. Servs. Admin., *Contract Opportunities*, SAM.GOV, HTTPS://PERMA.CC/RF9R-

the hundreds of grants and notices opportunities.[232] Additionally, the NIH website allows prospective funding applicants to search through all grants and contracts.[233] The webpage that advertises all available contracts and grant opportunities has search mechanisms to sort by organization within the NIH, as well as by activity code, type of research, and type of funding opportunity.[234] Contract Solicitations are available for prospective researchers to search in two locations. One location is a portal that allows searching through the available contracts posted by the Federal Government.[235] The second is specific to NIH opportunities.[236] Within the NIH-specific opportunities, prospective contractors have the ability to narrow RFPs by institute.[237] NIH can make locating funding opportunities more friendly toward alternative methods by adding in a search mechanism that lets researchers sort by non-animal models vs. animal models.

Allowing researchers to find available contracts and grants specific to alternatives will minimize the amount of time that researchers need to spend locating funding opportunities. Minimizing the time needed to search through the available opportunities makes the process of finding available funding less daunting and therefore more friendly toward alternative methods.

The peer review process works in conjunction with the actual application process because the reviewers determine the scientific merit of the project from what is included in the project application.[238] Making the available applications focused on alternatives easily identifiable will connect researchers interested in those projects more likely to apply for funding that suits their needs. By providing search criteria that meets the needs for researchers developing and using alternatives, the funding process as a whole will be more favorable toward the new methods. Tailoring the type of grants researchers using and developing alternatives may make them more successful when going through the peer review process since they will not be competing against projects using more traditionally accepted methods like animal testing models.

XZSW (accessed Oct. 25, 2022) (advertising "[c]ontract opportunities" for "[a]nyone interested in doing business with the government").

232 *Find Grant Funding*, CENT. RES. FOR GRANTS & FUNDING INFO., (Sept. 13, 2022), HTTPS://PERMA.CC/3JJ4-ZVMT (accessed Sept. 30, 2022).

233 *Id*.

234 *Id*.

235 *See* U.S. Gen. Servs. Admin., *supra* note 231 (providing a mechanism to search for contract opportunities for the U.S. government).

236 *See Contract Opportunity*, NIH OFF. MANAGEMENT, https://perma.cc/U29D-4DSJ (accessed Oct. 4, 2022) (listing contract opportunities for the U.S. government).

237 *Id*.

238 *Peer Review*, NIH (Oct. 24, 2021), https://perma.cc/T2DY-W254 (accessed Oct. 25, 2022).

F. Federal Legislative Initiatives—The Humane Research and Testing Act

The HRTA is a bipartisan bill that, if passed, would establish the National Center for Alternatives to Animal Research and Testing within the National Institutes of Health.[239] The HRTA was reintroduced in March of 2021 with minimal changes, including a provided definition of the term "animal"—a change that resolves an earlier criticism of the initial iteration of the bill.[240] The Humane Research and Testing Act was not reintroduced for the 118th Congressional Session, but the creation of a new center is included in the Humane and Existing Alternatives in Research and Testing Sciences Act of 2022 (HEARTS Act). The new center's proposed mission is to promote "alternative animal testing" and reduce the number of animals used in research.[241] Additionally, the bill would require federally funded research entities using animals for research and testing to report on and attempt to reduce their animal usage.[242]

The bill notes that a large portion of NIH research uses animals even though NIH policies mandate that the smallest number of animals necessary should be used.[243] The establishment of a center focused on developing, promoting, and funding alternatives, as well as curating a plan for the reduction of animal usage in other federally funded centers would help NIH not only match their policy of using the smallest number of animals in research necessary, but also NIH's mission as a whole.

The Center would provide additional support for researchers focused on the development of the usage of alternatives to animals including funding. The bill specifically identifies alternative methods to be promoted and funded including 3D organoids, microphysiological systems, and in silico modeling.[244] The availability of a center dedicated to the development and use of alternative methods has the potential to encourage researchers to apply for grants for projects focused on alternatives.

Throughout the funding process for contractors and grant applicants, there are openings for specific centers and institutes to put out their own requests for contractors or grant opportunities. Additionally, applicants can identify certain institutes and centers using the Public

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239 H.R. 8633, 116th Cong. (2020).

240 *See* Paul Locke et al., *The Humane Research and Testing Act: Advancing Science by Creating a New Center for Alternatives at the US National Institutes of Health,* 38 ALTEX 678, 678–79 (2021) (describing the proposed HRTA and its potential uses and impacts).

