The Struggle to Improve the Value, Reliability, and Ethics of Biomedical Research in the United States

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by

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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In the United States, biomedical research has supported remarkable advancements in understanding life, disease, and healthcare. Researchers rely heavily on animals for inventing and testing drugs, devices, and diagnostics that improve and prolong human lives. The US Food and Drug Administration (FDA) requires pre-clinical trials in non-human animals to demonstrate safety and efficacy before a novel drug or device can be tested clinically in humans and eventually brought to the market. The US Department of Agriculture (USDA) under the Animal Welfare Act (AWA) enforces standard practices, procedures, and ethical guidelines for animal research.

The value, ethics, and role of animal testing in biomedical research is an active debate within the US. While the debate is complex and sometimes divisive, there is general agreement that when animal research yields no better results than other methods, it is both wasteful and unethical. With widespread acknowledgment of inefficiencies, ethical concerns, and the reliability crisis in animal research, animal models are undergoing scrutiny. Animal advocates oppose animal research due its cruelty and inhumane nature, calling to decrease - in some cases, completely eliminate - animal testing. Researchers, animal advocates, and other experts agree the translatability of animal research to human benefit is low. Still, biomedical experts in commercial and research applications rely heavily on animal based research. Technological developments have made NAMs (Non-Animal Models, or New Alternative Methods) sufficiently useful in research to offer opportunities to reduce the animal burden in biomedical research.

Researchers and animal advocates have demanded wider adoption of NAMs to improve the low translatability of animal testing to human benefit, to support medical breakthroughs where animal models limit research, and to reduce the dependency on animal testing. Many

researchers and experts agree, however, that NAMs are not yet viable for replacing animal methods. With major implications for both human and animal health, the US is in the early stages of a research revolution. NAMs are on the verge of incorporation into standard research practices and regulatory processes. This report seeks to characterize the pressures shaping biomedical research reform in the US. It also summarizes the most relevant steps taken to promote and regulate valuable, reliable, and ethical research within the US.

Review of Research

The Role of Animal Models

Animal research and testing has yielded impressive results leading to widespread transformations in human healthcare. According to The Foundation for Biomedical Research, "If you've ever taken a medicine or had a medical procedure, you've benefited from animal research and testing" (FBR, 2025). In 2023, the USDA reported 774,065 animals (dogs, cats, hamsters, rabbits, guinea pigs, non-human primates, sheep, pigs, and other animals) were used in US research (USDA 2023). In 2022, the USDA reported 784,295 animals used for research, and in 2021, they reported 851,423 (USDA 2021; USDA 2022). USDA reports neglect statistics on rats and mice, whose numbers are estimated to be over 110 million annually in US research (Cait et al., 2022; Carbone, 2021). Because rats, mice, and birds are cold-blooded animals, they are not covered by the AWA and thus exempt from USDA reporting (US Congress, 1966).

The Rising Popularity of NAMs

The acronym NAM is generally accepted as New Approach Methods, Non Animal Models, or Novel Alternative Methods. These technologies and approaches aim to reduce the reliance on animals for biomedical and biochemical research and have the potential to offer insights that animal models cannot. NAMs include computational methods (in silico), cellular and tissue cultures (in vitro), and cell-free (in chemico) technologies.

Between 2003 and 2022, "the relative number of publications of research using NAMs-only has been higher than animal-based research…and is growing" worldwide across seven distinct research areas: breast cancer, lung disease, blood cancer, heart disease, neurodegenerative diseases, diabetes and toxicology (Katy, Stephanie, & Jarrod, 2024). "Recent scientific developments have led to multiple 'human-relevant' research models - those based on human biology - that have the potential to lead to improved understanding of human biology, disease pathophysiology, and therapeutic development" (Singer & Akhtar, 2024).

