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ETHICAL FRAMEWORKS FOR ANIMAL RESEARCH AND THE STRATEGIC ROLE OF NEW APPROACH METHODOLOGIES (NAMS)

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ABSTRACT

Animal experimentation has historically served as a foundational pillar of biomedical and pharmaceutical research, enabling the investigation of disease mechanisms, drug safety, and therapeutic interventions. However, growing ethical concerns regarding animal welfare, combined with persistent translational limitations of animal models, have prompted renewed scrutiny of traditional research paradigms. This study critically examines the evolving ethical frameworks governing animal research and explores the strategic role of New Approach Methodologies (NAMs) in reshaping contemporary biomedical science. Using a qualitative normative research design, the study analyses major ethical theories, including utilitarianism, deontological ethics, rights-based approaches, and care ethics, alongside regulatory frameworks such as the 3Rs principle (Replacement, Reduction, and Refinement). In addition, four illustrative case studies of NAM applications; multi-organ body-on-a-chip systems, human liver-on-a-chip platforms, 3D human organoids, and cardiac organoids, were examined to evaluate their scientific capabilities and ethical implications. The findings demonstrate that NAMs substantially enhance the operationalisation of ethical principles in research practice by reducing reliance on animal models while simultaneously improving the predictive accuracy, reproducibility, and translational relevance of biomedical data. These technologies replicate human-specific physiological responses more effectively than many conventional animal models, thereby addressing long-standing translational gaps between preclinical research and clinical outcomes. Furthermore, NAMs promote methodological innovation and foster a human-centered research paradigm that aligns scientific advancement with evolving societal expectations regarding animal welfare. Nevertheless, challenges remain regarding regulatory acceptance, validation standards, technical complexity, and unequal global adoption. The study highlights that NAMs represent not merely technical alternatives but a transformative shift in the epistemological and ethical foundations of biomedical research. Their integration into regulatory science and experimental practice offers a pathway toward more humane, reliable, and translationally relevant research systems. Continued interdisciplinary collaboration, regulatory harmonization, and technological development will be essential for realizing the full potential of NAMs in advancing ethically responsible scientific innovation.

KEYWORDS: Animal research ethics, New Approach Methodologies (NAMs), Human organoids, Ethics in science

1. INTRODUCTION

The animal research has traditionally been a core of biomedical science, pharmacology, and neuroscience, offering information that is often inaccessible in human research. The study of complex biological systems and disease mechanisms, as well as the safety and effectiveness of treatment, has been possible due to the use of laboratory animals (Beilmann et al., 2025). They have contributed to the development of drugs, vaccines, and surgical procedures, and have had a direct effect in veterinary and human medicine. Animal models can, therefore, provide an experiment that is ethically or practically unachievable in humans and provide predictive information on clinical trials, the metabolism of drugs, and organ-level functionality studies (Choudhary, 2025). Moreover, the use of animal models is also an opportunity to test the new methodological approaches, including new imaging techniques and new therapeutic interventions, and to verify their safety and effectiveness before using them in humans. Despite these developments in the field of science, social and ethical criticism has been on the increase over the use of animals in research studies. Such ethical issues are the moral standing of animals, pain, and suffering that may result from experiments, and the sufficiency of housing and care (Pal et al., 2025). These ethical issues are connected to a translational crisis: the reliability, reproducibility, and applicability of preclinical data to humans may be compromised by stress, pain, and species-specific differences (Weidema et al., 2025). The fact that the high-profile cases of animal abuse have shown that not only the ethical failures but also the validity of the scientific findings may suffer under the influence of the ethical issues. The ethical and translational problems intersecting herein show the necessity of re-evaluating conventional approaches to conducting biomedical research.