241 H.R. 8633, 116th Cong. § 485E (2020).

242 *Id*.

243 H.R. 8633, 116th Cong. § 2 (2020); *Animals in NIH Research*, NIH (Aug. 19, 2022), https://perma.cc/7GXK-NA8F (accessed Oct. 25, 2022).

244 H.R. 8633, 116th Cong. § 2 (2020).

Health Services Assignment Request Form.[245] The new Center has the potential to make scientists more familiar with alternatives to animal studies such as Organ Chips, and this familiarity may make scientists request animal studies less. Establishing a center dedicated to alternatives will open up more opportunities for researchers dedicated to using and developing alternatives and make the entire granting process more accessible to alternatives as a whole. Through making the granting process more accessible and increasing the familiarity of alternatives, NIH can work toward their mission to enhance health, lengthen life, and reduce the burdens of illness and disability.

V. Conclusion

NIH's mission and goals express its dedication to advancing biomedical research and human health.[246] Highlighting the need for, and the role of, non-animal alternative methods is not expressly stated as a goal of NIH.[247] As this Article shows, there are several ways NIH could contribute to a paradigm shift for human health by supporting human-centered testing models. Although there are ways to support alternatives for twenty-first century science through more time-consuming and demanding changes such as passing new laws or implementing new regulations, NIH is not a regulating body and can create significant change with small policy adjustments. The policy changes discussed in this Article could shape research in a way that supports both animal and alternative models to help gain knowledge about and find potential cures for human diseases.

From the start of the application process, NIH can create equal opportunities by catering its notifications of grant and contract availability. RFAs could be used to solicit research on alternatives just as they are for animal models or by identifying research, either using or developing alternatives as an area of special interest. NOSIs across all institutes of the NIH or within specific institutes could also be used for the development of alternatives.

The peer review process is an important step in the grant and contract process and within this step alone there are multiple changes NIH can implement for alternatives and animal models to be given the same consideration. These changes include adding specific requirements for the consideration of development and use of alternative models throughout the entire process, looking at the already established, required, criteria through a lens considering alternative options, or developing new criteria entirely. Additionally, the peer review process involves review groups that evaluate the applications. Applicants could have the ability to request their project be evaluated by certain institutes or review groups who may be more equipped to fairly

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[245] *PHS Assignment Request Form*, NIH, https://perma.cc/KGK4-SDDR (accessed Oct. 10, 2022).

[246] NIH, *supra* note 12.

[247] *Id*.

evaluate a project using or developing alternatives. NIH could even add in a new review group who is versed in alternatives or from a new center on alternatives should the HRTA be passed. NIH could also advertise which institutes or centers are already encouraging alternatives or are interested in pursuing alternative methods research so applicants can better direct their applications toward these centers and institutes.

In both the notice of award and reports stages of the grants and contracts process there are additional opportunities for NIH to make changes, such as a requirement for award recipients to document usage of alternatives, and if no alternatives were used, why not, publicly. The aforementioned changes would ensure accountability and transparency throughout the entire grants and contracts process. These small policy changes in the reports portion of the process would be more effective than the current requirements of researchers to state why they need to use animals since it is less of an afterthought.

The simplest changes the NIH could implement to help alternatives and animal model researchers to equally find funding opportunities are not even policy changes, but functional changes. NIH could create easier search mechanisms when it comes to locating funding opportunities including filters for opportunities available for those working with or developing alternatives to animal models. Easier, searchable, search criteria will allow prospective applicants to narrow down funding opportunities to those only for the development and use of alternatives. Additionally, NIH could create new activity codes for opportunities open to alternative models or specifically seeking alternative research—this activity code would represent a specific grant that directs funds only to researchers working on alternatives or using alternatives.

These policy and functional changes may incentivize researchers to look into alternatives by inspiring their entrepreneurial sprits and therefore help bring about a paradigm shift for research testing that can fill in the gaps that currently exist. Converting the funding process to be more equally oriented toward alternatives can help research of these methods cross a barrier to their development. The grants and contract process provides openings that NIH can use to improve science by increasing attention on alternatives. By changing the grants and contract process to be more accepting toward alternatives, NIH will be helping advance biomedical research by supporting the new developments and helping researchers to think more about human-relevant testing methods to further the development, use, and reporting of new technologies.