The Changing Role of Animal Research and the Rise of NAMs

Benefits of Animal Research

Researchers and companies use animals to study health conditions, injuries, and potential treatments, subjecting the involved animals to injury, disease, and death. This research has been vital for eradicating smallpox and polio, and helping to combat cancer, HIV/AIDS, Alzheimer's, hepatitis, and malaria among a plethora of other diseases and health conditions (FBR, 2025). "Animals are good research subjects for a variety of reasons. They are biologically similar to

humans and susceptible to many of the same health problems. Also, they have short life-cycles so they can easily be studied throughout their whole life-span or across several generations. In addition, scientists can control the environment around the animal (diet, temperature, lighting, etc.), which would be difficult to do with people" (APA, 2025).

Ethical Considerations

Animal research is a long standing ethical debate. Many advocates wish to end animal testing, while some try to find a balance in an ethical middleground. Huge research institutions, like Stanford Medicine, posit similar stances on animal research: "The use of animals in some forms of biomedical research remains essential to the discovery of the causes, diagnoses, and treatment of disease and suffering in humans and in animals" (2025). Harvard Medical School suggests that "The humane and regulated study of animals is indispensable for the pursuit of…understanding how diseases arise at the molecular level, how they cause dysfunction, and finding ways to combat suffering caused by disease" (2025). Still, animal advocates oppose using animals for research. Cruelty Free International believes "there is no moral or scientific justification for using animals in experiments." Humane Society International asserts, despite modern approaches to reduce animal suffering during experimentation, "there's no 'humane' way to poison animals with chemicals or to infect them with deadly diseases like rabies to test the effectiveness of a vaccine" (HSI, 2024). As a result, animal advocacies and researchers sympathetic to reducing animal suffering and increasing the value of biomedical research have advocated for increased use of non-animal research methods.

William Russell and Rex Burch coined the "3Rs" in their book, Principles of Humane Experimental Technique (1959). The 3Rs (replacement, reduction, and refinement), while not

legally enforced in the US, are widely accepted animal welfare guidelines that inform regulation and seek to reduce the suffering of animals undergoing scientific experimentation. Replacement calls for the substitution of conscious animals for insentient material; reduction aims to lower the number of animals used to obtain the required level of data precision; and refinement seeks to decrease the severity of inhumane practices and procedures (Russell & Burch, 1959). Huge pharmaceutical companies (eg. Pfizer, Eli Lilly, and Merck), medical device companies (eg. Medtronic and Abbott), and research institutions (eg. Harvard and Stanford) proudly claim adherence to the Three Rs.

The Three Rs, however, have been criticised for failing to acknowledge scientific validity and the necessity for reproducible results. Researchers Matthias Eggel and Hanno Wurbel propose a comprehensive protocol for evaluating animal research by combining the 3Rs with determinants of validity (3Vs) and a positive harm-benefit analysis (HBA) (Eggel & Wurbel, 2020). Their framework requires that an animal study protocol is "(a) suitable, (b) necessary and (c) reasonable for achieving its aims." For determining whether a study is suitable, the 3Vs interrogate a study's construct (quality of animal model), internal (cause and effect relationship establishment), and external (extent of inference space) validity. For determining its necessity, the 3Rs are satisfactory. For determining its reasonableness, an HBA ensures a study's benefit to humanity outweighs its harm to animals. Others support the 3Vs, noting that experimental strength is a key missing component of the original 3R model (Crister & Locke, 2024). These discussions highlight recent efforts to improve outdated guidelines and introduce metrics for value and rigor to animal research.

Systemic Inefficiency

"The cost of animal research is high—in dollars, delays in drug approval, and in the loss of potentially beneficial drugs for human use" (Norman, 2019). Moreover, animal based research has remarkably low translatability into human benefit. Infact, 92% of drugs that appear safe and effective in animals fail to meet standards in human trials (Akhtar et al, 2015). In 2004, Merck and Co. voluntarily withdrew its anti-inflammatory arthritis medication, Vioxx, from the market (Balcombe, 2010). Despite being approved for marketability after six successfully portrayed animal studies, the drug caused heart attacks and strokes in an estimated 88,000-139,000 patients, 60,000 of which were fatal (Lucas, 2015). In 2006, six volunteers underwent trials of a CD28 superagonist antibody, TGN1412. The drug seemed promising for fighting leukemia and rheumatoid arthritis (NIBSC, 2024). Despite taking a dose 500 times smaller than what had previously been found safe in animal studies, six out of the six volunteers experienced life threatening complications within 90 minutes of the very first infusion (Attarwala, 2010).