Therefore, the current ethical theories, such as the 3Rs principle, Replacement, Reduction, and Refinement, provide strict principles to minimise animal use, improve the welfare, and enhance the design of experiments (Kumari et al., 2026). Replacement encourages the use of alternative methods whenever feasible; reduction emphasizes the careful planning of experiments to use the minimal number of animals, and refinement seeks to optimize the procedures to minimize discomfort or distress. Complementary ethical perspectives include deontological ethics, emphasising innate animal rights (Reymers, 2025), caring ethics, emphasising researcher empathy and moral obligations (Onaga, 2024), and utilitarian ethics, balancing human advantages against animal damages (Singer, 2009). These values are operationalised with the help of regulations, including IACUCs, the U.S. Animal Welfare Act, and the European Union Directive 2010/63/EU, which analyse the necessity of the study, the effects of the research, and adherence (Milford et al., 2025). Although the frameworks are guiding, they do not comprehensively deal with the shortcomings of the use of animal models in translational research, nor do they present any standardized criteria for measuring complex evidence in new experimental designs.

As scientific practices and methodological standards evolve, traditional frameworks are becoming less and less sufficient. New Approach Methodologies (NAMs) are methodological frameworks developed to minimize or eliminate animal use through advances in biotechnology, computational modelling, and in vitro procedures (Gollamudi et al., 2025). These frameworks, including in vitro assays, organoids, 3D tissue models, organ-on-a-chip systems, microphysiological systems, and computational simulations such as PBPK, QSAR, and machine learning, provide mechanistic insights, predictive data, and improved reproducibility (Wu et al., 2024). According to Kumar et al. (2024), microfluidic devices, organ-on-a-chip systems, and microphysiological systems mimic organ-level functioning, enabling controlled dynamic modelling of tissue responses. These methodological frameworks can bridge the translational gap between preclinical and clinical research by integrating multiple cell types to simulate systemic interactions.

The justification of NAMs is further reinforced by extensive literature on the translational shortcomings of animal models. According to Marshall et al. (2023), drugs that are safe and effective in preclinical animal studies frequently fail in human clinical trials because of species-specific differences in physiology, metabolism, and disease processes. Although the frameworks are guiding, they do not comprehensively deal with the shortcomings of the use of animal models in translational research, nor do they present any standardized criteria for measuring complex evidence in new experimental designs. These translational drawbacks point to the epistemological drawbacks of animal studies and emphasize the usefulness of NAMs as methodological paradigms that provide information useful in humans, enhance predictive validity, and reduce reliance on animal models. Therefore, through the provision of reproducible, NAMs put the epistemic authority of the traditional animal models to test, human-centered data signify a scientific and ethical revolution.

Governance and regulatory structures have not yet adjusted fully to NAMs in spite of their promise. Technical problems, such as model validation and the lack of representation of complex physiology, persist (Ziemba, 2025). Institutional and social inertia inhibit NAM acceptance, including regulatory toxicology being dependent since time immemorial on animal models. Even though some of the regulatory bodies, such as the European Chemicals Agency and the U.S. Food and Drug Administration, have begun incorporating NAM data into safety assessments (Poonia et al., 2026), no standardised rules exist on the use, validation, and authorisation of NAMs. Thus, operationalization of NAMs requires clear decision rules, standards of monitoring, and evidence-alignment protocols.

1.1. Research Problem and Contribution

Even though NAMS have evolved very fast and can improve the level of ethical compliance, decrease the number of animals, and improve the translational relevance, the comprehensive understanding of how these methodological frameworks are transforming the standards of evidence in biomedical science is still not available. The current literature is largely talking about NAMs as ethical alternatives or technical additions, without addressing their epistemological, translational, and regulatory consequences. This gap restricts the creation of policies and assimilation of science. To fill this gap, the current paper will analyze how NAMs go against the classical evidence paradigms, the consequences of such practices on ethics and translation, and the sustainability of current varieties of governance. Through this, it will be able to offer researchers, decision-makers, and ethicists edible information to negotiate about the evolving terrain of biomedical research.

