SOCIETY for NEUROSCIENCE

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On behalf of the Society for Neuroscience (SfN), thank you for the opportunity to comment on the proposal from NIH's Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) to reorganize and establish the Office of Research Innovation, Validation, and Application (ORIVA) and the Office of Research Evidence and Policy Analysis (OREPA). As the world's largest organization dedicated to advancing the understanding of the brain and central nervous system, SfN is committed to advancing biomedical research that drives innovation, improves public health, and maintains the United States' global leadership in scientific discovery. SfN appreciates NIH's intent to strengthen integration with NIH-wide initiatives related to scientific innovation, alternative test methods, reproducible research, and regulatory translation. To achieve this, the ethical and responsible use of animal models remains essential in areas of research where New Approach Methodologies (NAMs) are not yet suitable for replacement.

Research with animal models is essential and irreplaceable in neuroscience because no non-animal model can replicate the brain's full complexity. These models are vital for advancing treatments for devastating brain disorders and injuries—such as Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), depression, autism, and sensory loss—that affect millions of people in the United States. The humane and carefully regulated use of animal models in research allows neuroscientists to understand the root causes of diseases and to find new cures and treatments for both humans and animals. Every major scientific breakthrough in neuroscience and every medical advance that has improved human health and well-being have benefited from the use of animals in research. To ensure that ORIVA can most effectively fulfill its mission and support the biomedical research ecosystem, SfN offers the following recommendations, elaborated further below.

**Key Recommendations**

1. Establish a standardized, comprehensive NAMs definition that fully encompasses all 3Rs (Replacement, Reduction, Refinement), not replacement alone.
2. Set realistic expectations for NAMs as many are still in developmental stages and limited in their ability to answer critical scientific questions central to neuroscience.
3. Add a third ORIVA division dedicated to integrating NAMs and animal models together to ensure scientific and translational continuity.
4. Ensure clear, consistent communication with stakeholders including setting realistic expectations about where animal models remain essential and where NAMs are ready to be implemented.
5. Ensure ORIVA's leadership, staff, and advisory processes reflect the full spectrum of expertise in both NAMs and animal research by not only engaging NAMs experts and technology developers, but also including laboratory animal scientists, veterinarians, animal care staff, and others with diverse perspectives.

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**Establish a standardized, comprehensive NAMs definition that fully encompasses all 3Rs**
As ORIVA develops guidance, priorities, and governance structures, NIH should adopt a standardized definition of NAMs that explicitly reflects all components of the 3Rs—replacement, reduction, and refinement—not replacement alone. A unified, NIH-wide definition emphasizing all 3Rs will ensure clarity, transparency, and accuracy in describing NAMs-related activities and goals across research communities, regulatory partners, and the public.

SfN appreciates these efforts and embraces the goal of the 3Rs of animal models in biomedical research, but much more research and time is needed before such a goal is attainable. Premature replacement of animal models may delay or prevent the discovery of treatments and cures, not only for neurological diseases, but also for communicable diseases and countless other conditions. It may also increase the risk to patients due to premature approval without adequate testing in appropriate animal models to understand the potential risks. There are currently no viable alternative models to fully understand the brain and nervous system, and this is the first step to find new as well as better treatments for diseases and disorders including autism, depression, addiction, post-traumatic stress disorders, and neurodegenerative disorders.

While SfN supports the thoughtful incorporation of validated and appropriate NAMs in biomedical research, these tools must complement, not replace, proven animal models. A hybrid approach, combining NAMs with essential animal models, enables researchers to refine their studies, reduce the number of animals used, and enhance the efficiency of biomedical research. SfN is committed to this integrated strategy and urges NIH to consider this approach while establishing ORIVA using the 3Rs as a framework.

**Set realistic expectations for NAMs**
While NAMs hold significant promises, many are still in developmental stages and limited in their ability to answer critical scientific questions central to neuroscience. ORIVA is well-positioned to guide the community toward appropriate, evidence-based science rather than prematurely accelerating transitions away from animal models.