Between 2012 and 2025, the FDA has recalled 12,077 biologics, 35,677 medical devices, and 16,746 drugs (FDA, 2025). These cases are economically costly and disastrous to human health. Current regulations and approval processes contribute to oversight errors, leaving the door open for poor research to pass undetected through regulatory agencies. As cases of faulty drugs arise and the damage is publicized, trust in biomedical research and its output is eroded.

Reproducibility Crisis

"Reproducibility and research integrity are essential tenets of every scientific study and discovery. They serve as proof that an established and documented work can be verified,

repeated, and reproduced" (Diaba-Nuholo & Amponsah-Offeh, 2021). Generally, reproducible results in empirical research offer more reliable and valuable findings.

In 2024, Kelly Cobey published results of a survey in which >1,600 biomedical researchers' were polled on their perspectives on the reproducibility crisis in biomedical research (Cobey et al., 2024). Of the participants, 72% agreed a reproducibility crisis in biomedicine exists, with 27% indicating it was "significant". "Pressure to publish" was deemed the leading cause, with roughly 62% of respondents indicating it "always" or "very often" contributes. "New knowledge in the biomedical science is built on the shoulders of established and proven principles. Thus, scientists must be able to trust and build on the knowledge of their colleagues… Poor reproducibility and integrity, therefore, may lead to ineffective interventions and applications" (Diaba-Nuholo & Amponsah-Offeh, 2021). Director of the Center on Knowledge Graphs at USC's Information Sciences Institute, Jay Pujara, explains "People will not believe in science if we can't demonstrate that scientific research is reproducible" (Cohen, 2022). Researchers who note the crisis offer rationales. "Inappropriate statistical methods, poor experimental design, and extreme standardization in trial design are some contributing factors to the problem" (Frommlet, 2020). Others go further to suggest design methodological changes to improve reliability. Through systematically introducing heterogeneity into animal study populations by "splitting an experiment into several 'mini-experiments' spread over different time points a few weeks apart' the poor reproducibility of single-laboratory studies can be improved (Kortzfleisch et al., 2020). Natasha Karp corroborates the idea of "multi-batch" design to improve robustness of efficacy and to reduce animal use (Karp et al., 2020).

Applications of NAMs

NAMs offer greater ability to assess the underlying physiological mechanisms being impacted by a substance of interest compared to animal models, which are better adapted for observing and measuring systemic effects (FDA, 2024). “In silico models encode and test hypotheses about mechanisms underlying the function of cells, the pathogenesis and pathophysiology of disease, and contribute to the identification of new drug targets and drug design.” They can be used to “screen a library for compounds using molecular docking techniques, rationally design novel drugs and analogues of existing drugs based on knowledge of protein interactions or their active sites, and investigate the mode of action of a drug or study drug-resistant mutants” (Valerio Jr., 2014). In silico models can be used to model and experiment on molecules, cells, tissues, organs, and full organ systems. Other NAMs seek to increase human translatability by utilizing human biology directly. For in vitro methods, samples of human cells, blood, saliva, or tissue are taken for experimentation and can be widely applied to detect infectious diseases and study oncology, cardiology, endocrinology, genetic testing, reproductive health, hematology, toxicology, autoimmune and allergy testing, and neurology” (BOYD Biomedical, 2024). In chemico methods offer high throughput, sensitivity, and accuracy allowing for rapid and valuable experimentation (Ferreira et at., 2023). When used together, and even when used independently, NAMs offer significant insights into biomedical research directly applicable to humans.