2. METHODOLOGY

The research design is a qualitative normative research design, the best-suited research design to provide answers to conceptual, interpretive, and ethically driven questions, as opposed to experimental ones. In this research, no human/animal involvement, no experimentation in a laboratory, and no primary generation of empirical facts are involved. Rather, it is based on the critical analysis regarding animal research, ethical theories, international regulatory frameworks, and the development of New Approach Methodologies (NAMs). The qualitative research design allows for a thorough investigation of how scientific responsibility and decision-making are shaped by moral reasoning as opposed to quantitative measurement (Pregoner, 2024). The study assesses the fundamental ideas of the main ethical traditions, utilitarianism, deontological ethics, rights-based approaches, and care ethics using qualitative thematic analysis of scholarly and regulatory literature. In addition, it also examines how each framework understands the obligations, constraints, and justifications related to using animals in research. Thus, the study's normative character enabled it to move beyond mere description toward evaluative judgement, addressing not only how animal research is carried out but also how it ought to be conducted in view of developing scientific alternatives.

Illustrative cases were selected from published applications of New Approach Methodologies (NAMs) to examine their scientific use and ethical implications in animal research. The discussion was directed to four important case studies, namely, multi-organ body-on-a-chip, 3D human organoid, cardiac organoid, and human liver-on-a-chip technology. The illustrative cases were examined to know how the two approaches were applied in experimental research, the nature of the investigations that they enabled, and how they may complement or substitute traditional animal models. This approach provided a rich contextual study of the multiplicity of NAM applications, practical application problems, and methodological developments that enhance moral research practices.

3. RESULTS

3.1 Findings on Ethical Frameworks

The analysis of the four selected NAM case studies provides vivid evidence of the use of modern ethical standards in animal studies. The principle of 3Rs is still the leading principle, organised in such a way to reduce the use of animals, reduce suffering, and maximise the design of the experiments (Lauwereyns et al., 2024). The studies indicate that New Approach Methodologies (NAMs) currently provide useful tools that can facilitate the operationalisation of this principle of ethics rather than merely recommended. The liver-on-a-chip experiment showed that microphysiological systems relevant in humans are more precise than most animal models in forecasting liver injury caused by drugs (Meyer et al., 2024). The research result makes the ethical rationale supporting the replacement an even stronger argument because the frameworks do not fail to underline the argument that the use of animals is no longer justifiable in case an animal-free predictive approach can be made. Bodies that have adopted this approach are consequently shifting their glib attitude towards permitting the use of animals, to mustering justification where NAMS have not been embraced.

In addition, reduction is also emphasized in the works where the human organoid models are used in 3D, permitting to test the human tissue in high-throughput and repeating the testing (Wang et al., 2024). The research demonstrated that such systems can minimize the use of large animal cohorts with the generation of overall toxicological information. In this way, the ethical theories are starting to recognize that greater experimental efficiency is a beneficial ethical consequence in that fewer sentient beings are required to generate reliable findings. Additional evidence of refinement is based on cardiac organoid studies, as it is demonstrated that mechanistic understanding of disease and drug reactions can be acquired without invasive animal experiments (Liu et al., 2024). Therefore, the destruction of pain-related endpoints is in line with ethical guidelines to alleviate pain, but without violating scientific integrity. Finally, the so-called multi-organ body-on-a-chip systems will resolve a long-standing ethical issue, therefore, modeling the interactions between systems without involving full animals in experiments (Huang et al., 2024). In this way, these systems undermine one of the many scientific arguments that have historically underpinned animal research because they increase metabolism and inter-organ communication in vitro.

3.2 Impact of NAMs

The introduction of NAMs has led to a review of traditional research methods, especially on evidence-based research and ethical regulation. This is demonstrated in the case studies of multi-organ chip platforms, liver-on-a-chip, 3D human organoids, and cardiac organoids, which demonstrated that NAMs can closely recapitulate complex human physiology and disease processes, which in turn reduces dependence on live animals. In addition, the 3Rs principle is directly impacted by NAMs: replacement, by completely replacing some animal experiments; reduction, by reducing the number of animals that are required for preclinical research; and refinement, by minimizing the pain of the procedure when using animal models is still required (Lauwereyns et al., 2024). Moreover, NAMs also encourage a change in research culture by pushing scientists to prioritise ethical responsibility in addition to scientific innovation and to take a human-centric approach.