SfN believes biomedical research should continue to operate within the laws and guidelines set by multiple oversight bodies and continue to use the appropriate model where necessary. The best research emerges when investigators can draw freely on the full spectrum of tools available, from cutting-edge NAMs to essential animal models, without additional barriers. With further hurdles for researchers engaging in critical research involving animal models, there would be limitations in understanding the brain and stalled progress in developing treatments for human brain disorders.

The ethical use of animal models for critical research is essential to advancing our knowledge of basic neuroscience processes and working toward curing disease. By setting realistic expectations, ORIVA can

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help prevent misinterpretation of NAMs as universally ready-to-replace animal studies; support investments that advance NAMs responsibly and sustainably; and protect scientific rigor and public trust by avoiding an overstatement of their capabilities.

**Add a third division dedicated to integrating NAMs and animal models within the translational research ecosystem**

As highlighted in the proposed reorganization chart, ORIVA will be divided into two offices: Division for Accelerating Innovation in Biomedical Research and Division of the National Interagency Center for the Evaluation of Alternative Test Methods. However, there is no explicit organizational home for addressing the scientific integration challenges that arise when developing NAMs alongside indispensable animal research.

In many fields—especially neuroscience—animal models are still essential for understanding how the body and brain function and provide the necessary evidence for regulatory approval. At the same time, NAMs are rapidly emerging, often with the potential to complement or enhance, rather than replace, animal-based approaches. To ensure coherence, SfN recommends establishing a third division within ORIVA such as a "Division of Integrated Translational Models and Research Assurance." This division could:

- Ensure scientific and translational continuity as NAMs are developed, refined, and scaled;
- Coordinate efforts to integrate NAMs with existing models, rather than advancing one at the expense of the other;
- Maintain stable and reliable animal research infrastructure; and
- Establish scientific guardrails to avoid premature or inappropriate substitution that could jeopardize scientific progress or public health. This function is critical to ensuring NIH's research ecosystem remains scientifically grounded, operationally viable, and aligned with mission-driven public health needs.

**Ensure clear, consistent communication with stakeholders**

NIH plays a central role in shaping public understanding of biomedical research and ORIVA should establish mechanisms for clear and accurate communication including:

- Where and why animal research remains essential;
- What NAMs can and cannot yet achieve, based on current evidence; and
- How integration of NAMs and animal models strengthens scientific rigor.

To achieve this, SfN recommends ORIVA have regular opportunities for public comment on programs, research priorities, major policy decisions, and routine communication with researchers, scientific societies, patient groups, and animal care professionals.

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**Ensure ORIVA's leadership, staff, and advisory processes reflect the full spectrum of expertise in both NAMs and animal research**

To be successful, ORIVA should be staffed and advised by experts with diverse perspectives in decision-making processes. This means not only engaging NAMs experts and technology developers, but also including laboratory animal scientists, veterinarians, animal care staff, and others who are uniquely equipped to provide insight into study refinement, animal care, ethical review processes, and post-study adoption efforts.

Experts in drug development would also be critical, as they have a deep understanding of what is necessary to safely bring new drugs to patients. Their voices along with other experts in this space are vital to shaping policies that are innovative, responsible, and sustainable.

**Conclusion**

SfN is committed to working with NIH to promote transformative science that improves human health and maintains the United States' global leadership in scientific discovery. Through these recommendations, SfN aims to help ensure ORIVA advances innovation while safeguarding the integrity and stability of the nation's biomedical research enterprise.

We appreciate the opportunity to submit comments and look forward to continued dialogue and collaboration as ORIVA develops. In our effort to bring new breakthroughs to help patients with neurological conditions, it is essential to have all the tools available to achieve this goal which is only possible when NAMs and animal models are both supported and available. Thank you in advance for your consideration, and please contact SfN's Director of Advocacy and Training, Adam M. Katz, at akatz@sfn.org, with any questions.

Sincerely,

David Beversdorf, MD
Chair, Committee on Animals in Research, Society for Neuroscience