Guidelines for Incorporating NAMs

Despite 92% of drugs that appear safe and effective in animals failing to meet standards in human trials, animal models remain the primary validation model within biomedical research.

However, initiatives pushing for more reliable, ethical, and efficient biomedical research are growing. Government organizations like the National Institute of Health (NIH) and the National Institute of Environmental Health Sciences (NIEHS) are updating regulations for proving safety and efficacy to improve the value and reliability of biomedical research and reduce unnecessary animal waste.

In December 2023, the NIH delivered a report, Catalyzing the Development and Use of Novel Alternative Methods. They classified NAMs into "three general categories of technologies: computational modeling and predictive technologies (*in silico*), cell-free methods and assays (*in chemico*), and cell-tissue-organoid culture models (*in vitro*)" (NIH, 2023). The report explains, "each model offers unique strengths that, when utilized individually or in combinations, expands researchers' toolboxes to improve upon and answer previously unanswerable biomedical research questions, and to ask new questions. For NAMs to be effective and reliable, these strengths and weaknesses should be assessed prior to incorporation into a study, and context of use should be considered in NAMs development." The report also provides seven "Recommendations to Catalyze the Development and Use of NAMs," contending that the "large-scale uptake of any new technology by researchers, practitioners, and patients will require a cultural shift" and that the success of adopting NAMs will require building confidence in NAMs among the "research and technology development community and the public"

In March 2024, The Interagency Coordinating Committee on the Validation of Alternative Methods, led by the NIEHS, released a report detailing recommendations for incorporating NAMs into biomedical research (ICCVAM, 2024). Its main objective was to "assist method developers, regulated industry stakeholders, and federal agencies in the development, validation, qualification, and acceptance of scientifically relevant NAMs." The

report stressed the importance of "communication between the developers, end users, and regulatory agencies" and hoped to "build confidence by describing concepts such as context of use, biological relevance, and technical characterization of NAMs."

These reports help to establish the potential benefits NAMs can provide to biomedical research, and suggest ways it can be done. These, and others, characterize the steps needed to incorporate and validate NAMs in a way that is reliable, helpful, and efficient for biomedical researchers and corporations engaging in biomedical research.

Educational Initiatives

Organizations are developing educational programs in response to the rise of and predicted future prevalence of NAMs in biomedical research. The Physicians Committee for Responsible Medicine "works with government and industry to replace the use of animal tests with modern methods to test the safety of cosmetics, chemicals, pesticides, drugs, and other products" (PCRM, 2025). To spread awareness, the Committee launched its "2024 Summer Immersion on Innovative Approaches in Science to Provide Early Career Researchers a Deep Dive in Human-Based Nonanimal Science" (PCRM, 2024). Its aim, "to educate the next generation of researchers on human-based, nonanimal methods for advancing biomedical science and regulatory safety testing of pharmaceuticals, medical devices, cosmetics, and other agricultural and industrial chemicals." The program provided "lecture style presentations, hands-on workshops, technology demonstrations, and case studies" to "provide an introductory overview and in-depth trainings on in vitro, in chemico, and in silico, and human ex vivo approaches and their many applications in basic, translational, and regulatory science" (PCRM, 2024).