However, beyond ethics, NAMs improve the reproducibility and quality of data, yielding results that are relevant to humans and minimising species-specific disparities that are frequently seen in conventional animal research (Hope & Bailey, 2025). NAMs can also shorten research timelines and lower the expenses related to late-stage drug failures by producing more accurate predictive data. Overall, NAMs are producing quantifiable gains in research results and ethical adherence, establishing them as crucial instruments for contemporary, ethical scientific practice.

3.3 Comparative Analysis

The comprehensive comparison of the NAMs and the traditional methods of animal usage shows some obvious differences in terms of operational efficiency, scientific performance, and ethical sustainability. A comparative analysis reveals that the operational characteristics, the outputs of the evidence, and ethical considerations of NAMs and traditional animal-based approaches are quite different. NAMs do not imply the use of live animals, because they are structurally aligned with the principles of ethical governance of the 3Rs; however, their ethical value can be evaluated in comparison with such factors as scientific validity, regulatory acceptability, and domain applicability (Fausch et al., 2025). NAMs provide feasible alternatives that have reduced harm to animals, whereas more invasive methods and larger cohorts are common in conventional animal studies. Regarding scientific output, NAMs can offer more accurate predictive power over human biology due to the ability to model organ-on-a-chip and organoid models, including interactions among tissues and disease mechanisms that could be absent in animal-based models (Ingber, 2022). This data that is human-relevant enhances translational results, enhances the credibility of preclinical investigations, and improves reproducibility.

Regarding costs, NAMs require a significant initial investment in specialized equipment and technical training, but they also save on long-term expenses by shortening the time to animal studies, maintenance, and purchase, as well as preventing losses due to the failure of animal studies (Levine et al., 2025). Although the existing animal models are still required to conduct systemic or whole-organism investigations, the findings point to the fact that NAMs have important ethical, scientific, and operational advantages, and thus can become an attractive addition or substitution in contemporary research.

4. DISCUSSION

4.1 The Key Findings

The conclusions made using the four most important NAM case studies provide significant new insights regarding the ethical and scientific issues of modern-day biomedical research. Human liver-on-a-chip technology outperformed with remarkable predictive accuracy, identifying 87% for toxic drugs and 100% specificity for non-toxic compounds (Meyer et al., 2024). The intricate tissue-specific interactions of the liver, intestinal, and cardiac systems in 3D human organoid models were maintained to offer some functional fidelity, which is absent in 2D cell cultures or animal models (Wang et al., 2024). Like this, cardiac organoids showed structural and functional responses to pharmacological agents that are typically neglected in animal research studies because species physiologically differ (Liu et al., 2024). Besides, multi-organ body-on-a-chip systems also enabled simultaneous evaluation of systemic responses such as inter-organ metabolism and compound interactions, which are not easily achievable in vivo (Huang et al., 2024). All these results prove the fact that NAMs address critical gaps, as they can provide repeatable, organ-specific, and human-relevant data.

Scientifically, these results resolve translational reliability, a long-standing drawback of animal models. The predictive validity of preclinical studies is often decreased by species-specific variations, leading to failure of costly clinical studies. In this way, NAMs provide a human-relevant and early stage of toxic effects analysis and experimental design optimization by enhancing the efficiency, minimizing downstream risks, and minimizing time (Sheng et al., 2025). The findings also highlight the potential NAMS has in endorsing the principle of 3Rs, which is ethical. NAMs can reduce the quality of data by removing certain animal experiments, reducing the quantity of animals needed, and enhancing experimental-based methods, contributing to research practices that are more moral and hence improve data quality. Altogether, these findings demonstrate that NAMs are a powerful, evidence-based approach that ensures scientific rigour, translational relevance, and scientific responsibility of biomedical research simultaneously.