Regulatory Initiatives

In September 2022, the FDA Modernization Act 2.0 was signed into law. The Act "authorizes the use of certain alternatives to animal testing, including cell-based assays and computer models, to obtain an exemption from the Food and Drug Administration to investigate the safety and effectiveness of a drug." These exemptions overturn a massive historical precedent and allow drug developers to utilize methods like computer modeling, cell-based assays, and organ on a chip technologies to lead to human clinical trials. Following its adoption, headlines like USA Today's "Testing Drugs on Animals Could End. When Will the Technology be Ready?" and The New York Times' "Could the Next Blockbuster Drug Be Lab-Rat Free?" suggest the bill will soon end animal testing in biomedical research (Brown, 2023; NYT, 2023). The Act, however, reflects the growing pressures for developers to "adopt the best practices of being purposefully thoughtful about the use of animals, seeking alternatives wherever possible" (Carratt et al., 2024). Food Drug Safety Research and Development professionals at Pfizer clarify the goals of the FDA Modernization Act 2.0 from an industry perspective: "although the current state of technology does not yet provide adequate models to fully replace in vivo studies, many models are sufficiently good for an augmented approach that will enhance our understanding of in vitro to in vivo correlations and advance the long-term goal of reducing animal use through innovative NAMs. The goal of future nonclinical safety packages is to advance the utilization of such enabling technologies toward appropriate human risk characterization" Despite the Act's adoption into law, the FDA has yet to update its regulations to conform. The FDA Modernization Act 3.0, which passed the Senate in December 2024, will require the "FDA to update its regulations within twelve months of the bill's enactment" if ratified (Cory Booker, 2025).

The United States has seen a push for NAMs outside of biomedical research as well. In June 2020, the US Environmental Protection Agency (EPA) released its New Approach Methods Work Plan to "prioritize agency efforts and resources toward activities that aim to reduce the use of vertebrate animal testing while continuing to protect human health and the environment" (EPA, 2025). The plan aims to "establish scientific confidence in NAMs and demonstrate application to regulatory decisions" and to "fill critical information gaps".

Potential Impact

Despite the excitement around NAMs, significant barriers stand in the way of their adoption and implementation. Animal methods bias has been identified as "a type of peer review bias characterized by a preference for animal-based research methods or lack of expertise to properly evaluate nonanimal methods, which affects the fair consideration of animal-free approaches" (Krebs et al, 2025). It is similarly defined as "a preference for animal-based methods where they may not be necessary or where nonanimal-based methods may be suitable, which affects the likelihood of a manuscript being accepted for publication" (Krebs et al. 2023). Furthermore, scientific confidence in current NAMs is varied (Zalm et al., 2022). Animal models, which biomedical research has relied upon for decades, offer advantages that NAMs do not. "Animal models provide a comprehensive, whole-organism perspective that alternative methods cannot yet fully replicate. They deliver critical insights into systemic interactions, long-term effects and multifactorial responses to treatments, which are essential for understanding complex diseases and developing effective therapies" (Chang & Grieder, 2024).

Animal models, while not perfect, have proven necessary and vital to the advancement of human healthcare. Recently, animal models allowed researchers in the US to respond to the

COVID-19 pandemic and develop effective vaccines in record breaking time, averting an estimated 8.1 million cases, 123.2 thousand deaths, and 0.7 million hospitalizations in the US that would have come about in their absence (Boyle, 2021; Yamana et al., 2023). Animal testing was vital to the nation's immediate and impactful response. In 2024 alone, animal research has led to breakthroughs in gene therapy restoring hearing in a toddler, a new device to treat epilepsy, an mRNA vaccine to fight cancer, insights for improving immunotherapies, and keys to understanding and combating many other diseases and health concerns (Rozenbaum, 2024). Still, however, animal models are highly criticized. Because NAMs are based on human biology, they have the potential to provide more accurate predictors of toxicity and allow for personalized medicine (Yugulis, 2023).

Conclusion

The US is undergoing a shift with huge implications for the future of biomedical research. Despite historical reliance on animal models, technological advancements have improved the reliability of NAMs which are being incorporated into regulations that inform and enforce biomedical research practices and the marketability of biomedical innovations. Animal advocates and researchers continue to highlight the pitfalls of animal research. Educational and research institutions have launched initiatives and comprehensive guiding frameworks to prepare the scientific community for transitioning to an environment in which NAMs are more relied upon and accepted. Responding to these pressures, government officials have proposed legislative initiatives to change regulations involving animal and NAM research, and require regulatory agencies to enforce updated regulations. NAMs have the potential to lead to biomedical breakthroughs that animal models are not sufficient for generating. They will likely

continue to improve over time, becoming more reliable and leading to exciting, valuable, and highly applicable findings for human health.

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