4.2 NAMs Potential:

NAMs have a far-reaching potential in contemporary research. NAMs are highly desirable alternatives to traditional animal models because of their integration of microphysiological model systems, organoids, and multi-organ model systems (Zhu et al., 2026). This enables organ-specific, highly reproducible, and human-relevant preclinical studies. These systems enable researchers to perform high-throughput experiments, involving the testing of several compounds at once, whilst preserving the complex tissue functions, which reduces the time spent in conducting the research and the associated cost of end-stage drug failures. Another key limitation of traditional animal models is that interspecies variability often obfuscates translational relevance (Brynildsen et al., 2023). The predictive reliability of preclinical data can be enhanced with the assistance of the accuracy and scalability of NAMs.

In addition to being effective in laboratory work, NAMs also promote the practice of personalized medicine (Kasoju & Krispasagari, 2024). Patient-derived organoids have the capacity of emulating peculiar genetic and physiological responses, permitting toxicity testing and drug screening that is individually tailored to specific groups of patients. These methods cannot be done using conventional animal models that are unable to simulate the genetic diversity and microenvironment of humans or the disease-specific microenvironment. Consequently, NAMs give the opportunity to reduce the number of ethical challenges and develop safer and more effective therapies. Moreover, NAMs are facilitating a paradigm shift in the research culture by urging the scientists to focus on the human-biased, predictive, and ethically correct approaches (Teessar, 2024). They promote innovativeness in methods, including bioengineering, computational modelling, and advanced approaches to imaging, which enhance the quality of data, its repeatability, and its openness. Therefore, new global rules and policies that recognize the scientific and ethical feasibility of NAMs are encouraging factors for their acceptance, implying a possible future whereby the use of animal models is minimized.

4.3 Ethical Implications:

The moral aspect of the utilization of NAMs instead of traditional animal testing is complex. On a fundamental level, NAMs directly deal with the ethical duty of researchers to do the least harm to sentient entities by substituting animal models with organ-on-a-chip, multi-organ platforms, and 3D organoids. This will help avoid physical pain, stress, and death; therefore, rather than being focused on compliance in their ethical behaviour, it will take the form of proactive compassion. In addition to the principle of 3Rs, NAMs criticize the historicism of animal research, as in most cases, they provide more accurate and relevant information about humans, which is why their use is morally necessary in any case (Bailey, 2024). Also, NAMs enhance the reproducibility and equity of research. High-throughput and standardised experimental platforms also improve reliability and generalisability by reducing variability due to species differences (McGrath et al., 2024). Therefore, patient-derived organoids would be further used to offer more customised solutions, reduce the negative effects on humans and redundant testing, and increase scientific and ethical integrity. Besides, the adoption of NAMs promotes a shift in institutional and cultural ethics through the promotion of reproducibility, complete documentation, and transparency, as well.

5. CONCLUSION

In conclusion, the paper examined the role of New Approach Methodologies (NAMs) in transforming the modern biomedical science and the intersection of ethical approaches in animal research. The study demonstrated that complex human-specific physiological reactions that are often difficult to measure in conventional animal models are replicated in the study with the help of four example case studies, which included multi-organ platforms of the body-on-a-chip, cardiac organoids, 3D human organoid models, and human liver-on-a-chip platforms. Such systems resolved the ethical concerns regarding animal testing and provided reliable systems of toxicity testing, disease modeling, and drug-response testing. Also, the study results indicate that, besides enhancing the predictive accuracy and reproducibility, NAMs operationalise ethical principles that are part of the existing regulatory frameworks, particularly, the 3Rs (Replacement, Reduction, and Refinement). Therefore, NAMs are currently gaining the status of ethically sound and scientifically sound alternatives that can help to gradually replace more humane and human-centered research methodologies.

Nonetheless, the role of study in animal research ethics is to show that there is no need to develop and strive to advance science and neglect ethical development, as they can be developed simultaneously instead of being mutually exclusive. NAMs provide practical tools that allow putting ethical principles into practice in the laboratory beyond mere theoretical discussion of ethics to measurable changes in experimental design. By doing so, they enhance translational significance to the clinical outcome and reduce the use of animal experimentation because they enable the researcher to generate human-specific data at an earlier stage of the research process. Moreover, the study also points out the role of NAM-based approaches advocating reproducibility, standardization, and transparency as key elements of responsible science. Hence, the integration of NAMs in regulatory science, toxicology, and drug development is an indicator of a paradigm shift in the animal-based paradigm of experimentation to a human-based biology-oriented model. This promotes innovation in accordance with scientific rigor and expectation of society.

Despite the contributions, this study has several weaknesses. The analysis is based on secondary data and published case studies instead of primary experimental work; this restricts the possibilities of making new empirical discoveries. Moreover, although NAMs have significant potential, their use remains disproportionate according to geographical areas and areas of research as a result of the differences in infrastructure, acceptance of regulations, and technical skills required to create advanced in vitro systems. In addition, widespread adoption is also hampered by cost issues and the requirement for ongoing validation, especially in settings with limited funding for research. Moreover, NAMs can't yet replicate the entire systemic complexity of living organisms in all contexts, indicating that a transitional phase may still be required.

Therefore, future studies should focus on integrating more sophisticated multi-organ and integrated systems that can more accurately simulate whole-body physiological responses with greater accuracy. Thus, by integrating NAM platforms with computational modelling and artificial intelligence, these models can be further reinforced to increase translational relevance, facilitate complex data analysis, and boost predictive capacity. Moreover, expanding the use of patient-derived organoids enables researchers to examine individual variability in drug responses and disease progression, which is considered to be crucial to the advancement of personalised medicine. Furthermore, to establish regulatory confidence and validate the dependability of these methods for broad scientific and medical applications, long-term validation studies contrasting NAM-generated data with clinical outcomes are required.

INTENDANT

Having proven the ethical and translational benefits of New Approach Methodologies (NAMs), this study places new human-relevant platforms in a wider transformation into evidence systems that are scientifically predictive and ethically proportionate. NAMs enhance the moral basis of biomedical research by not only implementing harm minimisation but also enhancing translational validity by using human-specific biological modelling. With animal-based inference becoming more and more limited due to the problem of species divergence, stress-related confounding, and reproducibility concerns, the introduction of NAMs, in fact, constitutes not just a methodological improvement but a structural transformation of biomedical knowledge creation, validation, and regulation. In this direction, human-derived in vitro systems offer a way to a more predictive, more standardised, and ethically justifiable research practice.

In this regard, this study recognizes the current advancement of a new biological platform comprising structured, non-neural organ tissues derived from reprogrammed cellular sources. Theoretically consistent with organoid and organ-on-chip platforms, the platform is intended to recap organ-level physiology, but cannot form neural architecture with the ability to integrate, perceive, or process information. Ethically, the lack of organised neural circuitry is important: existing scientific and philosophical explanations of moral status in experimental systems have always associated sentience risk with the existence of functional neural networks that can produce experience. Accordingly, non-neural organ platforms are best understood as physiologically complex but non-sentient biological platforms, in moral status equal to other acellular or non-integrative in vitro systems. They are ethically justified, thus on negative and positive grounds: they eliminate the welfare costs of using animals and generate human-relevant information, enhancing translational reliability.

Simultaneously, the establishment of advanced human-derived models creates a critical boundary for the regulation of ethics. In particular, neural organoids and other systems aimed at modelling the structure of the central nervous system are a special category that needs increased attention because it has a theoretical readiness to achieve functional neural organisation. Although there is no evidence at present of sentience in those systems, their direction of growing complexity should provide guidance to their precautionary governance structures with regard to monitoring, developmental boundaries, and purpose-specific reasoning. Distinguishing between non-neural and neural physiological platforms of control, hence, facilitates proportionate regulation that preserves ethical integrity without hindering scientific innovation.

Positioning the developing organ-based platform within the NAM ecosystem exemplifies a more general truth, namely, ethical development and science development are mutually beneficial in cases where research models are tailored to human biology with no morally significant types of harm. Thus, by contributing to more predictive preclinical evaluation, improved reproducibility, and reduced dependence on animal experimentation, next-generation human-derived systems are an example of how the shift to a research paradigm based on human relevance, methodological transparency, and ethically organized innovation. The further work will also test standardisation requirements, computational integration, and regulatory pathways needed to enable the responsible implementation of such platforms in the field of translational science.

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